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A Review of the Epidemiologic Studies of Trichloroethylene and Kidney Cancer and with Reference to Liver Cancer and non-Hodgkins Lymphoma

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Summary and Conclusions

On balance the epidemiology studies of workers exposed to TCE do not support a causal relationship between TCE and kidney cancer. Seven occupational cohort studies involving over 130,000 workers consistently show no significant increase in the risk of kidney cancer. The study by Henschler et al. has so many methodological problems that no valid conclusion is possible. The case-control study by Vamvakas et al. also has so many design flaws that it cannot be given any consideration.

Causal inferences from epidemiologic studies are generally based on several criteria including, 1) Strength of the association; 2) Consistency of the association; 3) Temporality of the association; 4) Coherence of the association; and 5) Specificity of the association. Other evaluation criteria are the quality of the exposure assessment, the absence of confounding and bias, and the statistical uncertainty in estimating the risk ratio for the outcomes of interest.

Based on these criteria, it is clear that the available epidemiologic data do not support a causal relationship between kidney cancer and TCE. With the exception of two poorly designed studies by Henschler et al. and Vamvakas et al., the results are not significant and do not suggest elevated risks among workers exposed to TCE.

Other cancers have also been considered in the evaluation of the carcinogenicity of TCE. A summary of the data on liver cancer and non-Hodgkins lymphoma from the above-mentioned studies is presented in Table 2. As can be seen from this summary none of the studies found a significantly elevated risk for these cancers.

Overall, these epidemiologic studies do not provide sufficient evidence of carcinogenicity in humans to support the NTP's classification of "known to be a human carcinogen."

Introduction

This review of the epidemiology of trichloroethylene (TCE) and kidney cancer focuses on the published occupational studies. The emphasis is on kidney cancer although data are provided on both liver cancer and non-Hodgkins lymphoma.

Occupational studies generally provide the most useful information on associations between chemical exposures and cancer. They are generally designed as retrospective cohort mortality studies where a defined group of workers are identified retrospectively from company records and their mortality experience is compared to that of a comparison group, usually the general population. Other types of studies, such as population-based case-control studies, are generally less persuasive primarily because of inadequate exposure information. In a population-based case-control study, cases and controls (or their next of kin if they are deceased) are interviewed about prior jobs they have held and companies where they have worked. These job/company combinations are then converted to exposures. There is generally a high degree of uncertainty in ascribing the exposures to individuals. Furthermore, these studies often suffer from selection bias, information bias and confounding. In some situations, case-control studies nested within an occupational cohort can provide a valid exposure assessment.

This review is presented in two sections. First is a summary of the seven occupational cohort studies conducted in the U.S., Finland and Sweden. This is followed by a more detailed review of the studies of renal cell cancer in Germany that report much higher risks than the other published studies (Henschler et al. 1995, Vamvakas et al. 1999).

Occupational Cohort Studies

The association between TCE exposure and kidney cancer has been studied in eight occupational cohort studies (Table 1): Garabrant et al. 1988, Axelson et al. 1994, Anttila et al. 1995, Henschler et al. 1995, Blair et al. 1998, Morgan et al. 1998, Ritz, 1999 and Boice et al. 1999. Seven of these eight cohort studies provide no evidence that occupational exposure to

TCE causes kidney cancer. The exception is the study by Henschler et al. (1995) which does report a significantly increased risk for kidney cancer. This study, built around a kidney cancer cluster, has many methodological problems and therefore its validity is questionnable. Four of the eight cohort studies provide incidence data and only one (Henschler et al.) has a significantly elevated standardized incidence ratio (SIR). For cancer mortality, only the Henschler et al. study has an elevated standardized mortality ratio (SMR), which was not statistically significant.

Garabrant et al. (1988) conducted a retrospective cohort mortality study of men and women employed in an aircraft manufacturing company where it was estimated that 37 percent of the jobs involved exposure to TCE. The mortality experience of the workers from 1958 to 1982 was compared to the mortality experience of the United States population and the population of San Diego County which was the location of the facility. A total of 14,067 workers contributed 222,100 person-years of follow-up. During the study period, 1,804 workers were identified as deceased and death certificates were obtained for all but 84 of these decedents. The observed number of kidney cancer deaths was less than the expected number (SMR=0.93, 95% CI, 0.48-1.64).

Axelson et al. (1994) published an update of a Swedish retrospective cohort incidence study at a TCE manufacturing facility where workers were offered free surveillance for trichloroacetic (U-TCA), a metabolite of TCE in urine. The study included 1670 workers who contributed almost 25,000 person-years of follow-up. There was no statistically significant increase in kidney cancer incidence. The observed number of cases was approximately equal to the expected number (O=6, E=5.2, SIR=1.16, 95% CI, 0.42-2.52).

Antilla et al. (1995) had access to a Finnish database of employees biologically monitored for occupational exposure to TCE during 1965 to 1982. Exposure was measured by urine concentration of trichloroacetic acid. In addition to the workers with urinary measurements of U-TCA, the database included 109 workers with no urinary measurements but who were listed in the registry of occupational diseases with trichloroethylene poisoning. Cancer cases were ascertained from 1967 to 1992 by linking the database of workers to the Finnish cancer registry, and cancer deaths from 1965 to 1991 were ascertained by linkage to the vital statistics records

from the Central Statistical Office in Finland. The study included 1,698 men and 1,391 women who contributed 31,552 and 28,353 person-years of follow-up, respectively. There were fewer kidney cancer cases observed than expected (SIR=0.87, 95% CI, 0.32-1.89) and there was no association with the number of years since the first measurement

Blair et al. (1998) provided an update of a retrospective cohort mortality study of workers at Hill Air Force Base in Utah. The purpose of the study was to evaluate potential disease risks associated with exposure to organic solvents, particularly TCE. A cohort of 14,457 workers who were employed at least one year between 1952 and 1956 were enrolled and followed through 1990. As of 1982, there were over 45,000 person-years of TCE exposure in this cohort (Spirtas et al., 1991). Exposure to TCE was determined through an extensive assessment of jobs, the workplace, chemical inventories, interviews and monitoring data. There was no statistically significant increase in deaths from kidney cancer (SMR=1.22, 95% CI, 0.85-1.74), no significant increase in the risk ratio comparing exposed workers to nonexposed workers (RR=1.6, 95% CI, 0.5-5.1), no increased risk with increased exposure and no significant increase for the most highly exposed group for both men and women. In addition, no significant increases in risk were found for any of the alternative methods of evaluating exposure including low level intermittent exposure, low level continuous exposure and frequent peaks. Incident cancer cases were identified through a linkage to the Utah cancer registry. No statistically significant increases in kidney cancer cases were found for men or women and there was no dose-response effect.

Morgan et al. (1998) studied 20,508 workers (461,618 person-years of follow-up) having worked at least one year during the period 1950-1985 at the Hughes Aircraft Company in Arizona. At this facility, TCE exposure occurred between 1952 and 1977 in vapor degreasing units and prior to 1981 through ingestion of contaminated well water on the site. A total of 4,052 deaths were identified between 1950 and 1993. No statistically significant excess of kidney cancer was found for the overall cohort (SMR=1.14, 95% CI, 0.78-1.61) or for the TCE-exposed cohort (SMR=1.32, 95% CI, 0.57-2.60) or for the TCE high exposed cohort (SMR=1.78, 95% CI, 0.72-3.66). An internal analysis, using Cox proportional hazard models, also did not show a significant increase in risk (RR=1.89, 95% CI 0.85-4.23).

Using data available from the Comprehensive Epidemiology Data Resource (CEDR), Ritz (1999) examined kidney cancer risk in association with TCE, cutting fluids and kerosene among 3,814 at a uranium production facility in Ohio. In this cohort there was 120,237 person-years of follow-up. Plant industrial hygienists classified job titles into TCE exposure groups (none, light, moderate, and heavy), with most workers classified into the "light" exposure category. Approximately 80% of the cohort had at least some exposure to TCE. There were fewer deaths from kidney cancer than expected (SMR=0.65, 95% CI, 0.21-1.51).

Boice et al. (1999) conducted a retrospective cohort mortality study of 77,965 workers, contributing 1,889,795 million person-years of follow-up, at the Lockheed Martin aircraft manufacturing facilities in California. There were fewer kidney cancer deaths than expected for the overall cohort (SMR=0.92, 95% CI, 0.76-1.09), significantly fewer than expected for those workers with the longest duration of employment (SMR=0.52, 95% CI, 0.26-0.93), fewer than expected for those exposed to TCE (SMR=0.99, 95% CI, 0.40-2.04) and a deficit of kidney cancer cases among those with the longest duration of exposure to TCE (RR=0.69, 95% CI, 0.22-2.12).

In summary, these seven occupational cohort studies of workers exposed to TCE, which were based on well-defined cohorts and exposure assessments involving either urine biomonitoring or some type of job exposure matrix, did not find significantly increased risks of kidney cancer.

The articles by Henschler et al.(1995) and Vamvakas et al.(1998) warrant more attention because their results have been quite different from the other epidemiologic studies of TCE exposure and they have been prominent in the more recent considerations of TCE carcinogenicity. The authors of these studies suggest that exposures to TCE significantly and substantially increase the risk of kidney cancer. They attribute their findings, which are contrary to the findings from the cohort studies, to the higher exposures in their study populations relative to the other cohort study populations. This is alleged despite the absence of specific data to substantiate their claim regarding exposures. The fact that these studies have received so much attention may be due to the reported results that show rate ratios in the range of 8 to 10. However, the size of the number should not detract from the numerous and serious methodological flaws with these two studies.

Henschler et al. 1995

Henschler et al. (1995) conducted a retrospective cohort study at a cardboard factory in Germany. One study group consisted of workers exposed to TCE for at least one year between 1956 and 1975. Of the183 eligible workers, 169 were included. A comparison (unexposed) group was ascertained of 190 male workers, matched on age and physical work activities, whose work did not involve exposure to TCE. There were 50 deaths among the exposed group and 52 among the unexposed group. The overall SMRs and 95% CI's were 0.68 (0.48-0.93) in the exposed group and 1.03 (0.77-1.35) in the unexposed group. There were two kidney cancer deaths in the exposed group (SMR=3.28, 95%CI, 0.40-11.84) and 0 (0.60 expected) in the unexposed group. There were five incident cases of kidney cancer (4 renal cell cancer and 1 urothelial cancer) among the exposed group and none among the unexposed group. For the exposed group, the SIR was 7.97 (95% CI=2.59-8.59) when compared to the Danish Cancer Registry and 9.66 (3.14-22.55) when compared to the Cancer Registry of the Former German Democratic Republic. The authors concluded that these results support a causal relationship between TCE and renal cell tumors. A careful review of the paper raises a number of serious issues that cast doubt on their conclusion.

This study appears to be an expanded investigation of a cluster of kidney cancer cases. If true, then causation cannot be inferred. Designing a study around a cluster and including the cluster cases in the study almost assuredly leads to a positive finding. Numerous issues in the design and conduct of the study and in the data presented in the published article, suggest many other problems with the study.

The unexposed group was matched on age to the exposed group yet there was a considerable difference in the age distribution between the groups. The median, minimum and maximum ages for the two groups were: exposed: 59, 40, 89; unexposed: 62, 28, 79. The study period was from 1956-1992, a maximum of 37 years (minus the one year enrollment criterion), however the median observation periods for the two groups as shown in Table 1 of the article were 34 years for the exposed group and 32 years for the unexposed group. Given that there were 50 deaths in the exposed group and 52 in the unexposed group, it would appear that all the

deaths would have had to occur toward the end of the study period for the median years of observation to be correct. This is a highly unlikely occurrence.

Other data in Table 1 of the paper are questionable. For example, results for smoking are presented for 175 exposed workers yet there were only 169 workers in the exposed group. It is interesting to note that data were available for everyone in the unexposed group indicating that no one refused to participate yet there were a number of refusals in the exposed group. A rather high percentage (22%) of people in the unexposed group used diuretics. Median blood pressures were identical between the two groups (140/80) despite the differences in the range.

Using the Danish Cancer Registry the authors computed that 0.628 kidney cancer cases would be expected in the exposed cohort (Table 2 of Henchler et al). This is essentially the same as the expected number of deaths presented in Table 5 of Henchler et al., a surprising result given the 5-year survival rate for kidney cancer.

The mortality data presented in Table 5 does not show any significantly elevated SMR except for brain cancer in the unexposed group (SMR=9.38, 95% CI, 1.93-27.37). The authors attribute this to a sensitivity bias. A similar bias could have influenced case ascertainment of kidney cancer in the exposed group since all members of this group received abdominal sonography.

There were no data on TCE air concentrations or on TCE metabolites in urine. Exposures were surmised from "walk-through surveys and extensive interviewing of long term employees". Of the five kidney cancer cases, three had jobs with relatively low exposure to TCE and two were in "highly" exposed jobs. However, one of these highly exposed workers was the urothelial cancer. Thus, it appears that one renal cell cancer case in the cluster worked in a "highly" exposed job.

Because of the many methodological problems and inconsistencies in the data, this study is difficult to interpret. It is likely that the Henschler et al. finding is due to chance based on a cluster investigation presented as a hypothesis testing study, to confounding, or to issues related to the design and conduct of the study.

The Case-Control Study by Vamvakas et al. 1998

Vamvakas et al.(1998) conducted a case-control study. Notwithstanding the earlier comments about case-control studies, this study is reviewed because it has received considerable attention in the evaluation of the carcinogenicity of TCE. The cases were defined as all renal cell cancer patients from the Urology Department of a country hospital in North Rhine, Westphalia who underwent nephrectomy between December 1, 1987 and May 31, 1992. After exclusions due to missing data and refusals, 58 cases and 84 controls were available for analysis. Comparing the "highest" exposed group to the nonexposed group gave an unadjusted odds ratio of 7.9 based on 8 exposed cases and 2 exposed controls. A small degree of misclassification or bias could significantly alter this risk. The authors present the adjusted odds ratio for the highest exposure category as 11.42 (95% CI, 1.96-66.79), the wide confidence interval reflecting the small numbers.

Cases included in an earlier study by Henschler et al. (1995) were excluded even though they might have been eligible by virtue of having undergone surgery at the study hospital. Two justifications for excluding these cases were provided. First, the authors wanted to avoid "double reporting" the cases; second, the authors limited cases to those employed in small, rather than large, factories. However, neither reason is justified, since both could result in selection bias. There is no inherent problem in including cases who might have participated in another study. Omitting selected cases who meet the study criteria could introduce a bias if they are different from cases included in the distribution of risk factors. Using factory size as a basis for exclusion of cases might have been acceptable had the same criterion been applied to controls. Apparently, it was not. A further problem in the case selection procedures is limiting the cases to those who underwent surgery, rather than to all histologically confirmed cases because the included cases may not be similar to the excluded cases in the distribution of risk factors.

An important issue in case-control studies is the selection of controls. Controls should be selected from the same source population or study base as cases (Wacholder et al. 1992). In this study, the authors selected controls from the accident wards of three hospitals, none of

which was the hospital from which cases were ascertained. Controls were selected from patients hospitalized during 1993, rather than from the same period as the cases (1987-1992) and there was no effort to ensure comparability on age between cases and controls. There are at least five reasons why this method of control selection is problematic and would result in selection bias. First, controls were selected from different hospitals than the cases. Without knowing hospital utilization and referral patterns in the area, it is impossible to conclude that controls were from the same study base as cases. Second, controls were selected from a specific diagnostic category. Since Berkson's classic paper in 1946, selection of hospital controls from a single hospital ward or disease category has been discouraged to guard against introducing bias (Berkson, 1946). Third, controls were selected from 1993, whereas cases were selected between 1987 and 1992. Thus, potentially eligible controls admitted to the hospital between 1987 and 1992 were excluded from consideration. This discrepancy between the eligibility dates for cases and controls is striking and highly unusual for case-control studies. Fourth, cases and controls were interviewed at different times, with up to six years between the initial interviews with the cases and controls. Fifth, the age discrepancy between the cases and controls bears directly on exposure potential. In this study, 8.6 percent of the cases were below the age of 50, whereas 44.0 percent of the controls were under 50. Therefore, cases had considerably more opportunity (more person-years of work experience) to experience the exposure of interest. It is especially noteworthy that the cases were first exposed in 1957 whereas the controls were first exposed in 1975 (Table 4 of Vamvakas et al. 1998). Thus, by itself, this design feature almost guaranteed that a positive association would be found. Age is a prominent risk factor for renal cell carcinoma. The age discrepancy between cases and controls would also affect confounding factors such as cigarette smoking, obesity, and diuretic use. It is important to note that adjusting for age would not satisfactorily resolve the concern about the striking age imbalance.

Another important consideration in case-control studies is information bias. This refers to systematic (as opposed to random) error that can occur if information about exposure is not valid. Information on previous jobs and exposures was obtained through a personal interview. The interviewers, who were physicians, were aware of who was a case and who was a control. Apparently, different physicians interviewed cases and controls. For cases who were deceased, information was obtained from former colleagues and relatives. Since none of the controls was

deceased, all of their information on exposures and confounding factors was obtained through a direct interview. Generally, in case-control studies such as this, every effort is made to design the study to minimize the opportunity for obtaining different quality of information from cases and controls. Such strategies would include blinding the interviewers as to case or control status of the participants and utilizing the same interviewers for both cases and controls. Using physicians in the area as interviewers rather than professionally-trained interviewers could result in considerable variability in the manner in which the interview was conducted and hence considerable bias in the responses. Another feature of the study that could have introduced information bias was the follow-back interviews. In this phase of the study, patients who reported any occupational exposure to trichloroethylene or tetrachloroethylene were recontacted to participate in another interview to assess conditions of exposure to these solvents in greater detail. The specific details of this procedure are not stated in the paper so it is not clear what the criteria for inclusion were or if a structured interview was administered.

The assessment of exposure was conducted through interviews with patients or informants. As stated in the paper, air or biological monitoring data were not available for any of the patients. To supplement the self-reported information, the investigators obtained more detailed information on work history from the Employer's Liability Insurance Association. This would suggest that for some, but not all individuals, and presumably those who filed a claim, additional information was obtained. It is likely that this information was more available for cases than controls.

Information on potential confounders was also collected through personal interview. There are a number of important risk factors for renal cell cancer such as smoking and obesity. Bias in the confounder information could also distort the results of the study.

Although it is difficult to know with certainty if this study is biased, there are some clues to suggest it may be. For example, there is a well-established association between renal cell cancer and cigarette smoking. In this study, 48 percent of the cases and 56 percent of the controls had ever smoked suggesting no positive association with renal cell cancer. Another important risk factor, obesity, was also not associated with renal cell cancer in this study. Body mass index was identical between cases and controls. The absence of these well-established

associations reinforces the argument that there was bias in the selection of study subjects and/or in the collection of the data.

Another potential source of bias is nonresponse. Not all selected subjects participated in the study. Overall, 79.5 percent of the cases and 75 percent of the controls agreed to participate. If the participants differed from the nonparticipants in exposure experience or in any of the important confounding factors, bias could have been introduced.

The authors conclude that bias could not account for their results, yet offer no evidence to support their position. Although it is difficult to know precisely the extent to which the many unusual features of this study may have biased the risk estimate, it is likely that the bias is not trivial.

Conclusions

Overall, these epidemiologic studies do not provide sufficient evidence of carcinogenicity in humans to support the NTP's classification of "known to be a human carcinogen."

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Table 1 – Summary of Occupational Cohort Studies of TCE Exposed Workers

Authors, Yr	Study Group	No. of Workers	Kidney Cancer
Antilla et al., 1995	Finnish workers monitored for TCE and other solvents	3,974	SIR= 0.87 (0.32 – 1.89)
Axelson et al., 1994	Swedish workers monitored for TCE	1,670	SIR= 1.16 (0.42 – 2.52)
Blair et al., 1998	Aircraft workers, Utah airforce base	14,457	SMR= 1.6 (0.5-5.1)
Boice et al., 1999	Aircraft manufacturing workers, Burbank, CA	77,965	SMR= 0.99 (0.40-2.04)
Garabrant et al., 1988	Aircraft manufacturing workers, San Diego CA	14,067	SMR = 0.93 (0.48-1.64)
Henschler et al., 1995	Cardboard factory workers, Germany	169	SIR= 7.97 (2.59-8.59)
Morgan et al., 1998	Aircraft manufacturing workers, Tucson , AZ	20, 508	SMR= 1.32 (0.57 -2.60)
Ritz, 1999	Uranium processing plant workers	3,814	SMR= 0.65 (0.21-1.51)

SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio. 95% confidence intervals in parenthesis

Table 2 – Summary of Occupational Cohort Studies of TCE Exposed Workers

Authors	Study Group	Liver Cancer	NHL
Antilla et al., 1995	Finnish workers monitored for TCE and other solvents	SIR= 2.27 (0.74-5.29)	SIR= 1.81 (0.78-3.56)
Axelson et al., 1994	Swedish workers monitored for TCE	SIR= 1.41 (0.38-3.60)	SIR= 1.56 (0.51-3.64)
Blair et al., 1998	Aircraft workers, Utah airforce base	SMR= 1.7 (0.2-16.2)	SMR= 2.0(0.9-4.6)
Boice et al., 1999	Aircraft manufacturing workers, Burbank, CA	SMR= 0.54 (0.15-1.38)	SMR= 1.19(0.65-1.99)
Garabrant et al., 1988	Aircraft manufacturing workers, San Diego, CA	SMR= 0.94(0.40-1.86)	SMR= 0.65(0.21-1.52)
Henschler et al., 1995	Cardboard factory workers, Germany	NA	SMR=1.10(.03-6.12)[1]
Morgan et al., 1998	Aircraft manufacturing workers, Tucson , AZ	SMR= 0.98 (0.36-2.13)	SMR=1.01(0.51-1.81)[2]
Ritz, 1999	Uranium processing plant workers	SMR= 1.66(0.71-3.26)	SMR= 1.28(0.90-1.77)[3]

SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio. 95% confidence intervals listed in parenthesis, NA= not available

1. Results are for lymphatic and hematopoietic tissue
2. Results are for cancer of all other lymphopoietic tissue.
3. Results are for lymphopoietic cancer