DEPARTMENT OF THE AIR FORCE
AIR FORCE INSTITUTE FOR ENVIRONMENT, SAFETY AND OCCUPATIONAL HEALTH RISK ANALYSIS (AFMC)
BROOKS AIR FORCE BASE TEXAS

1 December 2000

MEMORANDUM FOR DR. MARY S. WOLFE
P.O. BOX 12233, A3-07
RESEARCH TRIANGLE PARK NC 27709
ATTENTION: EXECUTIVE SECRETARY

FROM: AFIERA/RSRE
2513 Kennedy Circle
Brooks AFB TX 78235-5123

SUBJECT: NTP Board of Scientific Counselors RoC Subcommittee Meeting, 13 - 15 Dec 00

1. In reference to the Federal Register Notice (October 17, 2000, Vol 65 Number 210: 65352-61354), the U.S. Air Force would like to submit written comments regarding the proposed change in cancer classification for trichloroethylene recommended by the National Toxicology Program (NTP) (see Attachment). In addition, the U.S. Air Force requests time to speak on this topic at the up coming NTP Board of Scientific Counselors RoC Subcommittee, to take place 13 - 15 December, 2000. The U.S. Air Force oral comments will cover and possibly expand on key issues discussed in the submitted written comments.

2. Contact information for oral comments is as follows:

Elizabeth A. Maull, Ph.D.
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2513 Kennedy Circle
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(210) 536-6126
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3. I will be your point of contact for both the written and oral comments for the U.S. Air Force. Please address any questions or concerns to me at (210) 536-6126 or e-mail elizabeth.maull@brooks.af.mil. The attached written comments have also been posted through the regular mail.

ELIZABETH A. MAULL, Ph. D.
Toxicologist

Attachment:
SAF/MIQ Memo, 29 Nov 00, w/1 atch

cc:
SAF/MIQ

DEPARTMENT OF THE AIR FORCE
WASHINGTON DC

Office Of The Assistant Secretary

29 NOV 2000

MEMORANDUM FOR DR. MARY S. WOLFE
P.O. ~~BOX 12233, A3-07~~
RESEARCH TRIANGLE PARK NC 27709
ATTENTION: EXECUTIVE SECRETARY

FROM: SAF/MIQ
1660 Air Force Pentagon
Washington DC 20030-1660

SUBJECT: Comments for the National Toxicology Program Regarding the Upgrade of Trichloroethylene

The Department of Defense would like to thank the National Toxicology Program (NTP) for the opportunity to comment on their current recommendation to reclassify trichloroethylene (TCE) to "known to be (a) human carcinogen." Trichloroethylene is a chemical that has had widespread use throughout the DoD since the early part of this century. As a result, spent TCE was disposed of in accordance with the best practices of the day, although some release of TCE was unintentional. The DoD acknowledges responsibility for such environmental releases, including the need to reduce any associated risks to reasonable levels.

Based on the following criteria for the "known to be Human Carcinogen":

"There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer."

We do not believe the requirement for causality between exposures to TCE and human cancers has been met. Our specific comments are provided in the attachment. The Department of Defense recommends that the cancer classification remain as reported in the 9th edition of the Report on Carcinogens, "reasonably anticipated to be (a) human carcinogen."

There are wide variations in epidemiological study results, likely due to the inability to separate the health effects of TCE from those associated with other solvents. In those studies with positive findings, the strength of association is modest at best. Trichloroethylene has been re-evaluated by both the International Agency for Research on Cancer (IARC, 1995) and the American Conference of Governmental Industrial Hygienists (ACGIH, 1993). Neither of these groups found that there was sufficient information data to classify TCE as a known human carcinogen. In fact, ACGIH classified TCE as A5 - not suspected as a human carcinogen based on properly conducted epidemiologic studies in humans.

To rank a chemical as a known human carcinogen is obviously a major decision with wide-reaching impact; once so ranked, it will be extremely difficult to return to a lower classification rank. Consequently, it is very important that this be a well-informed decision based on a preponderance of scientific data. Without any clear-cut evidence that TCE is *causally* associated with cancer(s) in a significant manner, the Department of Defense takes exception to the National Toxicology Program's (NTP) proposal to elevate trichloroethylene to the status of "known to be human carcinogen."

Our point of contact is Dr. Elizabeth Maull, AFIERA/RSRE, (210) 536-6126 or e-mail elizabeth.maull@brooks.af.mil.

THOMAS W. L. MCCALL, JR.
Deputy Assistant Secretary
of the Air Force
(Environment, Safety, and
Occupational Health)

Attachment:
Technical Comments

cc:
DUSD(ES)
DASA (ESOH)
DASN (E&S)

Department of Defense
Technical Comments
Nomination to Upgrade Trichloroethylene

1. The Department of Defense (DoD) takes exception to the National Toxicology Program's (NTP) proposal to elevate trichloroethylene to the status of "known to be human carcinogen." To be so classified, NTP's criteria require that "(t)here is sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between exposure to the agent, substance or mixture and human cancer." The NTP has failed to demonstrate that this criterion has been met.

2. Although NTP gives consideration to all relevant information (to include but not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, and other data relating to mechanism of action) in categorizing chemicals as either reasonably anticipated to be, or known to be, a human carcinogen, there is a requirement for the latter category to apply that a causal relationship between the exposure to the substance (TCE in this case) and cancer be established through studies in humans.

3. Hill's criteria of causation (Hill, 1965, as cited in Lavin et al., 2000) are most frequently used for determining causality. Briefly, these postulates include:

   Temporality - The exposure must precede the disease for a causal relationship to exist;

   Specificity - A causal relationship is more likely to exist if the exposure is associated with a specific disease outcome than with a multitude of possible disease outcomes;

   Strength of association - The higher the estimate of risk, the greater the likelihood that the exposure is associated with the disease outcome being studied;

   Dose-response effect - If the risk of disease increases with increasing levels of exposure, then the likelihood that the exposure is causally related to the particular disease outcome becomes greater;

   Consistency - It is more likely that a causal relationship exists if similar effects are detected in multiple studies; and

   Biological plausibility - A greater likelihood of causality exists if other evidence such as animal studies or mechanistic data supports an etiological relationship between exposure and disease outcome.

   Strength of association means measures of risk such as risk ratios (RRs) or standardized mortality ratios, represented as point estimates along with their associated confidence intervals. In general, epidemiologists look for a point estimate for a risk ratio of somewhat greater than 2 to support causality. Risk ratio point estimates less than 2 are considered to demonstrate weak associations. These point estimates represent best guesses of the actual risk. The uncertainty surrounding these estimates are reflected by the confidence intervals, which represent the range in which truth is expected to be found 95% of the time.

4. Based on the requirement that a causal association be demonstrated in humans, a review of the recent human studies was performed.

   a. NTP included four each of cohort studies (Blair et al., 1998; Morgan et al., 1998; Boice et al., 1999; and Ritz, 1999) and case control studies (Vamvakas et al., 1998; Fritschi and Siemiatycki, 1996; Dosemeci et al., 1999; and Greenland et al., 1994), and 3 reviews the human cohort studies(Weiss, 1996; McLaughlin and Blot, 1997; and Wartenberg et al., 2000) in their current TCE background document for the RoC, 10th ed not covered in the previous background paper.

   b. Within all of these studies there are methodological problems and discrepancies which do not support a causal association between exposures to TCE and cancers. Wartenberg et al. summarized these limitations most succinctly:

      1) All of the exposure information is crude and it does not isolate TCE exposures from other possible solvent exposures.

      2) Few of the traditional confounders have been assessed in any study.

      3) Limited dose response information exists, limiting the ability to make inferences.

      4) Diseases of interest are relatively rare thus limiting the sensitivity of the studies reviewed.

      5) Specifically for the Wartenberg study, the fashion in which the different studies were categorized was subjective and could influence the summary relative risks.

   c. Reviews of the Literature

The three review papers covered a total of 8 occupational cohort studies of TCE exposed workers. For the Wartenberg et al. work, we are only considering his best-characterized exposure group, the Tier I studies. Dr. Weiss, being the earliest paper, considered only 4 of the eight common papers; McLaughlin and Blot included 6 of eight studies; and Wartenberg et al., covered 7 of eight original studies. Results for these papers were reported as either Standardized Incidence Ratios or Standardized Mortality Ratios. The only obviously significant measure was that for kidney cancer in Henschler et al., 1995. Neither Weiss nor McLaughlin and Blot were in favor of including the Henschler et al. paper as it was undertaken as the result of a cancer cluster investigation. The study of Henschler et al. and the follow on studies will be discussed separately. For the reviews cited, with the exception of Wartenberg et al., the authors are in general agreement. Both Weiss and McLaughlin and Blot view the human data associating TCE with cancer in humans as weak. Weiss did acknowledge that the only plausible excesses suggested by the data were for liver, biliary tract and kidney cancers and for non-Hodgkin's lymphoma; however, a direct causal relationship was unlikely due to the relatively small relative risk and the lack of clear exposure-response patterns. McLaughlin and Blot (1997) conclude that there was "no credible evidence for an association between the risk of renal cell

cancer and TCE". The data failed to meet Hill's criteria of strength of association (in the form of relatively small relative risks) and the lack of a clear exposure-response pattern.

The last review considered by the NTP was completed in 2000 by Wartenberg et al. This study was mislabeled in the NTP TCE background document as a meta-analysis. In fact, the authors have recommended that a meta-analysis be done on the extant data. The Wartenberg et al. study is a complicated analysis where studies are ranked according to the best characterized exposure (Tier I), putative exposure (Tier II), dry cleaners and laundry workers (Tier III). Although it is likely that all of these are mixed exposures, only the Tier III is labeled as being exposed to a variety of solvents. Some of the controversial German studies have been included in the Tier I studies despite the fact that they are considered to be the outgrowth of a cancer cluster investigation. Based on the Tier I studies, Wartenberg et al. have identified 11 cancers with relative risks > 1.2 for the incidence of cancer (cervical cancer, skin cancer, liver cancer, kidney cancer, rectal cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, lymphohematopoietic cancer, larynx cancer, and prostate cancer). For four of these sites (cervix, larynx, rectum and skin), the relative risk is based on only one study. Six of these sites were included in more than one study with the null value included in the associated confidence interval (failing individually to fulfill the criteria for association). The only site with an increased average relative risk that included in multiple investigations and exceeded unity within the confidence interval, suggesting statistical significance, was for kidney cancer. If one goes further and looks at the individual studies, however, the increased average relative risk was driven by Henschler et al. study. This review fails to demonstrate consistency across studies.

d. Case Control Studies

Four additional case control studies were considered for the 10th edition of the Report on Carcinogens: Dosemeci et al. (1999), Fritschi and Siemiatycki (1996), Greenland et al. (1994) and Vamvakas et al., (1998). In general, case control studies are not considered to be as powerful as cohort studies. All of these studies have flaws in them that would limit the support they provide for classifying TCE as a "known human carcinogen." The study of Dosemeci et al. was a population-based case control study conducted in Minnesota looking at the impact of exposures to a variety of chlorinated aliphatic hydrocarbons on the risk of developing renal cell carcinoma. Although overall, exposure to TCE resulted in an increased risk for RRC, this increase was only considered significant in women, and the confidence interval included the null value. The authors indicate that there is no clear evidence to explain the gender differences and that these results could be explained by chance alone, based on the small number of cases. This study was limited by the inability evaluate the risks by level of exposure to individual solvents. In addition the authors only had limited occupational histories. Greenland et al. (1994) were restricted to looking at TCE exposed vs unexposed for their study in a Massachusetts transformer manufacturing plant. This study cannot provide any data regarding dose response. They were unable to demonstrate any statistically significant elevations in odds ratios for the cancers examined. Limitations of this study include selection bias, exposure misclassification, loss to follow up and uncontrolled confounding.

e. Occupational Cohort Studies

The NTP background document includes an additional 4 occupational cohort studies beyond those covered in the previous RoC. Of the 4 cohort studies, Blair et al. and Morgan et al. are follow-ups of previous cohort groups. These cohorts included the following numbers of workers (TCE exposed and total workers): 7,204 and 14,457 (Blair et al., 1998), 2,267 and 77,965 (Boice et al., 1999), 4,733 and 20,508 (Morgan et al., 1998), and 3,814 and 3,814 (Ritz, 1999).

For the Blair et al. paper, all of the confidence intervals surrounding the point estimates, with the exception of asthma, include the null value, suggesting non-significance for TCE exposures as a possible interpretation. In addition, the RRs among workers exposed to other chemicals, but not TCE, often had RRs as large as workers exposed to TCE. In Blair et al., the authors state that their data fail to support Hill's Criteria because there is insufficient evidence for strength of association, dose-response, or consistency.

Morgan et al. (1998) have similar conclusions; their data offer little support for any association between TCE exposure and cancer mortality from leukemia, cancer of the hematopoietic tissues, or digestive, liver and respiratory cancers. Although they did find a slight excess of cancers of the kidney, bladder, prostate, and ovarian cancer, the results were not significant and thus causality was not supported. In addition, small numbers, lack of information on confounding factors such as smoking, and lack of quantitative exposure information limit the findings of Morgan et al.

Boice et al. (1999) examined several chemical exposures (TCE, perchloroethylene, asbestos, and chromate) commonly found in aerospace manufacturing processes. As with the above-mentioned studies, they found little evidence that exposures to TCE in aerospace industry resulted in measurable increases in any cancer. In fact, Boice et al. was unable to confirm the non-significant increases observed in either Blaire et al. or Morgan et al. This does not demonstrate consistency in findings between studies, an important criterion for causality.

The analysis of Ritz (1999) shows the strongest association between biliary and liver cancer and TCE exposures (RR = 12, CI = 1.03 to 144). However, this is based on the incidence of one cancer. It is also important to note the extremely wide confidence intervals. In this study, because of the paucity of tumors, some cancers needed to be grouped. Therefore it is impossible to tease out the liver cancers from biliary cancers. There were trends for an increase in other cancers associated with TCE, but kidney cancer was not one of the increased cancers. This cohort as a whole had non-significant increases in mortality for cancers of the esophagus, stomach, liver, pancreas, prostate, brain, and lymphopoietic cancer and Hodgkin's disease. This study is at odds with the other 3 additional cohort studies considered since the RoC, 9th edition. However, this is a difficult study to interpret. No where is there a clear explanation of the comparison group. It is also unclear as to how many individuals were exposed to TCE alone, although there are comments to the effect that most of the TCE exposed individuals were exposure to other solvents.

One final concern with all of these studies is that although exposure reconstruction is attempted, there are no quantitative measurements for exposure. In all likelihood, TCE exposure did not occur by itself. Several studies suggest that exposures to additional solvents results in increased cancer incidences similar to TCE or that the non-chemically exposed had similar risk ratios as the TCE exposed (for example see Boice et al., Table 8 and Blair et al., Table 3, kidney cancers). The collective trend demonstrated in all of these cohorts is that TCE exposure is not unequivocally causally associated with increased risk of cancers.

f. Additional Studies

Wartenberg et al. suggests evidence supporting a hypothesis of an association between TCE exposure and cancer is as strong or stronger for the kidney as for any other site. There is some concern, however, that most of the data supporting this hypothesis has been generated by a select group of scientists in Germany and has not been replicated elsewhere. It is not our intention to find fault with either these scientists or their work. There is abundant discussion in the literature addressing the controversial nature of these studies, beginning with the criticisms of the original study (Henschler et al., 1995). These German studies have been considered to be flawed. However, they may be useful in estimating the TCE exposure levels that may possibly be associated with renal cell carcinoma. Vamvakas et al. (1998), Henschler et al. (1995), Bruning et al. (1997) and Brauch et al. (1999) all suggest that although no quantitative exposure data exists for their cohorts, it is likely that these individuals were exposed to extremely high levels of TCE in the workplace based on recollections of pre-narcotic effects.

The exact role of TCE exposures in the development of renal cell carcinomas (RCC) has yet to be conclusively demonstrated. Bruning et al. (1997) and Brauch et al. (1999) provide a hypothesis that exposures to high concentrations of TCE for prolonged periods of time result in mutations within the von Hippel-Lindau tumor suppressor gene. Bruning et al. suggest that exon 2 of the gene is a "hot spot" for TCE induced mutations. This is supported by Brauch et al. who suggests that nucleotide 454 of the VHL gene is a specific target for these mutations. However, there are some inconsistencies between these two studies. In Bruning et al., 100% of the TCE exposed RCC patients were observed to have mutations in the VHL gene; 44% of those mutations occurred in exon 2. In the second paper, 75% of the TCE exposed had mutations in the VHL gene, but in this case 52% of the mutations were in exon 1. A third paper (Schraml et al., 1999) examined RCC from the Berlin area and found no differences between the population of non-TCE exposed and the TCE exposed in terms of histological tumor type or in the percentage of VHL mutations. Schraml's study group was small and it is hard to draw firm conclusions from it. The authors also suggest that the patients in their study may have been exposed to lower doses of TCE than in the Brauch et al. and Bruning et al. papers. The results of the three groups indicate that more research is required before definitive conclusions can be drawn regarding VHL mutations and TCE exposures.

5. It is possible, under the conditions cited by the numerous German investigators, that a "maximum tolerated dose" was achieved in some of these workplaces during the time of their investigations. Under these high exposure conditions, the oxidative pathways for TCE metabolism were saturated and more TCE was metabolized through the GSH-conjugative pathway leading to renal damage. Other evidence, both animal and human, suggests that the necessary precursor event for the induction of cancer is nephrotoxicity, resulting in repair and proliferation mechanisms. This is likely to be a non-linear process for the induction of cancer, again suggesting that at lower exposure levels (consistent with contemporary regulations and engineering controls) TCE exposures would not result in kidney cancers. It is important to note that these investigators did not report increased liver cancer even at these high dose exposures.

6. Given that one of the classifications provided by the NTP is reasonably anticipated to be (a) human carcinogen, it would be prudent to use the "known" category for those toxicants that have consistently been demonstrated to support a significant risk of cancer in humans in well-designed studies. From the perspective of the DoD, it is the responsibility of the regulatory promulgate standards that protect the public from significant risk. Although the NTP is not regulatory in nature, classification changes will have repercussions in the regulatory arena. We are concerned that these recent studies have not demonstrated obvious and significant increases in cancer due to exposures to TCE to warrant a change in classification. Our concern relates not only to the fact that the only significant work effort supporting an increase in renal cell carcinoma has been generated in a single geographic location and may actually be describing something other than TCE-induced cancers, but we are also concerned that the cohorts being studied have been exposed to high levels of TCE that are by law prohibited in our work places. It is important that agencies to start to consider, as NTP suggests in its introductory material, dose response effects. If the German renal cell carcinomas were induced by exposures to TCE, it is more than likely because the oxidative metabolic pathway had been saturated due to high exposures. It is unlikely that such high exposures would be replicated in the workplace today based on the implementation of engineering controls. Other evidence, both animal and human, suggests that the necessary precursor event for the induction of cancer is nephrotoxicity, resulting in repair and proliferation mechanisms. These are likely to be non-linear processes for the induction of cancer, again suggesting that at lower exposure levels (consistent with contemporary regulations and engineering controls) TCE exposures would not result in kidney cancers.

In general, the human studies considered since the publication of the 9th edition of the Report on Carcinogens fail to meet the criteria used by the National Toxicology Program, that is, they fail to demonstrate causality in human studies. As the studies do not support causality, the Department of Defense recommends that the cancer classification remain as reported in the 9th edition of the Report on Carcinogens: reasonably anticipated to be (a) human carcinogen.