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Trichloroethylene: Assessment of Human Carcinogenic Hazard

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European Centre for Ecotoxicology
and Toxicology of Chemicals

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ECETOC Technical Report No. 60

TRICHLOROETHYLENE: ASSESSMENT OF HUMAN CARCINOGENIC HAZARD

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Erratum in ECETOC Technical Report No. 60.

Trichloroethylene: Assessment of Human Carcinogenic Hazard

On page 1, 3rd paragraph, the 4th sentence should read 'The second reported mortality as well as morbidity ...' (delete 'examined civilian aircraft maintenance workers and').

Brussels, 4 August 1994

SUMMARY AND CONCLUSION

Trichloroethylene (TCE) has been manufactured on an industrial scale since the beginning of this century and it is used for many different purposes.

The potential carcinogenic effect of occupational exposure to TCE has been the subject of a number of epidemiological studies conducted during 1978-1990, including 4 cohort studies, 2 cancer case-studies without control, one small cohort study without control and one colon cancer case-control study. Each of the above studies has some shortcomings, e.g. flawed study design or small study size. None of the studies demonstrate a link between exposure to TCE and an increase in cancer mortality or excess incidence of liver and colon cancer.

More recently 2 well-designed and well-conducted studies were published. The first, from the US National Cancer Institute studied mortality in a cohort of 6,929 workers with a follow-up of up to 30 years. This study included an extensive exposure assessment which indicated high exposures, in particular during the first part of the study period. The second examined civilian aircraft maintenance workers and reported mortality as well as morbidity in an extension of the initial cohort to 1,670 workers, with a follow-up period of 37 years. Both studies showed no association between exposure to TCE and cancer in general or any specific cancer.

Taken together, five cohort studies report on 18,183 workers with a follow-up period of more than 25 years for 4 out of five studies. None of these studies demonstrate a link between exposure to TCE and an increased risk for cancer in general or for any specific type of cancer in man.

These important findings contrast with the results from animal studies where evidence of carcinogenicity has been demonstrated. The principal tumour sites in the mouse are the liver and the lung (separate studies) and in the male rat, the kidney. The occurrence of an increased incidence of mouse liver tumours (hepatocellular carcinomas and adenomas) is the most frequently reported and significant observation in lifetime cancer bioassays of TCE following exposure by either inhalation or gavage. Increased incidences of lung tumours (adenocarcinomas) have been observed in female mice only.

Small increased incidences of kidney carcinomas were found in male Sprague-Dawley, F344 and Osborne-Mendel rats but not in female rats or in any of the other strains tested (ACI, August, Marshall and Wistar) although almost all rats exposed to high TCE levels had tubular cell

cytokariomegaly. The carcinogenicity results may have been confounded by the reduced survival due to the nephrotoxic effect of excessive doses of TCE.

A substantial number of biochemical studies have identified mechanisms for the development of the rodent tumours which do not require a direct interaction between TCE or its metabolites and DNA. In each case the mechanism is thought to be linked to species specific metabolism of TCE and to a range of biochemical responses which are either specific to rodents or are not seen at dose levels relevant to human exposure. The excess tumour incidences in the liver, lung or kidney in either mice or rats exposed to TCE are, therefore, considered to be of no real relevance to human carcinogenic hazard.

The mutagenic potential of TCE has been studied widely in *in vitro* and *in vivo* test systems. In many of the reported studies the purity of the test sample is not stated, although potentially mutagenic epoxide stabilisers were almost certainly present. Overall there is no convincing or conclusive evidence that pure TCE is genotoxic.

Taking all of this information into account, it is concluded that exposure to TCE does not present a carcinogenic hazard to man at levels of current occupational exposure standards.

SECTION 1. INTRODUCTION

Trichloroethylene (abbreviation TCE, CAS No. 79-01-6, IUPAC name: trichloroethene) has many synonyms, e.g. ethylene trichloride and tradenames, e.g. TRI. It is a colourless, volatile liquid used in metal degreasing and as a solvent in the textile and chemical industries. Commercial grade TCE is 99.9% pure, although up to 0.2% stabilisers such as 1,2-epoxybutane or diisopropylamine are added to commercial formulations. Occupational exposure to TCE vapours by inhalation or, to a lesser extent, to liquid TCE by skin contamination may occur in the workplace, especially in surface metal cleaning processes in non-closed systems.

The question of whether TCE presents a carcinogenic hazard to man has been the subject of much debate. TCE has been shown to be carcinogenic in animals, causing principally liver and lung tumours in mice and kidney tumours in male rats only. In contrast, epidemiological studies using large groups of exposed workers have shown no evidence of an association between exposure to TCE and the occurrence of cancer in man.

This report reviews TCE studies with respect to cancer epidemiology, animal carcinogenicity, metabolism and kinetics, mutagenicity and mechanisms of tumour formation. An assessment of the extent to which it represents a carcinogenic hazard for man is presented.

SECTION 2. CANCER EPIDEMIOLOGY

TCE has been manufactured and used extensively since the beginning of this century. Its use as an industrial solvent, metal cleaning agent, and historically as an inhalational anaesthetic and as an additive in drugs, food and consumer products, indicate that widespread human exposure has occurred (IARC, 1979; ACGIH, 1992). The potential effects from TCE on human health, in particular the risk for cancer, have been studied for many years among occupational groups and among other populations, with environmental exposure e.g. via drinking water.

There exist a multitude of studies of human health effects of TCE. The older studies in particular have significant limitations, but recently well-designed studies of occupationally exposed groups have become available. This overview concentrates on studies reporting on occupational groups but a few other studies with relevance for TCE will also be discussed briefly. Historically, the study of occupational groups has contributed most to our understanding of the potential risks associated with exposure to chemicals because workers typically had higher exposures for longer periods of time than other populations.

2.1 REVIEW OF COHORT STUDIES ON CANCER INCIDENCE AND MORTALITY

Axelson *et al* (1978) was the first to report an epidemiological study of workers exposed to TCE; their study was triggered by the carcinogenic findings in experimental animals. The authors identified exposed workers by means of a laboratory register of urine trichloroacetic acid (TCA) measurements, kept from 1950 by the sole Swedish manufacturer of TCE. The register is complete as from 1967. Participation in the monitoring program was voluntary and free of charge. The initial study concerned 582 workers exposed to TCE prior to 1970. The cohort was expanded and studied on 2 further occasions. At the first update Axelson (1986) reported on 1,424 male and 249 female workers exposed before 1975.

Subsequently the study was further updated by Axelson *et al* (1994) to encompasses 1,670 workers (1,421 males and 249 females) involved in the manufacture or use of TCE from 1950 through 1979. Follow-up was up to and including 1985. All had been monitored by analysis of TCA (a metabolite of TCE) in the urine. The mean urinary TCA level for each worker was used as an index of exposure. The majority of the subjects had mean urinary TCA levels below 50 mg/l, which the authors state roughly corresponds to an average exposure level of 20 ppm TCE in air (8-h time-weighted average). Mortality as well as morbidity was reported. Total male mortality was

significantly lower than expected (SMR, Standardised Mortality Ratio = 0.65: 95% CI, Confidence Interval: 0.47-0.89). Male mortality from disease of the circulatory system was slightly increased, reaching borderline statistical significance (SMR= 1.17: 95% CI: 1.00 - 1.37). Dose-response was studied using 3 subgroups based on overall mean TCA levels (<49, 50-99, >100mg/l) and by considering exposure time and 10 years of latency. The subcohort with the shortest exposure time had a slightly higher overall mortality than that with the longer exposure time. Morbidity analysis gave the same picture, with a borderline statistically significant increase in malignant skin tumours (SMR=2.36: 95% CI: 1.02 - 4.65) (Table 1). This excess as well as non-significant excesses of liver cancer, prostatic cancer and lymphomas occurred essentially in the low exposure group or after a short duration of exposure or both. However, these types of cancers were not increased in the medium or high exposure groups. The results from this study do not suggest an increased cancer risk from exposure to TCE at the exposure levels experienced by the cohort (Axelson *et al*, 1994).

This conclusion has a considerable weight as it is based on analysis of mortality as well as morbidity, while considering dose-effect, exposure time and latency. In addition, there are 2 arguments for assuming a higher level of TCE exposure than reported by the authors (20 ppm). First, assessing exposure from urinary levels of metabolites only gives a valid estimate when urine samples are collected at the appropriate time after exposure, which depends on the kinetics of excretion. The authors did not mention a prescribed sample collection procedure for the biomonitoring of TCE exposure. It is well accepted that random urine sampling will underestimate exposure (Lauwerys, 1983). Second, elevated exposures can be assumed to have existed during the first years of using TCE, when procedures and engineering controls to reduce exposure were not yet optimal. These high exposure levels are hidden by averaging all biomonitoring results obtained for a person during his entire working period, as has been done in this study.

A similar approach was used by Tola *et al* (1980), who identified Finnish workers with TCA exposure from a register of biological monitoring. Biological monitoring was part of the mandatory routine periodic medical examination. The cohort consisted of 1,148 men and 969 women (total 2,117) exposed to TCE between 1963 and 1976. 89 persons who had shown symptoms of acute toxicity due to TCE exposure during this period and 33 workers identified by employers as TCE exposed were included in the cohort in addition to the workers from the registry. Follow-up was up to and including 1976. TCE exposure was considered to have started at the time of the first urinary measurements for registered workers and follow-up commenced as of that date. The registered workers were grouped according to their highest recorded urinary TCA measurement. Ninety-one % of the registered workers had maximum urinary TCA measurements below 100 mg/l, which corresponds to 40 ppm TCE in air (Axelson *et al*, 1994). For the total cohort, observed deaths were

Table 1 Cause-specific SIR[a] and 95% CIs[b] Adjusted for Age and Calendar Period: White Men (<80 y) Exposed to TCE, Swedish Cohort (Axelson *et al*, 1994)

IDC 7[c]	Site	Observed	Expected	SIR	95% CI
140-209	All	107	111.9	0.96	0.80-1.16
151	Stomach	5	7.2	0.70	0.23-1.62
153	Colon	8	7.8	1.04	0.44-2.03
155	Liver	4	2.8	1.41	0.38-3.60
157	Pancreas	1	4.1	0.25	0.01-1.38
161	Larynx	2	1.4	1.39	0.17-5.00
162	Lung	9	13.2	0.69	0.31-1.30
177	Prostate	26	20.7	1.25	0.84-1.84
178	Testis	2	1.0	2.03	0.25-7.31
180	Kidney	6	5.2	1.16	0.42-2.52
181	Bladder	8	7.9	1.02	0.44-2.00
191	Skin	8	3.4	2.36	1.02-4.65
200	Non-Hodgkin lymphoma	5	3.2	1.56	0.51-3.64
201	Hodgkin's lymphoma	1	0.9	1.07	0.03-5.95
202	Other lymphoma	0	0.1	-	0.00-33.72
203	Multiple myeloma	1	1.8	0.57	0.01-3.17
	Other	21	31.2	0.67	0.43-1.03
	Person-years:	23,516			

a Standardised Incidence Ratio
b 95% Confidence Interval
c International Statistical Classification of Diseases and Related Health Problems

compared with expected deaths based on Finnish national mortality data. Overall mortality and cancer mortality were below expected (respectively 58 deaths observed vs. 84.3 expected; SMR = 69: 95% CI: 52-89, and 11 observed vs. 14.4 expected; SMR = 77: 95% CI: 38 -138). When allowing for a short latency period the results were essentially identical.

This study was not able to consider mortality outcome by a measure of cumulative exposure. It was also not possible to examine mortality for longer than 14 years after the presumed first exposure (although this is probably underestimated). Urine samples were not collected after potential exposure to TCE but during the routine periodic medical examination. Therefore, actual exposure levels were probably higher than those reported. In summary, the study did not demonstrate an increased cancer risk among workers including a group of very heavily exposed persons. However, this conclusion has limited weight due to the limitations of the study.

An American cohort mortality study of workers exposed to TCE was reported by Shindell and Ulrich (1985). They studied the workers in a manufacturing plant in which TCE was used for vapour degreasing and whose employees also drank water containing low levels of TCE. A total of 2,646

employees were identified who worked at least 3 months between 1957 and 1983. Expected mortality was determined using national rates. The data did not permit analysis by duration of exposure or cumulative exposure. Cancer mortality was less than expected for both sexes and races. Among white males there were 20 total cancer deaths and 32.2 expected (SMR=62: 95% CI: 38-95). The authors apparently included in this study everyone who had worked in the plant during the period of observation, including management, clerical and shipping personnel who were unlikely to have been exposed to TCE as part of their work. Moreover, there was no separate analysis for the groups of workers who were more likely to have been exposed. Because of these shortcomings, the conclusions fom this study are of limited value.

In 1985, the Hughes Aircraft Company commissioned a cohort mortality study of its workers in its Air Force plant No. 44. This investigation, conducted by Wong and Morgan (1990) of ENSR Health Sciences, has not been published. The study was initiated because of the detection of TCE in wells supplying water to the plant and to the surrounding community. It was believed that because the plant workers were exposed to TCE via degreasing operations inside the plant as well as via the water, their exposures must have been substantially higher than those of the community residents not employed in the plant. Therefore, any excess cancer risk would have been expected to be more readily detectable among the employee population. The investigators studied a total of 20,535 male and female employees of whom 4,733 were determined to have had occupational TCE exposure. Mortality follow-up was conducted from 1950 through 1985; approximately one-third of the cohort was observed for more than 25 years but another third had five or less years of follow-up. Both US and local county mortality rates were used to determine expected numbers of deaths for the study cohort. Duration of employment was used as an index of total TCE exposure. Also in this study a statistically significant deficit was observed for all cancers combined among the male and female workers. There were 125 cancer deaths observed compared with 159.7 expected (SMR=78: 95% CI: 65-93). For no specific anatomical site was the SMR for cancer mortality statistically elevated, although the SMR for liver cancer (including biliary passage cancer) was found to be elevated (SMR=184: 95% CI: 60-430). An SMR exceeding 200 was found for benign neoplasms (SMR=296: 95% CI: 109-646). Small deficits of mortality were observed for lung and kidney cancer. All-sites mortality appeared to increase somewhat by duration of employment, but in each category the SMR value was below 100. Three liver/biliary cancers were observed in the < 10 years employment category with none in the 10-20 years category and 2 in the longest duration category. The respective SMR's (178 and 434) were not statistically different from 100 (Wong and Morgan, 1990). The most important limitations of this study are the generally low TCE exposures reported for the employees and the small number of subjects with long duration of employment and