HALOGENATED SOLVENTS INDUSTRY ALLIANCE, INC.
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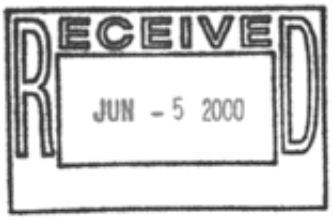

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
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Re: Comment on Additional Substances Proposed for Listing in the Report on Carcinogens, Tenth Edition

Dear Dr. Jameson:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents the producers and users of chlorinated solvents, including trichloroethylene. Trichloroethylene is one of eleven substances nominated for review by the National Toxicology Program (NTP) in 2000. 65 Fed. Reg. 17889 (April 5, 2000). Trichloroethylene has just been listed as a substance reasonably anticipated to be a human carcinogen in the Ninth Report; NTP now proposes to change that listing to a known human carcinogen in the Tenth Report. *Id.* For the reasons discussed below, HSIA objects to the proposed listing and urges NTP to eliminate trichloroethylene from consideration for "upgrading" in the Tenth Report.

This comment addresses the following points. First, it demonstrates that NTP has not provided sufficient notice to allow for informed public comment on the proposed upgrading of trichloroethylene by the comment deadline of June 5, 2000. Second, this comment discusses the criteria adopted by NTP for listing a substance as a known human carcinogen. Third, it reviews the available human evidence on trichloroethylene, and demonstrates how this evidence cannot possibly support listing as a known human carcinogen under the NTP criteria. For these reasons, HSIA urges NTP to drop trichloroethylene from consideration for listing as a known human carcinogen at this time.

A. NTP Has Provided Inadequate Notice to Allow Informed Public Comment

The Administrative Procedure Act (APA) provides courts the authority to set aside "agency action" that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). *Synthetic Organic Chemical Manufacturers Association v. Secretary, Department of Health and Human Services*, 720 F. Supp. 1244, 1249 (W.D. La. 1989) ("SOCMA"), makes clear that the process of publishing the Report on

Carcinogens constitutes "agency action" and "fits squarely within the type of decision that Congress intended to be reviewable under the APA." It is fundamental that, to meet the standards of the APA, agency action must be rationally based on reasoned analysis and informed conclusions. Here, NTP has indicated that trichloroethylene was "[r]ecommended by RG1 to be upgraded to a known human carcinogen based on recent published data that indicate an excess of kidney cancers in workers exposed to trichloroethylene." 65 Fed. Reg. at 17891. HSIA sought from you, as the NTP contact person, the background information supporting this nomination. HSIA was informed that the background document will not be available until approximately October 2000.

Upgrading of trichloroethylene to a known human carcinogen qualifies as a rulemaking proceeding under the APA. Under the APA, a rule is a statement "designed to implement, interpret, or prescribe law or policy . . . ." 5 U.S.C. § 551(4). Because publication of the Report on Carcinogens implements the provisions of the Public Health Service Act and triggers a series of regulatory actions, the *SOCMA* court held that publication of the Fifth Report constituted rulemaking under the APA. *SOCMA*, 720 F. Supp. at 1248-49. Similarly, the process leading to the publication of the Tenth Report constitutes a rulemaking proceeding.

The published proposal to upgrade trichloroethylene is an invalid rulemaking because the public failed to receive a sufficient opportunity to notice and comment as required by the APA. 5 U.S.C. § 553. When the basis of a rule is a scientific determination, the scientific data which support the rule must be made available to the public during the notice period. *United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240, 252 (2d Cir. 1977); *see also Connecticut Light and Power Co. v. NRC*, 673 F.2d 525, 530-31 (D.C. Cir.), *cert. denied*, 459 U.S. 835 (1982) (stating that "an agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary"). Because NTP has not provided the background information to support its decision to upgrade trichloroethylene, the public has been deprived of the opportunity to test the agency's reasoning and provide informed comment. Unless NTP can provide more than one sentence to support the proposed listing, going forward with this process for trichloroethylene would be arbitrary, capricious, and an abuse of the agency's discretion.

B. Criteria for Listing As a Known Human Carcinogen

The notice states the following:

> The criteria used in the review process are as follows:
>
> Known To Be Human Carcinogens
>
> 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.
> 65 Fed. Reg. at 17889.

Several points become clear after a careful review of the foregoing language. The term "studies in humans" plainly excludes reliance on evidence from studies in animals. It also plainly excludes reliance on data from *in vitro* experiments, such as exposure of cell cultures or tissue samples to a substance while in laboratory containers. "Studies in humans" are studies of health effects in whole humans exposed while living; the term cannot include studies "in animals" or "in glass." The plain wording of the criteria, and NTP's consistent practice, show a clear distinction between evidence from studies in humans as distinct from evidence from studies in animals or *in vitro*.

The criterion quoted above also requires evidence from human studies that are "sufficient" to indicate a "causal relationship." The requirement that human evidence be "sufficient" to indicate a "causal relationship" is in clear contrast to the weaker requirement of the "reasonably anticipated" category that the human evidence can be "limited" and that a "causal relationship is credible, but that alternative explanations, such as chance, bias or confounding factors could not adequately be excluded." The terms "sufficient" and "limited" have been consistently used to make this distinction both by NTP and by the International Agency for Research in Cancer (IARC) for at least the past 15 years. The terminology and concept of "causal relationship" are central to the science of epidemiology, and are recognized and understood by other scientists and laymen who are familiar with epidemiology. The term "causal relationship" is used in contrast to the term "association."

Two notices published in 1999 as "clarifications" to the criteria attempt to introduce confusion into the otherwise straightforward interpretation set forth above. These were apparently published in an effort by NTP to create a justification for its decision to classify dioxin as a known human carcinogen after this decision was challenged in court. The notice published on April 19, 1999 attempts to rewrite the criteria so that the final paragraph, which appears under the heading "2. Reasonably Anticipated to be Human Carcinogens," applies both to that classification and to the known human carcinogen classification. (64 Fed. Reg. 19188, 19189). The validity of this rather shameless, though creative, attempt to rewrite the criteria will be determined by the courts. In any event, the notice published on April 2, 1999 (64 Fed. Reg. 15983) expressly confirms that "[t]he known human carcinogen category *requires* evidence from studies of humans . . . ."

In listing trichloroethylene in the Ninth Report as a substance "reasonably anticipated to be a human carcinogen," NTP necessarily determined that there was "less than sufficient evidence of carcinogenicity in humans." The Ninth Report was only published last month. Without having sight of the background document for the Tenth Report, it is impossible to know how NTP could support a change in the classification even though the most recent epidemiology studies consistently show that workers exposed to trichloroethylene do not have any increased risk of cancer. These studies are discussed more fully below.

C. The Human Evidence Does Not Support Listing of Trichloroethylene As a Known Human Carcinogen

The analysis above clearly shows that a listing as "known human carcinogen" requires evidence from studies of humans, although it is recognized that mechanistic information may assist the interpretation of epidemiology studies. A critical evaluation of the information from currently available epidemiology studies does not support classification of trichloroethylene as a "known human carcinogen", and even brings into question the NTP listing as "reasonably anticipated to be a human carcinogen".

1. Derivations of Current IARC and NTP Classifications

In NTP's recently published Ninth Report on Carcinogens, the epidemiological evidence used to support listing trichloroethylene as "reasonably anticipated...." is drawn from the IARC analysis of 1995 with the addition of a cohort study (Henschler et al 1995a). It should be noted that the IARC Epidemiology Working Group did not consider the Henschler et al (1995a) study to be suitable for classification purposes; the characteristics of this study are discussed below. The IARC review relied, primarily, on evidence from three cohort studies (Axelson et al 1994, Anttila et al 1995, Spirtas et al 1991) with limited reference to a study by Garabrant et al (1988) in which it was not possible to identify the specific sub-cohort exposed to trichloroethylene. Several small case control studies contributed little to the analysis. The IARC group was unable to use information from a large cohort study based on workers at the Hughes Aircraft Company factory, Arizona, because the results had not been published in the open literature. Across the three primary studies, small, non-statistically significant elevations in the incidence of biliary and liver cancer (combined) and non-Hodgkin's lymphoma were considered to meet, by a narrow margin, the IARC criterion of "limited evidence in humans" based on the restrictive definition used by IARC i.e. "a positive association has been observed between exposure....and cancer for which a causal relationship is....credible, but chance bias or confounding could not be ruled out with reasonable confidence". The next lower category would have been "inadequate evidence". The shortcomings of the inflexible and narrow approach to the application of epidemiological information in the IARC classification process have been analyzed by Weiss (1996). The combination of this marginal epidemiological classification of "limited", in combination with the IARC toxicology group's "sufficient" categorization of carcinogenicity in animals, automatically leads to the IARC category Group 2A (probable human carcinogen).

There are many similarities between the IARC process of classification and that employed by NTP. The evidence presented in NTP's Ninth Report in support of listing trichloroethylene as "reasonably anticipated to be a human carcinogen" makes extensive reference to the IARC analysis of epidemiological information, and the only significant difference is the unqualified presentation by NTP of data from Henschler et al (1995a). As in the IARC review, NTP finds that there is "limited evidence of carcinogenicity in humans".

In the absence of a draft Background Document in support of the recommendation to list trichloroethylene, we are forced to speculate about the new evidence from human studies that is considered strong enough to raise the recent categorization of "limited evidence" to a level supporting a classification of "known". A review of the most relevant recent evidence follows, and comment on the Henschler et al (1995a) study is included because NTP, in contrast to the IARC Working Group, has chosen to use it as evidence.

2. Recent Epidemiology Studies

i) Henschler et al (1995a).

The authors characterize this study of workers at a cardboard factory in Germany as a "retrospective cohort study" in which the incidence of kidney cancer in trichloroethylene exposed workers was compared with that in unexposed workers and with cancer registry information from other countries (Denmark and GDR – the plant was in the FDR). This is a small study; there were 169 workers in job areas regarded as involving exposure to trichloroethylene: locksmith's area, electrician's area and board machine area. The control group consisted of 190 workers presumed not to have had exposure to trichloroethylene. There were 5 cases (0.628 expected based on the Danish cancer registry) of kidney cancer in the exposed versus none in the non-exposed (0.648 expected). This result appears to be spectacular at first sight. However, certain modifiers apply: One of the 5 cases was a urothelial cell cancer of the renal pelvis, and this is histopathologically distinct (more akin to bladder cancer) from the renal cell cancer that the Henschler group considers mechanistically linked with trichloroethylene. Although the registry combined the two types of cancer, there is no reason to do so in this study. Of the remaining 4 subjects, one was exposed to trichloroethylene for three years only in an area (electrician's) where levels would be expected to be lower – although potentially still possible, it is unlikely that this case can be associated with trichloroethylene. Taking the cohort as a whole, the expected incidence is slightly above one – and this expected case could appear with almost equal probability in the exposed or the unexposed group. Thus the excess incidence may be only two cases. Another factor that plays into the number of cases detected is that abdominal sonography was employed to find tumors and this is clearly not the basis for incidence in cancer registries.

Much has been made of the "very high levels of exposure" in the cardboard factory. In particular workers in the board machine area have been said to be severely exposed based on the reporting of pre-narcotic symptoms. However, the procedures used to clean the machines were employed periodically, not daily. Exposures to high levels probably occurred for 8 to 10 hours per month making the average exposure similar to those of many in the Blair et al (1998) and Morgan et al (1998) cohorts discussed below. The exposures in the locksmith's and electrician's areas are likely to have been comparable to those in the two US cohort studies. Despite the assumption that the very high levels in the board machine area played a part in the incidence in this factory, only one of the four renal cell carcinomas was in a worker from this area.

The Henschler et al (1995a) study has been strongly criticized (Bloemen and Tomenson 1995, Swaen 1995) and Henschler et al (1995b) have responded. Most significantly, it is the Henschler group's own response (Henschler et al 1995b) that most effectively rules this study out of consideration for the NTP classification process. Henschler et al acknowledge (and in Vamvakas et al 1998) that this study is of a pre-recognized cluster of cases. In their response, the claim is made that clusters are "useful", and sometimes they are. However, it is an immutable rule in the science of epidemiology that an incidence having the status of a cluster of this type can only be used in "hypothesis setting" and nothing more. This was the reason that the Henschler et al (1995a) study was not given any weight in the deliberations of the IARC Working Group, and it is the reason that NTP reviewers should not use this study as contributing to the weight of evidence in any way.

ii) Vamvakas et al (1998)

This is a case control study conducted by members of the same German group responsible for the Henschler et al (1995a) study and, at first sight, might be taken to be capable of addressing the hypothesis raised by the cluster study. However, significant methodological concerns are apparent. The selection of control subjects in case control studies is critical. In this study, the criteria for selection are not fully described but it is possible to recognize that, not only were the controls from different hospitals and drawn from different time periods but appear to have very different "life experience". The last problem arises largely because of a distinct age difference between the cases and the controls. Another concern in the design and conduct of case control studies is the manner in which information is obtained at interview and it unfortunate that further criticism can be leveled at this study: the nature of the interviews, although conducted by a single individual were different since a number of the cases were deceased and all of the controls were alive. Also, the interviewer was fully aware of whether interviewees represented cases or controls. There are concerns regarding the exposure assessments employed in the study since additional information collected was for cases rather than controls. Many of the methodological concerns regarding this study have been presented by Green and Lash (1999) which stimulated a recent response from Vamvakas et al (2000). Although the differences in findings between this study and others (an odds ratio of 10.8 versus no or marginal elevations) is claimed to be the result of very high exposures, the nature of exposures in the cohort studies of Blair et al (1998) and Morgan et al (1998) are likely to be comparable.

It should be noted that the authors conclude that an "association" has been demonstrated, not a causal relationship. Clearly, the apparent findings reported in this study require careful review such that they can be given an appropriate weighting in any classification process – they cannot be taken as definitive evidence that trichloroethylene causes kidney cancer.

iii) Blair et al (1998)

This study is an extension of the Spirtas et al (1991) investigation of workers engaged in aircraft maintenance at Hill Airforce Base, Utah that was used by IARC. The total cohort now includes 5,727 deaths and of these subjects, 2,813 were judged to have been exposed to

trichloroethylene. No epidemiology study is perfect. However, this investigation, as in the case of the recent cohort studies of employees in the aerospace industry, has been honestly performed and reported by a team of experienced epidemiologists, from NCI in this case. As in the earlier phase of the investigation, small increases in relative risk were found for liver cancer, non-Hodgkins lymphoma, and kidney cancer plus several other tumor types in comparison with workers at the base not exposed to chemicals. However, the relative risks were inversely related to cumulative exposure to trichloroethylene. Thus the authors conclude that "These findings do not strongly support a causal link with trichloroethylene because the associations were not significant, not clearly dose related, and inconsistent between men and women".

iv) Morgan et al (1998)

This is the updated study of the Hughes Aircraft Company cohort and is now reported in a peer reviewed publication. Exposures to trichloroethylene were primarily the result of vapor degreasing operations. The full cohort includes 4,052 deaths and 917 of these subjects were considered to have been exposed to trichloroethylene. The study found no evidence of an association between trichloroethylene and liver cancer or non-Hodgkins lymphoma when compared with rates in the US population. A very slight increase in kidney cancer (8 observed vs. 6.1 expected, SMR 1.32) showed a deficit in the low exposure group and somewhat higher, non-significant, SMR in the high exposure group. However, the number of kidney cancer cases was too small to allow conclusions regarding any dose relationships, and the Cox Proportional Hazards Model used to differentiate exposures and to adjust for the healthy worker effect is unsuitable for use with such low incidences.

v) Boice et al (1999)

This extremely large cohort study explored cause of death among employees of the Lockheed Martin aircraft manufacturing facilities in California. The study included 20,236 deaths overall and, of these subjects, 1,110 were considered to have been exposed to trichloroethylene. The levels of exposure were considered by the authors to be generally lower than those in the Blair et al (1998) and Morgan et al (1998) investigations. The study showed no association between trichloroethylene exposure and liver or kidney cancer and the incidence of non-Hodgkin's lymphoma was close to the expected value (14 observed, 11.9 expected). Although the SMR for non-Hodgkin's lymphoma increased slightly with cumulative exposure to trichloroethylene, this was not statistically significant and the authors put this into context with other studies suggesting that trichloroethylene was not responsible for the marginal increase. As the most recent cohort study, the discussion in this paper reviews the evidence from the previous cohort studies in relation to its own findings and concluded "...our investigation provides little evidence that exposure to trichloroethylene in the aerospace industry has resulted in a measurable increase of any cancer".

2. Additional Information

Since kidney cancer has been the focus of epidemiological and mechanistic studies, a brief review of recent developments appears to be of value.

i) Mutation of the von Hippel-Lindau Gene

Reference is made in the NTP Ninth Report to the paper by Bruning et al (1997) that relates to somatic mutations in the von Hippel-Lindau (VHL) tumor suppressor gene in relation to renal cell cancers possibly associated with trichloroethylene exposure. The publication from the same group (Brauch et al 1999) provides updated information in this area. The later publication reports that 33 of 44 renal cell cancers in subjects believed to have been exposed to trichloroethylene showed mutations of the VHL gene and these were frequently multiple and accompanied by loss of heterozygosity. A mutational "hot spot" was detected in 13 (39%) of the patients. These unusual findings were of concern to HSIA and the opinions of independent experts were sought. The experts confirmed the potential significance of the findings but expressed reservations. The finding of multiple mutations in a single gene was surprising to the experts because multiple mutations are unlikely to confer selective advantage to the transformed cells. Thus the initial mutational frequency would have to be "astronomically high" to allow multiple mutations in a single gene to occur and this is unlikely at non-lethal dose levels. This is the first study to report a mutational "hot spot" in VHL gene mutation studies. Because of the potential significance (and possible methodological concerns) the experts consider that it is essential that the effect be confirmed by other workers in other regions. Overlying the gene mutation analyses are substantial concerns regarding the selection of patients and the assessment of trichloroethylene exposures.

It is worth noting that an initial report (Schraml et al 2000) of renal cell cancers in 12 subjects exposed to trichloroethylene did not confirm the findings of Brauch et al (1999). No evidence of differences in phenotype, genotype or mutation pattern was found by Schraml and his co-workers (including T. Bruning – a co-author of the Brauch paper). Also, Brauch herself has a very recent publication reporting that the renal cell cancers in subjects not exposed to trichloroethylene may display complex patterns of mutations of the VHL gene including a hot spot (Brauch et al 2000). These most recent findings of Brauch et al (2000) relate to the stage of the development of the tumor and this adds a dimension that was not taken into account in the earlier paper. It is clear that we are a long way from, unambiguously, associating exposure to trichloroethylene with specific mutational events in the VHL gene.

ii) Biochemical Mechanisms in Relation to Kidney Tumors

Although a classification of "known human carcinogen" by NTP is dependent upon human *in vivo* evidence, it is likely that some reference may be made to the underlying mechanisms that might contribute to the development of kidney tumors. It has appeared extremely straightforward as an explanation: a minor metabolic pathway in the rat leads to a

trichloroethylene-glutathione conjugate that is cleaved to release (1,2-dichlorovinyl)-L-cysteine (DCVC). The hypothesis is that DCVC is activated in the kidney by β-lyase to release reactive (and genotoxic) thioketene products. The hypothesis has this mechanism responsible for both kidney damage and the low incidence of kidney tumors seen in rats in long term studies of the effects of trichloroethylene. The metabolic pathway exists in man and hence appears to support the opinions of the Henschler group (e.g. Vamvakas et al 1998) on trichloroethylene and kidney cancer. However, as expressed in the detailed and balanced review by Dekant and Henschler (1999) and in direct language by Green et al (1998), the DCVC story may not explain the observations in rat long term studies. Briefly: the mouse should be more susceptible to trichloroethylene induced kidney tumors than the rat – it is not. The levels of DCVC generated from trichloroethylene are three orders of magnitude below an acute no effect level. Moreover, this low level of DCVC does not explain the incidence of tumors when direct administration of DCVC at several orders of magnitude higher levels did not induce kidney tumors in the rat. Recently, Green and co-workers (Green et al 1998, Dow and Green 2000) have begun exploring an alternative hypothesis. It has been found that trichloroethylene administered at the levels employed in long-term studies causes, in the rat, excretion of nephrotoxic levels of formic acid. In experiments designed to remove the DCVC component, formic-acid induced kidney damage was as severe as that observed in long term studies. Prolonged kidney damage has been considered a probable major contribution to the induction of rat kidney tumors by trichloroethylene. Preliminary evidence shows that man does not excrete elevated levels of formic acid when exposed to trichloroethylene.

It is clear that the mechanism of action of trichloroethylene underlying the induction of the low incidence of rat kidney tumors, and its relevance to man, have yet to be defined.

3. Conclusions

- It is extremely difficult to comment on a scientific case supporting a recommendation when the details of that case are not available. There must be some basis already for the RG1 recommendation to upgrade the classification of trichloroethylene, and this should be made available for public review.
- Human *in vivo* data is required for a determination of "known human carcinogen"
- The mechanism of action of trichloroethylene in the induction of rat kidney tumors, and its relevance to man, remain an open investigation.
- The results of the Henschler et al (1995) study are unsuitable for use in the NTP classification process because it is limited to "hypothesis setting".
- The case control study Vamvakas et al (1998) has serious methodological shortcomings and its radically different results from well conducted US cohort studies cannot be explained by differences in levels of exposure. Until the findings are confirmed in an independent investigation, this study must carry less weight than the cohort studies.
- Much remains to be learnt about mutations and the von Hippel-Lindau gene.

- The most relevant data for NTP classification purposes are the results of the most recent, well-conducted, large scale epidemiology studies. These results do not support a conclusion of "known human carcinogen" for trichloroethylene.

Respectfully submitted on behalf of the Halogenated Solvents Industry Alliance, Inc by

[redacted]

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Director of Scientific Programs

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