

Comments on the *Draft Report on Carcinogens Background  
Document for Trichloroethylene*

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## 1. Introduction

In this commentary, we analyze the conclusions of the *Draft Report on Carcinogens Background Document for Trichloroethylene*.<sup>1</sup> We focus on the conclusions based on epidemiologic evidence. In so doing, we find that the *Draft Report* is seriously flawed. Neither the methods employed nor the results presented in this *Draft Report* constitute a reliable analysis or a basis for causal inference. In the proper light, it becomes clear that the proposal to reclassify ("upgrade") trichloroethylene (TCE) as a chemical "known to be a human carcinogen" should be rejected. This is because the actual epidemiologic results on TCE, with respect to its possible carcinogenicity, are most consistent with the null hypothesis – that is, with the hypothesis that TCE is not a cause of human cancer. For each type of cancer evaluated, suggestive results are weak, extremely unstable and inconsistent with the weight of the epidemiologic evidence, or better explained by alternative hypotheses.

In the early and mid-1990's, the accumulated epidemiologic data on TCE were judged as insufficient (ACGIH, 1993)<sup>a</sup> or "limited" (IARC, 1995).<sup>2, b</sup> Additional epidemiologic data on TCE have been generated since, so that a re-analysis is timely. As shown below, no coherent analysis of these data would suggest "sufficient" evidence for TCE of human carcinogenicity. Although the *Draft Report* does conclude that the evidence is sufficient, it does so through a selective, incomplete, insufficiently detailed, and insufficiently critical analysis. Such an analysis cannot be relied upon for scientific decision making. Moreover, recent thorough reviews of the epidemiologic evidence on TCE and cancer come to different conclusions from those given in the *Draft Report*.<sup>3-5</sup>

## 2. Method of our analysis

We have organized our comments to follow the summary conclusion of the "Human Cancer Section" of the *Draft Report* (its Chapter 3). That conclusion is:

The number and sophistication of studies assessing the possible carcinogenicity of TCE is impressive. Although the studies are not perfectly consistent, strong patterns emerge. In particular,

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<sup>a</sup> The American Conference of Governmental Industrial Hygienists classified TCE in its "Group A5, Not Suspected as a Human Carcinogen," finding that TCE "has been demonstrated by well controlled epidemiological studies not to be associated with any increased risk of cancer in exposed humans."

<sup>b</sup> The International Agency for Research on Cancer found "limited evidence in humans for the carcinogenicity of trichloroethylene," writing, "Overall, the most important observations are the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for non-Hodgkin lymphoma in all three of the most informative cohort studies." As discussed here, follow-up studies and new epidemiologic results available since February 1995 (when the IARC Working Group met) alter these observations. Further, even at the time (February 1995), about half of the members of the Working Group felt that the epidemiologic evidence on TCE was "inadequate," not even "limited" (Parker, U.S. EPA, 1995, personal communication with LCG).

associations with TCE exposure generally were observed for kidney cancer, liver cancer, non-Hodgkin lymphoma, multiple myeloma, and prostate cancer. Particular aspects of design or implementation may limit the usefulness or interpretation of individual studies, but, by and large, these studies were well designed and executed. Viewed from the perspective of Hill's aspects of causation (Hill, 1965), several of the criteria are fulfilled.

This summary from the *Draft Report* organizes the task before us. For each of the types of cancer listed in this summary as having associations with TCE, we begin by summarizing the IARC review<sup>2</sup> of the human evidence for that cancer type (in part because the IARC review seems to have been a basis of the *Draft Report*). Second, we examine evidence that has been published since the IARC review,<sup>2</sup> to see whether the new evidence ought to modify the conclusion reached by IARC.<sup>2</sup> Third, we examine the pattern of evidence, which *The Draft Report* characterizes as “strong,” presumably with the meaning that the pattern strongly suggests a causal relation. Finally, we interpret the evidence for each cancer type, considering the evidence that had been gathered at the time of the IARC review, the new evidence, and the total pattern of results. Examining the primary epidemiologic studies, we arrive at a very different conclusion than the *Draft Report*. For each cancer type, we find that the overall pattern does not strongly support the causal hypothesis, and sometimes strongly supports the null hypothesis. The evidence clearly fails to establish TCE as a cause of human cancer.

Moreover, we have found that the *Draft Report* obscures — rather than fairly weighs — the epidemiologic evidence as a whole. The two tables (tables 3-1 and 3-2 on pages 31-35 of the *Draft Report*) in which the epidemiologic studies are summarized present only those relative measures of effect that exceed 1.2, and none of the similar measures that are less than 1.2, including ratios that are smaller than 1.0. Clearly a tabulation of only positive results cannot serve as a fair representation of all of the results. Readers of the *Draft Report* who may be unfamiliar with the primary epidemiologic literature on TCE would be seriously misled by its selective treatment in this Report.<sup>a</sup>

The *Draft Report* argues that strong patterns of evidence emerge to support the causal hypothesis for TCE and the types of cancer it lists. This conclusion is said to be based on summary results from literature syntheses. Are such patterns in fact apparent in the epidemiologic data? Let us look. In particular, for each of the cancer types at issue, let us plot the accumulated results graphically. For each cancer type, we have sorted the published epidemiologic results (SMRs, RRs, and/or ORs) in ascending order. We then plot the results and their 95% confidence intervals, with distinct symbols representing

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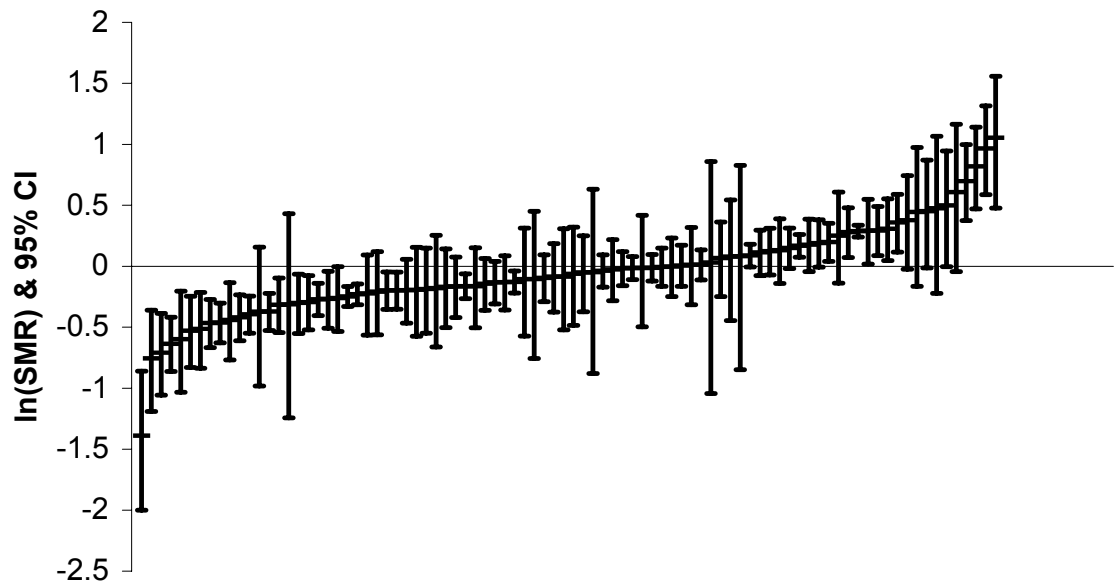
<sup>a</sup> In this regard, it is odd and unfortunate that the authors of this *Draft Report* are anonymous. The title page notes only that the document was prepared by Technology Planning and Management Corporation, an organization that does not, judging from its website, do epidemiologic or toxicologic work or analysis, but instead seems to specialize in “Information Technology Consulting,” “Software Engineering,” “Web Application/eBusiness Solutions,” and other, non-biological fields of endeavor. Perhaps the omissions and misinterpretations in *The Draft Report* merely reflect the scientific inexperience of the anonymous authors.

cohort and case-control studies. These plots describe the patterns of evidence associating TCE exposure with the particular cancer type. If the pattern of evidence suggests a null association, the following characteristics of the plot are expected:

- The pattern of results from cohort studies should be approximately equally distributed below and above the null. Retrospective occupational cohort studies often examine a wide range of diseases. They are expensive and time consuming undertakings, so usually are published once completed regardless of the result being null, causal, or protective.
- If case-control studies of the association have been conducted, they may concentrate above the null. Case-control studies often examine a number of exposures associated with a single disease. The exposures that prove to be positively associated with the disease tend to be those published or emphasized in publications. Null associations are not so often published or emphasized in publications. Thus, for a truly null association, studies that spuriously suggest a causal direction are more likely to be published than studies that spuriously suggest a protective direction, because the causal association has a stronger prior expectation. For cancer types that have been studied by case-control design, we would therefore expect that the case-control studies would concentrate in the section of the plot above the null, and that this effect would shift the entire distribution towards a positive effect.
- The intervals about estimates of effect that show a strongly protective or strongly causal association will be wider than estimates of effect that suggest a null association. Thus, the widest intervals will be on the left side and right side of the plot, while narrower intervals will surround the estimates of effect near the null at the center of the plot. This pattern is expected because estimates of effect based on small numbers are more likely to deviate from the truth and will have wider intervals. Methods have been suggested to correct for this phenomenon<sup>6</sup> and have been applied in other settings,<sup>7</sup> but have not been applied here because the pattern is an important clue to discern a true null effect.

The following plot provides an example of the pattern expected for a null distribution of cohort studies. The data derive from a published series of SMRs associating lung cancer risk with various occupations thought *not* to cause lung cancer.<sup>8</sup> The SMRs and their intervals are plotted (here and throughout) on the log-scale so that the distribution is symmetrical about the null, which equals 0 on the log scale. Note that the SMRs in this distribution ranged from 0.25 to 2.87, suggesting that the range of observed SMRs for null associations can deviate substantially from a narrow range around 1.0.

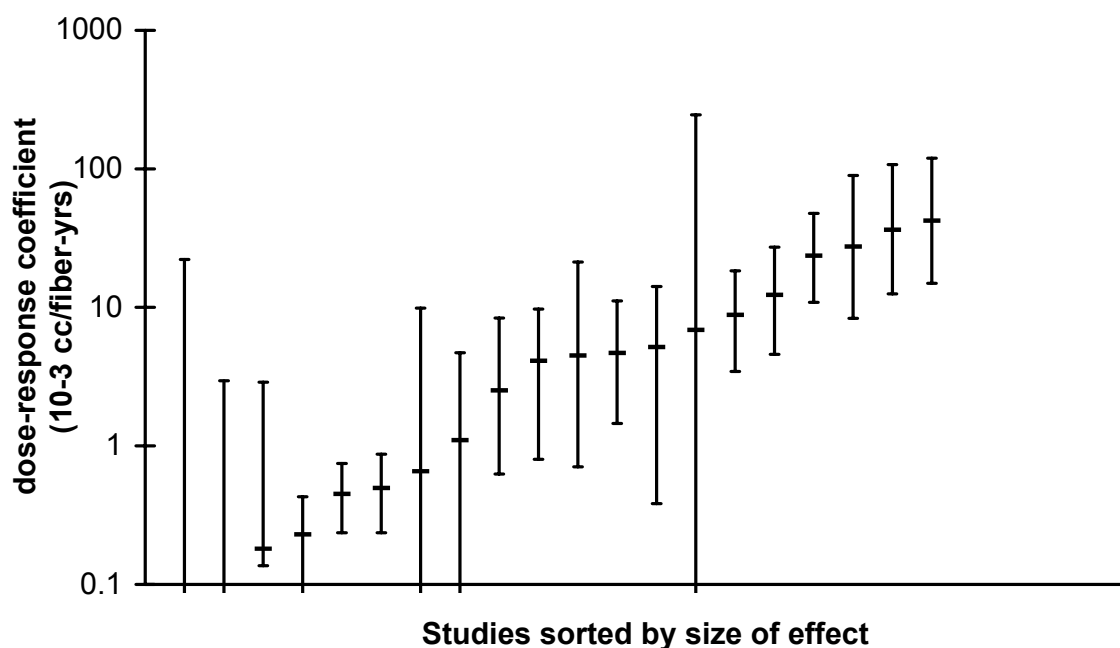
**Lung cancer SMRs & their 95% CIs from studies of occupational exposures  
not thought to cause lung cancer**



**studies sorted by size of effect**

Plots of this type can also provide strong visual evidence of a truly causal association. For example, the next plot shows the slope of the dose-response coefficient relating cumulative exposure to asbestos and relative risk of lung cancer.<sup>9</sup> Note that all but two of the twenty estimates of effect exceeded the null (a slope of 0), that the intervals seldom cover the null, and that the width of the intervals is not dependent on the size of the effect. That is, the widest intervals are not at the left and right sides of the plot.

### Asbestos dose-response coefficients & their 95% CIs



## 3. Cancer types

Our review of the association between trichloroethylene exposure and the cancers at issue follows.

### 3.1. Kidney and renal cell carcinoma

#### 3.1.1. Summary of IARC 1995 review

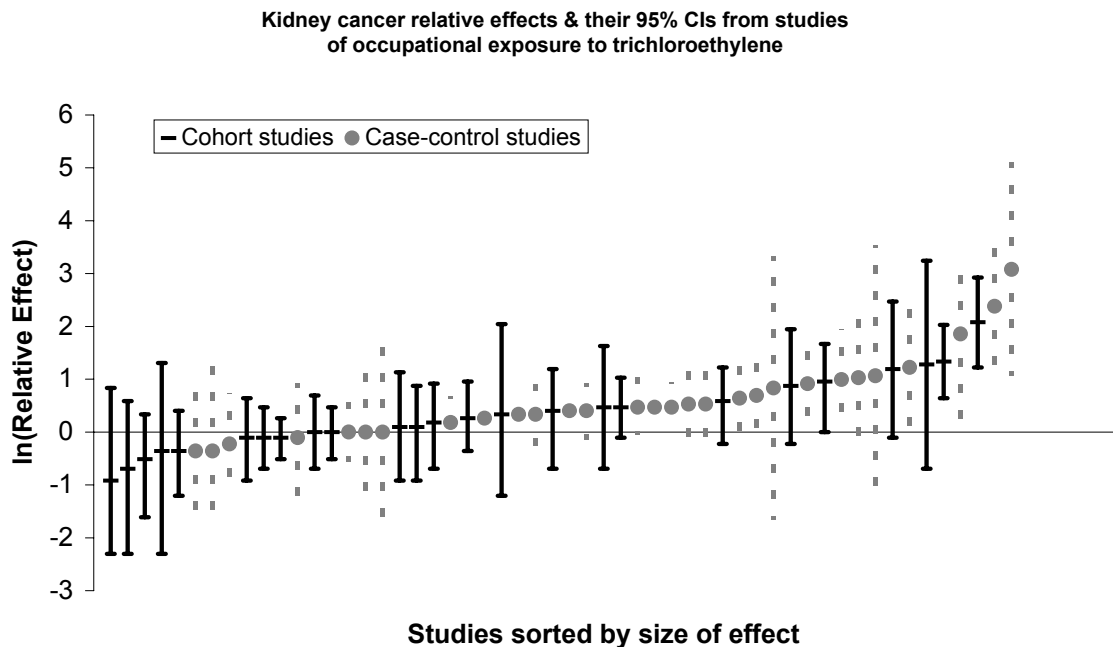
The IARC 1995<sup>2</sup> review dismissed cohort studies of dry cleaning workers because they were not relevant to trichloroethylene exposure *per se*, given the extensive exposure of dry cleaners to other solvents. Cohort studies of workers whose exposure to trichloroethylene was documented by biologic monitoring were given the most emphasis, although cohort studies of workers in other industries were given consideration as well. In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC<sup>2</sup> made no mention of the kidney cancer findings, although the findings were available for review. In its description of four of the five cohort studies of miscellaneous manufacturing industries, IARC<sup>2</sup> similarly made no mention of the kidney cancer findings. The fifth cohort is the cohort of cardboard manufacturing in Germany,<sup>10</sup> which we discuss at length below in section 3.1.3.1. In addition to the issues we raise in that section and the criticisms published elsewhere,<sup>3-5,11</sup> IARC<sup>2</sup> noted that measurements of exposure to trichloroethylene were not available, and workers were classified as exposed or unexposed on the basis of job categories. This classification could be subject to differential misclassification given that the outcomes and hypothesis were known before the investigation began.

In its review of case-control evidence associating trichloroethylene exposure with renal cell carcinoma, IARC<sup>2</sup> reviewed a single case-control study of exposure to degreasing solvents. This study was not specific to trichloroethylene exposure.

In its summary of the human carcinogenicity data, IARC<sup>2</sup> stated that the occurrence of cancer of the kidney was not elevated in the cohort studies, except for the single study introduced above.<sup>10</sup> They gave limited credence to that study because it had been initiated after the observation of a cluster. IARC said that the case-control data were discordant and not specific to trichloroethylene. They did not list the kidney cancer among the types of cancer with even limited epidemiologic evidence of elevated risks associated with trichloroethylene exposure.

### 3.1.2. Summary of new evidence

Since the IARC 1995 review, five cohort studies and five case-control studies have examined the association between occupational exposure to trichloroethylene and the risk of kidney cancer in general, or renal cell carcinoma in particular.<sup>5</sup> Some of the cohort studies are updates of earlier investigations. In these new cohort results, the relative risks of kidney cancer associated with occupational exposure to trichloroethylene have ranged from 0.7 (95% CI 0.3–1.5)<sup>12</sup> to 3.6 (95% CI 0.5–25.6).<sup>13</sup> The latter result applied to women only. The same study found an SMR of 0.4 (95% CI 0.1–2.3) among men. In the new case-control results, the relative risks of kidney cancer associated with occupational exposure to trichloroethylene have ranged from 0.7 (95% CI 0.2–3.6)<sup>14</sup> to 10.8 (95% CI 3.4–34.8).<sup>15</sup> The following figure shows results of all of the studies of the association between occupational exposure to trichloroethylene and kidney cancer or renal cell cancer.<sup>5</sup>



As can be seen, the distribution is what one would expect for a truly null association. That is, the results from cohort studies are centered about the null, and the studies with the widest intervals are nearer the left and right sides of the distribution. Case-control studies more often are towards the right side of the distribution, reflecting the tendency to publish or emphasize exposures with positive findings from case-control research. Given this tendency, the entire distribution seems somewhat shifted towards causal associations, but this is best viewed as an artifact of the aforementioned publication bias. In contrast to the opinion expressed in the *Draft Report*, no “strong pattern” evoking causality is evident.

There are four results with substantially elevated causal associations at the far right side of the plot. Two of these results are the cohort<sup>10</sup> (SMR = 8.0, 95% CI 3.4–18.6) and case-control<sup>15</sup> (OR = 10.8, 95% CI 3.4–34.8) studies generated by a German research group. Were these results valid representations of the effect of trichloroethylene on kidney cancer risk, then one would expect a much more consistently positive result from all other investigations. Instead, the consistent result favors the null hypothesis. This discrepancy begs for an explanation, and we present one alternative hypothesis for this select set of findings below in section 3.1.3.1.

The third of these studies is a case-control study with exposure classification defined as solvents,<sup>16</sup> so is not specific to trichloroethylene. The estimate of effect is restricted to women. The estimate of effect for the same exposure definition in males yielded a relative risk of 1.5 (95% CI 0.9–2.4).

The fourth of these studies is a case-control study in which the exposure was defined as occupational exposure to trichloroethylene and solvents, so again is not specific to TCE.<sup>17</sup>

### 3.1.3. Interpretation

Before interpreting the studies of the association between trichloroethylene and kidney cancer or renal cell cancer, we present an alternative hypothesis that may explain some or all of the observed association in the German cohort<sup>10</sup> and case-control<sup>15</sup> studies. We also discuss limited data associating Von Hippel Lindau mutations in kidney cancer patients with occupational exposure to trichloroethylene. We conclude with our interpretation of the literature.

#### 3.1.3.1. Alternative hypothesis

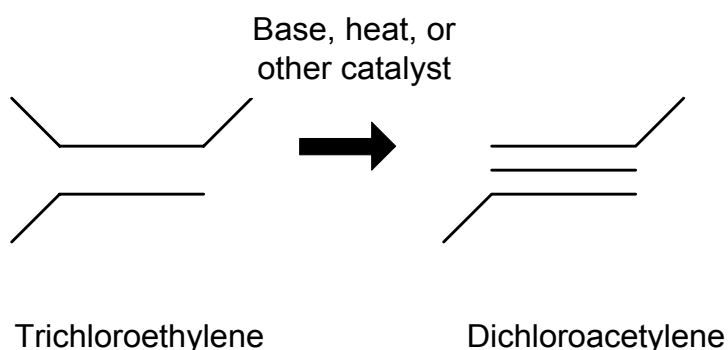
A minority of recent analyses<sup>10, 15</sup> suggest that occupational exposure to trichloroethylene may cause renal cell carcinoma. These observations require an explanation for the disparity between the majority of the published results of the association between occupational exposure to trichloroethylene and the risk of renal cell cancer — which support a null association — and this limited subset of studies that suggest a strong association. We propose an alternative hypothesis to explain why most studies are null, but a limited subset might be positive. Until this hypothesis is fully investigated, one cannot conclude that trichloroethylene *per se* causes kidney and renal cell cancers in humans. The hypothesis is this.

- Under specific, physical and chemical conditions, TCE decomposes *via* dehydrochlorination to the compound dichloroacetylene (DCAene).

- This decomposition of TCE to DCAene has occurred in certain, limited occupational settings, and during specific anaesthetic uses of TCE, but *does not* occur in most occupational settings, *cannot* occur in environmental settings — such as in contaminated water or ambient air — and *cannot* occur *in vivo via* metabolism
- DCAene is a potent nephrotoxin in laboratory rodents, as well as a potent cause of renal cell carcinoma in both sexes of two species, mice and rats.
- To the extent that occupational cohorts using TCE may have been at increased risk of kidney cancer, the increase is more plausibly due not to TCE *per se* but instead to chronic exposure to low but significant levels of DCAene that formed inadvertently.

The evidence supporting this hypothesis is as follows. For much of the 20<sup>th</sup> century, TCE has been used as an inhalation anaesthetic and analgesic agent.<sup>18-21</sup> Anaesthesia is typically induced by levels on the order of 5,000–10,000 parts TCE per million parts air,<sup>19</sup> and reversed without incident upon cessation of exposure. Occasionally, however, not only reversible narcosis but also neuropathy results, with distinct, toxic effects on the patient's trigeminal nerve. The circumstances and causes of this toxicity are of interest both with respect to the nervous system and, more relevant for this commentary, with respect to kidney toxicity and kidney cancer.

The cause of the trigeminal neuropathy is not TCE *per se*, but instead the dehydrochlorination breakdown product of TCE — namely, dichloroacetylene (DCAene; see Figure below). TCE, like other inhalation anaesthetics, can be administered in one of two ways: (a) in a re-breathing circuit,<sup>22</sup> the purpose of which is to deliver to the patient oxygen and anesthetic gases, and eliminate exhaled carbon dioxide (typically *via* soda lime absorption); or (b) in a non-rebreathing circuit. For TCE, only the second method is safe.



As became evident early on, use of soda lime in a re-breathing circuit is a dangerous way to administer TCE, since the sodium hydroxide catalyzes dehydrochlorination of TCE to form the potent toxin, DCAene.<sup>20-25</sup>

Moreover, as in operating rooms, use of TCE in factories can sometimes involve conditions under which dehydrochlorination is catalyzed. Case reports of trigeminal or other facial nerve damage in workers exposed to breakdown products of trichloroethylene parse into two categories of exposure. First, industrial exposure to trichloroethylene vapors that have been heated or passed over fine metal shavings can involve generation of toxicologically

significant quantities of DCAene. Second, in other cases, workers have inhaled TCE through face masks or other absorbers in place to reduce their exposures to carbon dioxide. Unfortunately, the alkaline absorbers (soda lime or its equivalent) served also to catalyze the formation of DCAene, thereby unfortunately causing toxicity rather than preventing it.<sup>26–32</sup>

Nervous system toxicity aside, DCAene is also a specific nephrotoxin in laboratory animals, as well as a potent cause of renal cell cancer in these animals. Bioassay data show DCAene to be a potent inducer of kidney tumors in mice and rats of both sexes.<sup>33</sup> TCE, in contrast, is a weak inducer of kidney tumors in male rats alone. It fails to induce kidney tumors in female rats<sup>a</sup> or in mice of either sex (see Table 1, below). The difference in carcinogenic potencies is striking: comparing TD<sub>50</sub>'s, one finds that DCAene is at least 65 to 1,600 times more potent an inducer of kidney tumors than is TCE.

*Table 1: TD<sub>50</sub>'s<sup>b</sup> (in mg/kg-day) for kidney tumors in laboratory rodents administered TCE or DCAene.*

	Rats		Mice	
	Males	Females	Males	Females
Trichloroethylene <sup>c</sup>	1700	NSR <sup>d</sup>	NSR <sup>d</sup>	NSR <sup>d</sup>
Dichloroacetylene <sup>e</sup>	26	12	12	11

Of course, if exposures to TCE necessarily or often involve exposures to DCAene, the practical distinction between the two might be unimportant. That is, if DCAene often forms from TCE, the distinction between the two chemicals might be more academic than otherwise. Importantly, this is not the case. Instead, DCAene formation is rare, is catalyzed by specific, physical and chemical conditions, persists only under certain conditions, and is not a metabolite of TCE or other compounds in any species. In the environmental setting, the chemical conditions required for TCE to breakdown to DCAene, *and* for DCAene to persist once formed, are not those that accompany domestic uses of water or air contaminated with TCE, however heavily. Even in the occupational (and anesthetic) setting, absent strong alkali, heat, and/or catalytic metal surfaces (or other

<sup>a</sup> The *Draft Report* implies that TCE is known to cause kidney cancer in both female and male rats, but this is incorrect.

<sup>b</sup> The TD<sub>50</sub> is the dose at which chronic administration of the chemical throughout the standard life-span of the species halves the probability of the animals remaining tumor-less. In cases in which the tumor type occurs in 0% of control animals, the TD<sub>50</sub> is simply the dose of the chemical that induces tumors (of a specified type) in 50% of dosed animals. The *inverse* of the TD<sub>50</sub> is a measure of the carcinogenic potency of the test chemical — that is, the smaller the TD<sub>50</sub>, the more potent the chemical as a carcinogen.

<sup>c</sup> *Sources:* Maltoni, *et al.*, 1986; National Toxicology Program (NTP), 1988; NTP, 1990.

<sup>d</sup> NSR = No significant response.

<sup>e</sup> *Source:* Reichert *et al.*, 1984.

conditions conducive to solid-phase dehydrochlorination), the generation of DCAene from TCE is the exception, not the rule.<sup>34-38</sup>

With this understanding of the chemistry and toxicology of DCAene<sup>a</sup> (and the quite different toxicology of TCE), one begins to understand why the vast majority of epidemiologic studies of TCE-exposed workers fails to find any elevation in risk of kidney cancer, even as the epidemiologic results from a small minority of these investigations<sup>10, 15</sup> seem to indicate an elevation in kidney cancer risk. There are, as published elsewhere,<sup>3-5, 11</sup> significant methodologic weaknesses in the apparently positive studies, such that the odds ratios are strongly biased away from the null. The point here, though, is that if there is some actually elevated risk of kidney cancers for the workers therein studied, the risk is more plausibly due to DCAene, and implausibly due to TCE. Moreover, it is in exactly the workplace settings studied by Vamvakas<sup>15</sup> and Henschler<sup>10</sup> (because of the simultaneous presence of strongly alkaline materials, such as cardboard starches made up in 50% NaOH) that DCAene formation would be predicted.

### 3.1.3.2. Von Hippel-Lindau mutations

*The Draft Report* discusses (section 6.5) recent studies in which mutations were analyzed in the Von Hippel-Lindau (VHL) genes of patients with renal cell carcinomas. Two studies by the same group ostensibly find unusual patterns of VHL mutations in renal cell carcinoma (RCC) patients with prior TCE exposure, compared to RCC patients without such exposure.<sup>39, 40</sup> As the *Draft* also notes, a similar investigation by Schraml *et al.*<sup>41</sup> failed to find any differences in VHL genes between TCE-exposed and unexposed patients. We have several comments on the studies by the first group.

- Because the patient populations studied by Bruning *et al.*<sup>39</sup> and Brauch *et al.*<sup>40</sup> evidently overlapped substantially, the findings of these related studies need to be evaluated in another population.
- Most patient numbers and ages at diagnosis listed by Bruning *et al.*<sup>39</sup> appear in Brauch *et al.*'s<sup>40</sup> population; however, not all subjects examined by Bruning *et al.* are also studied by Brauch *et al.*, and no reason for the discrepancy is given. Some ages at diagnosis disagree.
- Bruning *et al.*<sup>39</sup> used no concurrent controls.
- In Brauch *et al.*<sup>40</sup> only TCE-exposed patients and controls were given questionnaires exploring various disease risk factors. Such information was not gathered from unexposed renal cell carcinoma patients or controls.

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<sup>a</sup> This well-known breakdown product of TCE, namely DCAene, is not even mentioned in *The Draft Report*, let alone analyzed with respect to its toxicity. The best one finds therein is the partially correct statement (on page 3), "In the presence of moisture and light, TCE decomposes by forming hydrochloric acid." This is rather like saying, "Rome burns, forming water." Hydrochloric acid is the *leaving group*, of course, in the breakdown of TCE; it is not the toxic material of interest; DCAene is.

- Whether familial VHL disease occurred in any of the patients was not discussed.
- In each patient population, ages at diagnosis range from 38 to 84. There is no discussion about whether RCC mutations may vary with age, and controls or comparison populations are not identified as to age.
- Sexes of patients are not given, nor is there any discussion of whether this variable may be important. The sex distributions of comparison populations are not specified.
- There is no discussion of smoking history in the Bruning *et al.* study.<sup>39</sup> In the Brauch *et al.* paper,<sup>40</sup> 58% of TCE-exposed patients with VHL mutations were said to be smokers. No definition of “nonsmoker,” the only other category, is given. It is unclear how former smokers would be classified. Smoking histories of the whole population are not given, nor is there any discussion of the possible significance of smoking to the occurrence of VHL mutations. Cigarette smoking is an established cause of renal cell cancer.
- The methods used by Brauch *et al.*<sup>40</sup> to analyze DNA from tumor and normal kidney tissue are very unclear. In particular, it is unclear whether tumor samples had been preserved by the same method in each of the three study groups (one exposed, two unexposed). It is also unclear whether tumor tissue from 73 unexposed patients was analyzed in the same manner as tumor tissue from exposed patients.
- Controls were underutilized by Brauch *et al.*<sup>40</sup> Lymphocyte DNA (taken as indicative of germ-line VHL status) was analyzed only for the mutation at nucleotide 454, and not for any other VHL mutation. Analyses of tumor DNA from unexposed patients are designated as unpublished, and given in a summary fashion in Table 4. Only a subset of unexposed patients (73/107) was completely assessed for VHL mutations, and no explanation is given for the absence of such data for the remaining 34 subjects.
- Brauch<sup>40</sup> and others have recently presented evidence suggesting that VHL mutations are more frequent with advanced cancer stage (Brauch *et al.*, 2000).<sup>42</sup> However, tumor stage was not identified in the TCE-exposed patient populations assessed by Brauch *et al.* and the comparison groups.<sup>40</sup>

How are these data to be interpreted? Cautiously, we suggest, given the flaws noted above. Certainly, hypotheses other than TCE-induced mutation must be considered. For example, the TCE used in industry likely contained stabilizing chemicals, which should themselves be assessed for possible mutagenicity. Second, a physical breakdown product of TCE, dichloroacetylene, may be the causal agent, as discussed above. Third, TCE exposure may apply selective pressure to cancer (or pre-cancerous) kidney cells and give a survival advantage to cells with particular VHL mutations, independent of any mutagenic effect of TCE. Finally, the biologic plausibility of TCE-induced mutation must be questioned, since the putative mutagenic metabolite, chlorothioketene, is unstable in aqueous environments and is not expected to react with DNA.

With respect to the application of this molecular genetic data to low-dose environmental exposure to TCE, additional caution is warranted. TCE may indeed cause renal cell carcinoma at high levels of exposure, yet be unable to do so at lower levels. Possible mechanisms are: (1) C to T mutations occur as a byproduct of a toxic inflammatory response to high-dose TCE exposure through free-radical-induced deamination of cytosine nucleotides; and (2) nephrotoxicity must be sustained to promote existing and/or TCE-induced mutations, as posited by Bruning and Bolt.<sup>43</sup>

### 3.1.3.3. Conclusions

There have been important new results published since the IARC review<sup>2</sup> regarding the association between occupational exposure to trichloroethylene and the risk of kidney and renal cell carcinoma. Most of these studies are consistent with the literature published before 1995. That is, the distribution of results appears exactly as one would expect for a null association. There are four discrepant results that suggest a causal association. Two of these derive from case-control studies in which the exposure definition may have included trichloroethylene, but were certainly not specific to trichloroethylene.<sup>16, 17</sup> One of them,<sup>17</sup> and two others with exposure classifications more specific to trichloroethylene,<sup>10, 15</sup> derived from occupational settings in which trichloroethylene may have dehydrochlorinated to form dichloroacetylene. Dichloroacetylene is a potent nephrotoxin and a far more potent kidney carcinogen than trichloroethylene in laboratory rats and mice. The epidemiologic data as a whole suggest both that trichloroethylene *per se* is not a cause of kidney cancer in humans, and that dichloroacetylene may be such a cause.

## 3.2. Liver and biliary tract

### 3.2.1. Summary of IARC 1995 review

In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC<sup>2</sup> reported SMRs for liver cancer of 1.4 (95% CI 0.38–3.6) and of 1.9 (95% CI 0.86–3.6). The SMR was higher in the latter study for men with higher exposure and after twenty years latency. In its review of four cohort studies of miscellaneous manufacturing industries, IARC<sup>2</sup> made no mention of liver cancer findings in two although the findings were available for review, and reported SMRs of 0.94 (95% CI 0.4–1.9) and 2.2 (95% CI 0.96–4.4) in the other two.

IARC<sup>2</sup> also reviewed three case-control studies, all of which considered exposure to mixed solvents. No case-control study specific to trichloroethylene was reviewed.

With this evidence, the review concluded that the cohort studies consistently indicate an excess relative risk for cancer of the liver and biliary tract. They recognized that the case-control studies of mixed solvents, with very few subjects reporting exposure to trichloroethylene, were of little value. They concluded that there was limited evidence of an association between trichloroethylene exposure and liver cancer in the epidemiologic results.

### 3.2.2. Summary of new evidence

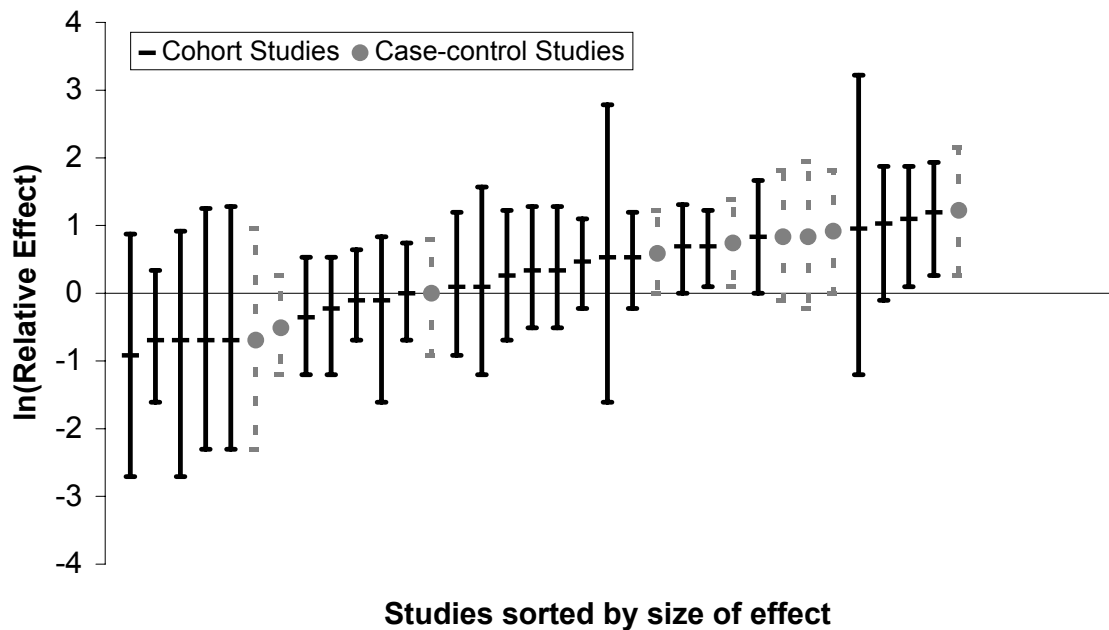
Since the IARC review,<sup>2</sup> four cohort studies and one case-control study have examined the association between occupational exposure to trichloroethylene and the risk of liver or biliary tract cancer.<sup>5</sup> The first cohort study is an update of an earlier investigation. The results from the update are an SMR of 1.7 (95% CI 0.2–16.2)<sup>13</sup> for liver cancer mortality and an SMR of 2.6 (95% CI 0.3–25) for liver cancer incidence among men.<sup>13</sup> The SMR for liver and biliary tract cancer mortality was 1.3 (95% CI 0.5–3.4) and the SMR for incidence among men was 1.1 (95% CI 0.3–4.8). This result derived from a cohort exposed to trichloroethylene and other organic solvents, as described in the published title. Boice *et al.* reported an SMR for liver or biliary tract cancer mortality of 0.5 (95% CI 0.2–1.4),<sup>44</sup> Morgan reported an SMR for liver or biliary tract cancer mortality of 1.0 (95% CI 0.5–2.1),<sup>45</sup> and Ritz reported an SMR for liver or biliary tract cancer mortality of 1.7 (95% CI 0.8–3.3).<sup>12</sup> The majority of evidence accumulated since the IARC review<sup>2</sup> supports the null hypothesis.

In the new case-control study, the relative risk of liver cancer associated with occupational exposure to dry cleaning solutions equaled 0, as there were no exposed cases.<sup>14</sup>

There is no new evidence published since the IARC review<sup>2</sup> that would lead one to conclude that trichloroethylene should be “upgraded” from a probable to a known cause of liver cancer in humans.

The following figure shows all of the studies of the association between occupational exposure to trichloroethylene and liver or liver and biliary tract cancer.<sup>5</sup> The distribution is what one would expect for a truly null association. That is, the results from cohort studies with the widest intervals are nearer the left and right sides of the distribution. Case-control studies more often are towards the right side of the study, reflecting the tendency to publish or emphasize exposures with positive findings from case-control research. Given this tendency, the entire distribution seems somewhat shifted towards causal associations, but this is best viewed as an artifact of the aforementioned publication bias.

**Liver and biliary tract cancer relative effects & their 95% CIs from studies of occupational exposure to trichloroethylene**



### 3.2.3. Interpretation

There is no new evidence to suggest that trichloroethylene is a cause of human liver cancer. In fact, the new evidence most strongly supports the null hypothesis. The complete distribution of results is as expected for a truly null association.

## 3.3. Non-Hodgkin Lymphoma

### 3.3.1. Summary of IARC 1995 review

In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC<sup>2</sup> reported SMRs for non-Hodgkin lymphoma (NHL) of 1.6 (95% CI 0.51–3.6) and 1.8 (95% CI 0.78–3.6). In its review of four cohort studies of miscellaneous manufacturing industries, IARC<sup>2</sup> made no mention of NHL findings in three although the findings were available for review, and reported an SMR of 2.9 (95% CI 0.78–7.3) for women in the fourth. The SMR for men and women combined in the fourth cohort was 1.3 (95% CI 0.68–2.1), suggesting a counterbalancing “protective” effect of trichloroethylene exposure in men.

IARC<sup>2</sup> also reviewed one case-control study of NHL, which considered exposure to mixed solvents. Although TCE specific data were available, only a crude result was reported. No case-control study specific to trichloroethylene was reviewed.

With this evidence, the review concluded that the cohort studies consistently indicated a modest excess relative risk for NHL. They concluded that there was limited evidence of an association between trichloroethylene exposure and non-Hodgkin lymphoma in the epidemiologic results.

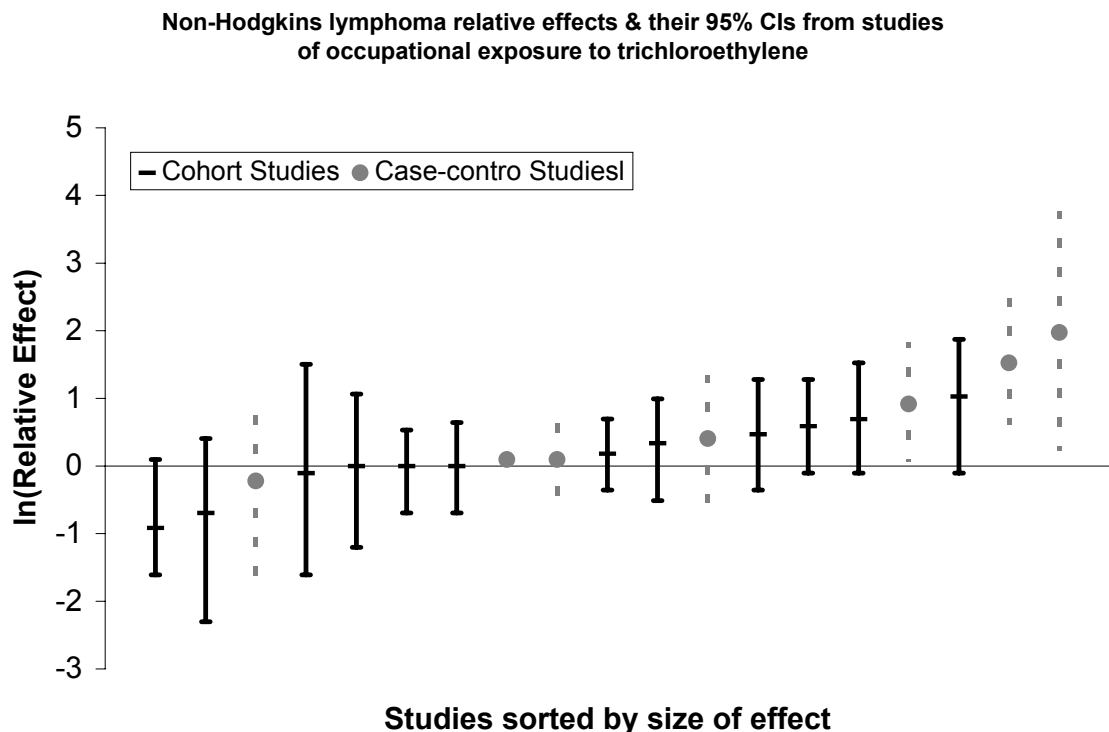
### 3.3.2. Summary of new evidence

Since the IARC review,<sup>2</sup> three cohort studies and one case-control study have examined the association between occupational exposure to trichloroethylene and the risk of non-Hodgkin lymphoma.<sup>5</sup> The first cohort study is an update of an earlier investigation. The results from the update are an SMR of 2.0 (95% CI 0.9–4.6)<sup>13</sup> for NHL mortality, an SMR of 1.0 (95% CI 0.3–2.9) for NHL incidence among men, and an SMR of 0.9 (95% CI 0.2–4.5) for NHL incidence among women.<sup>13</sup> This result derived from a cohort exposed to trichloroethylene and other organic solvents, as described in the published title. Boice *et al.* reported an SMR for NHL mortality of 1.2 (95% CI 0.7–2.0)<sup>44</sup> and Morgan reported an SMR for NHL mortality of 1.0 (95% CI 0.5–1.7).<sup>46</sup> The majority of evidence accumulated since the IARC review<sup>2</sup> supports the null hypothesis.

In the new case-control study, the relative risk of NHL mortality associated with occupation as an aircraft mechanic, as described on the death certificate, equaled 2.5 (95% CI 1.1–6.0).<sup>47</sup> This definition of exposure is not specific to trichloroethylene.

There is no new evidence published since the IARC review<sup>2</sup> that would lead one to conclude that trichloroethylene is a known cause of NHL in humans.

The following figure shows all of the studies of the association between occupational exposure to trichloroethylene and non-Hodgkin lymphoma.<sup>5</sup> The distribution is what one would expect for a truly null association. That is, the results from cohort studies with the widest intervals are nearer the left and right sides of the distribution. Case-control studies more often are towards the right side of the study, reflecting the tendency to publish or emphasize exposures with positive findings from case-control research. Given this tendency, the entire distribution seems somewhat shifted towards causal associations, but



this is best viewed as an artifact of the aforementioned publication bias.

### 3.3.3. Interpretation

There is no new evidence to suggest that trichloroethylene is a cause of non-Hodgkin lymphoma. Instead, the new evidence supports the null hypothesis. The complete distribution of results is as expected for a truly null association

## 3.4. Multiple myeloma

### 3.4.1. Summary of IARC 1995 review

In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC<sup>2</sup> reported no SMRs for multiple myeloma. In its review of four cohort studies of miscellaneous manufacturing industries, IARC<sup>2</sup> made no mention of multiple myeloma findings. Findings were available for review, but not discussed.

IARC<sup>2</sup> reviewed no case-control studies of the association between trichloroethylene exposure and the risk of multiple myeloma.

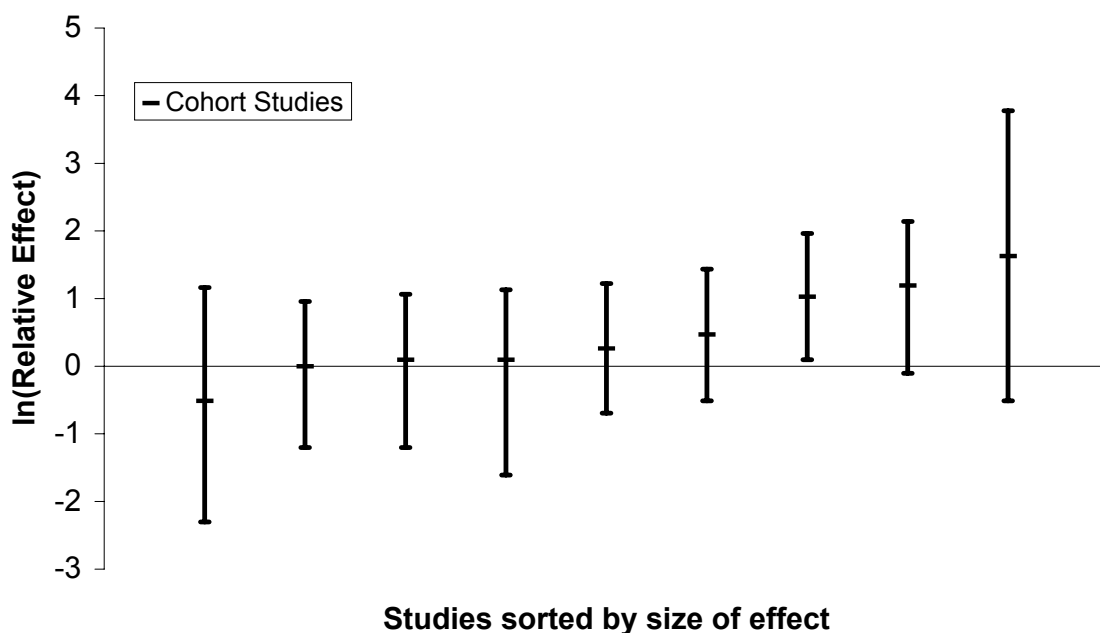
With no evidence reviewed, IARC<sup>2</sup> offered no conclusion about the strength of the evidence associating trichloroethylene exposure with the risk of multiple myeloma.

### 3.4.2. Summary of new evidence

Since the IARC review,<sup>2</sup> two cohort studies have examined the association between occupational exposure to trichloroethylene and the risk of multiple myeloma.<sup>5</sup> The first cohort study is an update of an earlier investigation. The results from the update are an SMR of 1.3 (95% CI 0.5–3.4)<sup>13</sup> for mortality attributed to multiple myeloma, and an SMR of 5.1 (95% CI 0.6–43.7 for multiple myeloma incidence among men.<sup>13</sup> This result derived from a cohort exposed to trichloroethylene and other organic solvents, as described in the published title. Boice *et al.* reported an SMR for mortality attributed to multiple myeloma of 2.8 (95% CI 1.1–7.1).<sup>44</sup> These SMRs are based on 14, 5, and 4 cases, respectively. Thus, the most stable estimate is the null SMR reported first. While the new evidence suggests a potential association, the accumulated evidence is far too unstable to warrant a conclusion that the association is causal. This is particularly true in light of the evidence that preceded these recent results — evidence upon which that IARC<sup>2</sup> did not comment. That evidence suggests a null association between trichloroethylene exposure and the risk of multiple myeloma.

The following figure shows all of the studies of the association between occupational exposure to trichloroethylene and multiple myeloma.<sup>5</sup> The distribution is what one would expect for a truly null association. That is, the results from cohort studies with the widest intervals are nearer the left and right sides of the distribution. The most stable estimates concentrate about the null, and only one result's 95% confidence interval excludes the null.

**Multiple myeloma relative effects & their 95% CIs from studies of occupational exposure to trichloroethylene**



### 3.4.3. Interpretation

While recent evidence suggests that there may be an association between trichloroethylene exposure and the risk of multiple myeloma, that evidence derives from a very small number of cases. Preceding evidence, based on a larger number of cases, suggest no association. Taken together, the results do not establish that trichloroethylene causes multiple myeloma.

## 3.5. Prostate cancer

### 3.5.1. Summary of IARC 1995 review

In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC<sup>2</sup> reported an SMR for prostate cancer of 1.3 (95% CI 0.84–1.8) from one study. For the second study, IARC reported an overall SMR of 1.4 (95% CI 0.73–2.4), an SMR of 0.68 (95% CI 0.08–2.4) for men with the highest exposure, and an SMR of 3.6 (95% CI 1.5–7.0) for men with a 20-year latency. In its review of four cohort studies of miscellaneous manufacturing industries, IARC<sup>2</sup> reported no prostate cancer SMR for two, an SMR of 0.80 (95% CI 0.5–1.2) for a third, and an SMR of 0.93 (95% CI 0.60–1.4) for the fourth.

IARC<sup>2</sup> reported an odds ratio of 1.8 (95% CI 0.7–4.7) associated with at least five years of exposure at a presumably medium or high concentration and frequency from one case-control study.

The prostate cancer associations were not mentioned in the summary section of IARC,<sup>2</sup> in which it was concluded that there was limited human evidence to suggest that trichloroethylene was carcinogenic.

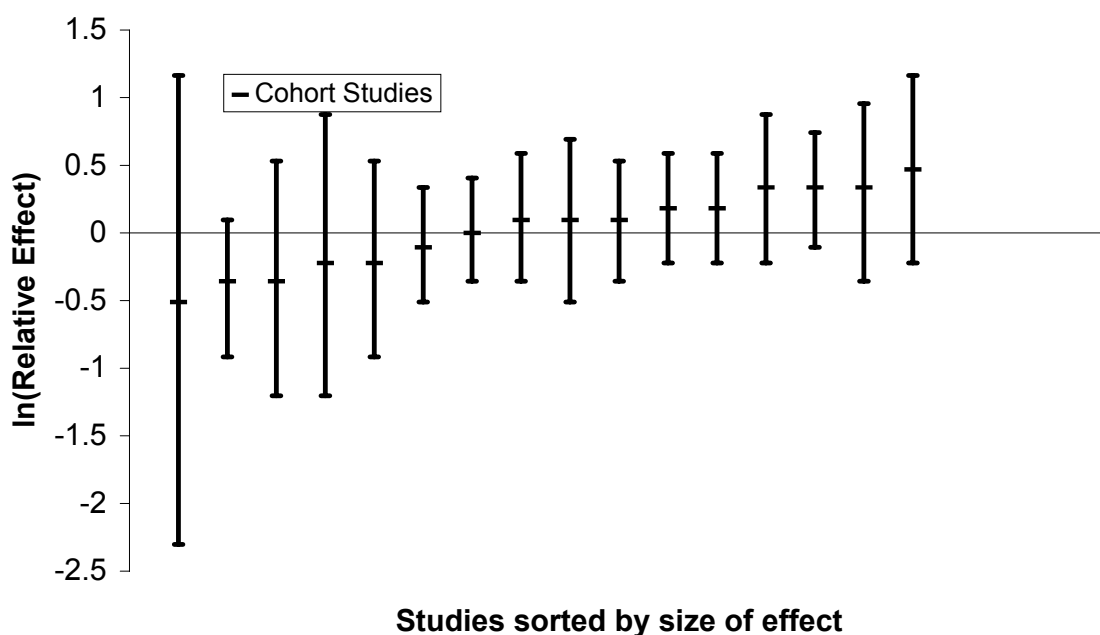
### 3.5.2. Summary of new evidence

Since the IARC review,<sup>2</sup> four cohort studies have examined the association between occupational exposure to trichloroethylene and the risk of prostate cancer.<sup>5</sup> The first cohort study is an update of an earlier investigation. The results from the update are an SMR of 1.1 (95% CI 0.7–1.8)<sup>13</sup> for prostate cancer mortality and an SMR of 1.2 (95% CI 0.8–1.8) for prostate cancer incidence among men.<sup>13</sup> Boice *et al.* reported an SMR for prostate cancer mortality of 1.0 (95% CI 0.7–1.5),<sup>44</sup> Morgan reported an SMR for prostate cancer mortality of 1.2 (95% CI 0.8–1.8),<sup>48</sup> and Ritz reported an SMR for prostate cancer mortality of 1.4 (95% CI 0.9–2.1).<sup>12</sup> The majority of evidence accumulated since the IARC review<sup>2</sup> supports the null hypothesis.

There is no new evidence published since the IARC review<sup>2</sup> that would lead one to conclude that trichloroethylene causes prostate cancer.

The following figure shows all of the studies of the association between occupational exposure to trichloroethylene and prostate cancer.<sup>5</sup> The distribution is what one would expect for a truly null association. That is, the results from cohort studies are centered about the null with the widest intervals nearer the left and right sides of the distribution.

Prostate cancer relative effects & their 95% CIs from studies of occupational exposure to trichloroethylene



### 3.5.3. Interpretation

Results published since the IARC review<sup>2</sup> regarding the association between occupational exposure to trichloroethylene and the risk of prostate cancer are consistent with the findings published before 1995. That is, the distribution of results appears as one would expect for a null association.

## 4. Additional flaws in the *Draft Report*

- Sections 5.3 and 6.6.4 present information on vinyl chloride and other compounds “similar” to TCE (termed “structural analogues”). This “arguing by analogy” is highly inappropriate, and should be removed entirely from the *Draft Report*. Just as no sensible analyst would, for example, discuss methanol toxicology and epidemiology in a monograph on ethanol, no one writing about TCE should rely on the toxicology and epidemiology of vinyl chloride.

## 5. Conclusion

Neither the *Draft Report* nor the primary epidemiologic and toxicologic information on trichloroethylene provides compelling evidence that the chemical is a cause of human cancer. As a matter of public health policy, we might wish to regard TCE as if it were a risk factor for human cancer. Since the 1970's, U.S. EPA and others have been doing just that. But public policy decision making is not scientific decision making, and conflating the two processes makes for neither good policy nor good science. As the above analysis makes plain, the scientific evidence cannot be fairly judged as implicating TCE as a *bona*

*fide* cause of cancer in humans — not even for those most likely to have been most highly exposed in the workplace, let alone for others.

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