Comments on the National Toxicology Program's *Draft Report on Carcinogens Background Document for Trichloroethylene* (2000)

by:

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1. Introduction

In this commentary, we analyze the conclusions of the *Draft Report on Carcinogens Background Document for Trichloroethylene.*[1] We focus on the conclusions based on epidemiologic evidence. In so doing, we find that the *Draft Report* is flawed. Neither the methods employed nor the results presented in this *Draft Report* constitute a reliable analysis or a basis for causal inference. Upon reviewing the primary evidence, 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 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)[a] or "limited" (IARC, 1995).[2, b] 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 quite different conclusions from those given in the *Draft Report.*[3–5]

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:

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[a] 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."

[b] 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 at TCE Workshop, Williamsburg, Virginia).

> 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, 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[2] 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,[2] to see whether the new evidence ought to modify the conclusion reached by IARC.[2] 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 the selective treatment given in this Report.[a]

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

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[a] 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.

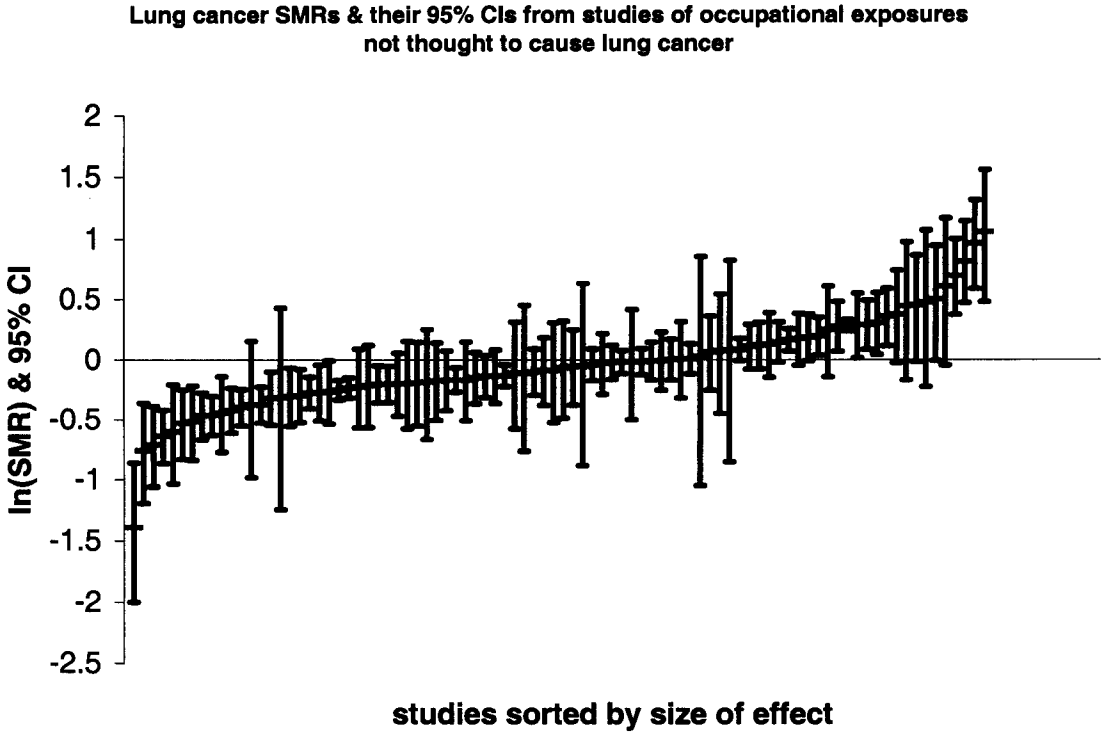
epidemiologic data? Let us look. In particular, for each of the cancer types at issue, let us plot the accumulated results graphically. For each cancer type, we have sorted the published epidemiologic results (SMRs, RRs, and/or ORs) in ascending order. We then plot the results and their 95% confidence intervals, with distinct symbols representing 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.

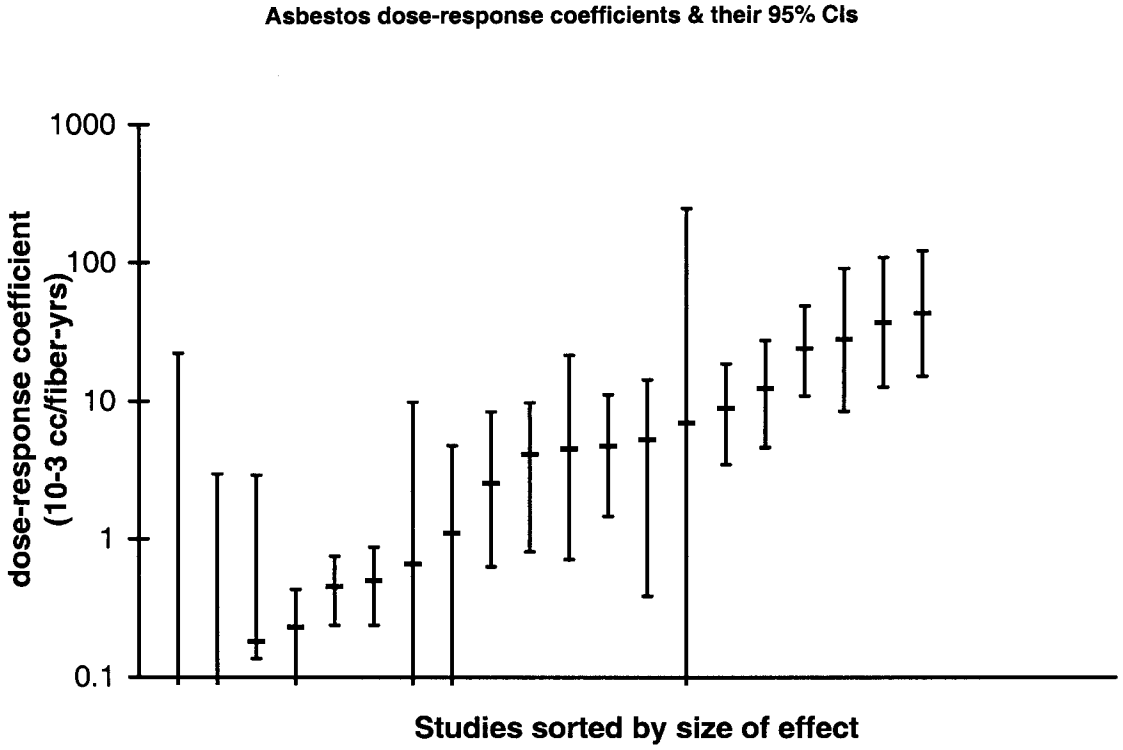
- If case-control studies of the association have been conducted, they may tend to concentrate above the null. Case-control studies often examine a number of exposures associated with a single disease. The exposures that prove to be positively associated with the disease tend to be those published or 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 tend to 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[6] and have been applied in other settings,[7] 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.[8] The SMRs and their intervals are plotted (here and throughout these comments) on the logarithmic-scale, so that the distribution is symmetrical about the null (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.



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.[9] The publication from which this distribution derives is attached. Note that all but two of the twenty estimates of effect exceed 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.



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[2] 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[2] 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[2] similarly made no mention of the kidney cancer findings. The fifth cohort is the cohort of cardboard manufacturing in Germany, [10] 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,[3–5, 11] IARC[2] noted that measurements of exposure to trichloroethylene were not available, and workers were classified as exposed or unexposed on the basis of job

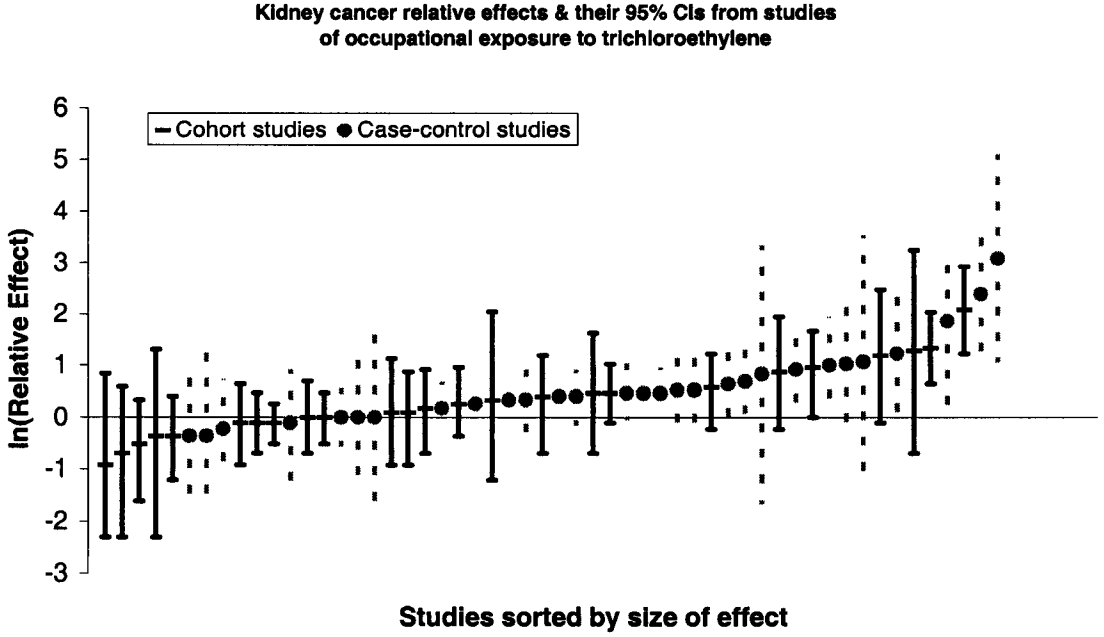
categories. This classification could be subject to differential misclassification given that the outcomes and hypothesis were known before the investigation began.

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

In it summary of the human carcinogenicity data, IARC[2] stated that the occurrence of cancer of the kidney was not elevated in the cohort studies, except for the single study of from a cardboard box-making plant introduced above.[10] 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.[5] 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)[12] to 3.6 (95% CI 0.5–25.6).[13] 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)[14] to 10.8 (95% CI 3.4–34.8).[15] The Figure shows results of all of the studies of the association between occupational exposure to trichloroethylene and kidney cancer or renal cell cancer.[5] 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 associations at the far right side of the plot. Two of these results are the cohort[10] (SMR = 8.0, 95% CI 3.4–18.6) and case-control[15] (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 occupational exposures to trichloroethylene on kidney cancer risk, then we should see a much more consistently positive result from other occupational investigations (assuming roughly equal levels of TCE exposure). 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,[16] 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.[17]

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[10] and case-control[15] 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[10, 15] 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 further investigated, one should not conclude that trichloroethylene *per se* causes kidney cancer in humans. The hypothesis is this.

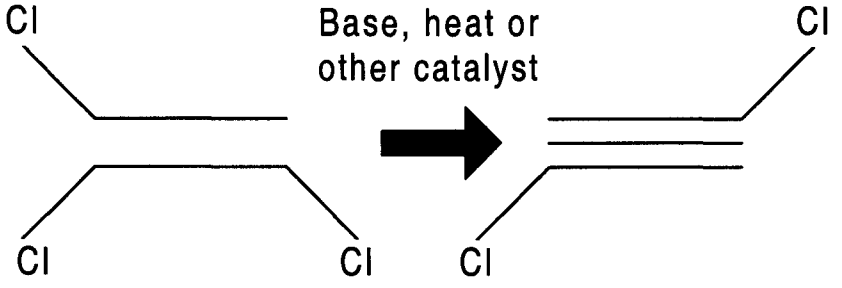
- Under specific, physical and chemical conditions, TCE decomposes *via* dehydrochlorination to the compound dichloroacetylene (DCAene).

- 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 toxicologically significant levels of DCAene that formed inadvertently.

The evidence supporting this hypothesis is as follows. For much of the 20th century, TCE has been used as an inhalation anaesthetic and analgesic agent.[18–21] Anesthesia is typically induced by levels on the order of 5,000–10,000 parts TCE per million parts air,[19] 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 anesthetics, can be administered in one of two ways: (a) in a re-breathing circuit, 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.[20–25]

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.[26–32]

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.[33] TCE, in contrast, is a weak inducer of kidney tumors in male rats alone. It fails to induce kidney tumors in female rats[a] or in mice of either sex (see Table 1, below). The difference in carcinogenic potencies is striking: comparing TD_{50}'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_{50}'s[b] (in mg/kg-day) for kidney tumors in laboratory rodents administered TCE or DCAene.

	Rats		Mice	
	Males	Females	Males	Females
Trichloroethylene[c]	1700	NSR[d]	NSR[d]	NSR[d]
Dichloroacetylene[e]	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)

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

[b] The TD_{50} 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_{50} is simply the dose of the chemical that induces tumors (of a specified type) in 50% of dosed animals. The *inverse* of the TD_{50} is a measure of the carcinogenic potency of the test chemical — that is, the smaller the TD_{50}, the more potent the chemical as a carcinogen.

[c] *Sources*: Maltoni, *et al.*, 1986; National Toxicology Program (NTP), 1988; NTP, 1990.

[d] NSR = No significant response.

[e] *Source*: Reichert *et al.*, 1984.

setting, absent strong alkali, heat, and/or catalytic metal surfaces (or other conditions conducive to solid-phase dehydrochlorination), the generation of DCAene from TCE is the exception, not the rule.[34–38]

With this understanding of the chemistry and toxicology of DCAene[a] (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 an elevation in risk of kidney cancer, even as the epidemiologic results from a small minority of these investigations[10, 15] seem to indicate a sizable elevation in kidney cancer risk. There are, as published elsewhere,[3–5, 11] 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 cancer 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[15] and Henschler[10] -- 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 report unusual patterns of VHL mutations in renal cell carcinoma (RCC) patients with prior TCE exposure, compared to RCC patients without such exposure.[39, 40] As the *Draft* also notes, a similar investigation by Schraml *et al.*[41] failed to find any differences in VHL genes between TCE-exposed and unexposed patients. We have several comments on these studies.

- Because the patient populations studied by Bruning *et al.*[39] and Brauch *et al.* [40] 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.* [39] appear in Brauch *et al.*'s [40] 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.* [39] used no concurrent controls.

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[a] 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.

- In Brauch *et al.*[40] 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.

- 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.[39] In the Brauch *et al.* paper,[40] 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.[42]

- The methods used by Brauch *et al.*[40] to analyze DNA from tumor and normal kidney tissue (and from lymphocytes) 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). Tissue from exposed RCC patients had been formalin-fixed and embedded in paraffin; DNA from such samples is likely to be highly damaged. Tissues preserved in this way are not comparable to fresh tissue or cells. It is also unclear whether tumor tissue from 73 unexposed patients was analyzed in the same manner as tumor tissue from exposed patients.

- There was no positive control for the method used to identify nt454 mutations. Thus, failure to find such mutations may be due to experimental error.

- Controls were underutilized by Brauch *et al.*[40] 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.

- An internet database of VHL mutations (www.umd.necker.fr) indicates that a nt454 hotspot had not previously been identified. Brauch *et al.*'s findings of multiple mutations in the gene are also highly inconsistent with previous data. We wonder whether Brauch *et al.*'s findings are artifacts of their methods.

- Brauch and others have recently presented evidence suggesting that VHL mutations are more frequent with advanced cancer stage (Brauch *et al.*, 2000).[43] However, tumor stage was not identified in the TCE-exposed patient populations assessed by Brauch *et al.* and the comparison groups.[40]

- The descriptions of the TCE exposures experienced by the most highly exposed cases suggest frankly toxic exposures – concentrations apparently high enough to induce narcotic symptoms. Also, as noted above, these cases may have been exposed to the potent nephrotoxin, dichloroacetylene.

How are these data to be interpreted? Cautiously, we suggest, given the flaws and uncertainties noted above. Certainly, hypotheses other than TCE-induced mutation must be considered. For example, the TCE used industrially contains stabilizing chemicals, which may be or are known to be mutagenic. Alternatively, industrial exposure to TCE may apply selective pressure to cancerous (or pre-cancerous) kidney cells and give a survival advantage to cells with particular VHL mutations, independent of any mutagenic effect of TCE. Such an hypothesis has recently been proposed for lung cancers in smokers and the p53 tumor suppressor gene (Rodin and Rodin, 2000). 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.[44]

3.1.3.3. Conclusions

There have been important new results published since the IARC review[2] 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 is consistent with 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.[16, 17] One of them,[17] and two others with exposure classifications more specific to trichloroethylene,[10, 15] 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 both sexes of 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[2] 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[2] 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[2] 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.

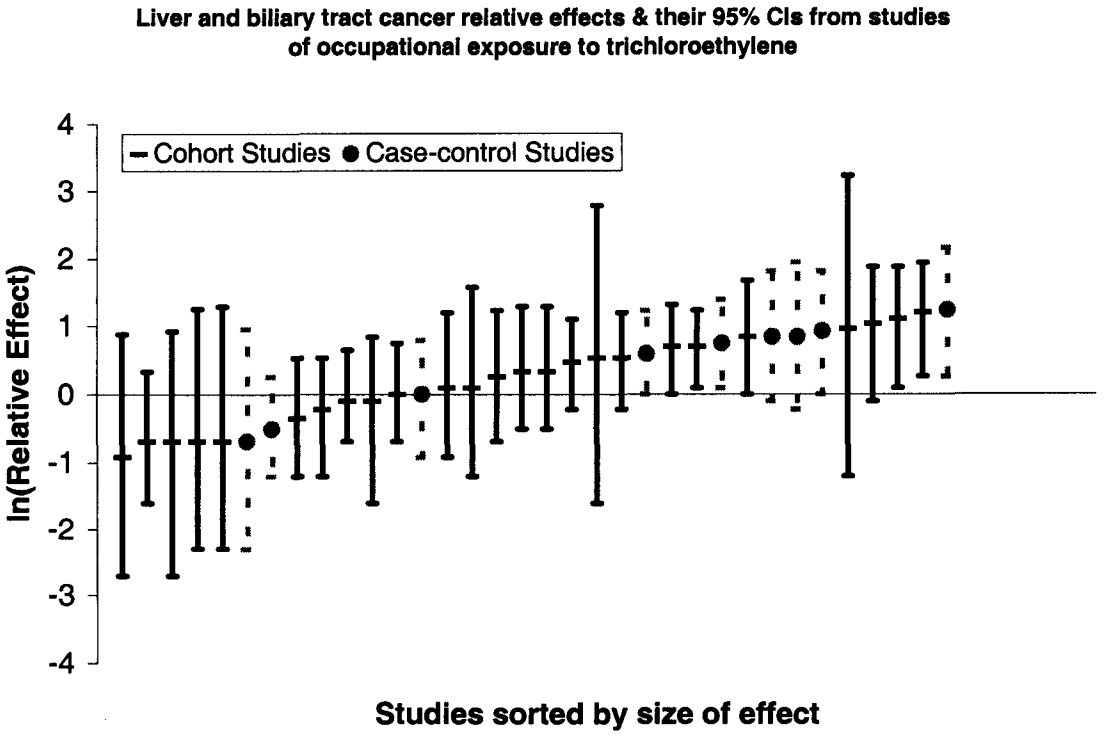
3.2.2. Summary of new evidence

Since the IARC review,[2] 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.[5] 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)[13] for liver cancer mortality and an SMR of 2.6 (95% CI 0.3–25) for liver cancer incidence among men.[13] 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),[45] Morgan reported an SMR for liver or biliary tract cancer mortality of 1.0 (95% CI 0.5–2.1),[46] and Ritz reported an SMR for liver or biliary tract cancer mortality of 1.7 (95% CI 0.8–3.3).[12] The majority of evidence accumulated since the IARC review[2] 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.[14]

There is no new evidence published since the IARC review[2] 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.[5] 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.



3.2.3. 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[2] 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[2] 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).

IARC[2] 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,[2] three cohort studies and one case-control study have examined the association between occupational exposure to trichloroethylene and the risk of non-Hodgkin lymphoma.[5] 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)[13] 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.[13] 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)[45] and Morgan reported an SMR for NHL mortality of 1.0 (95% CI 0.5–1.7).[46] The majority of evidence accumulated since the IARC review[2] supports the null hypothesis.

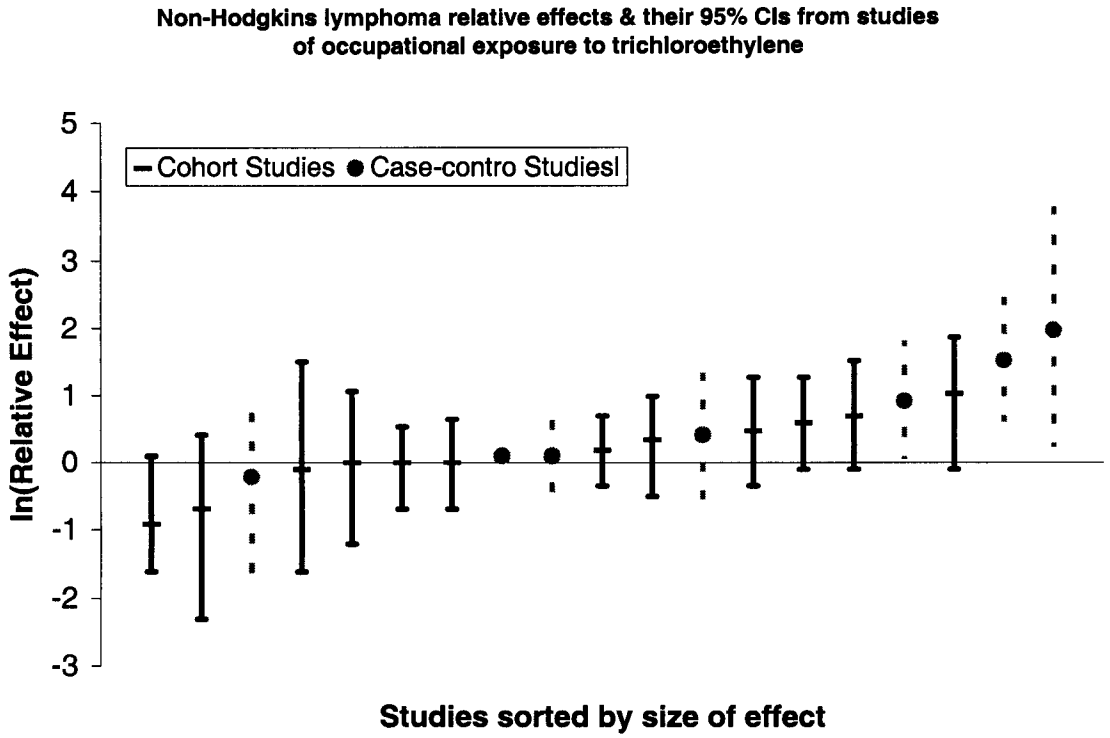
In the new case-control study, the relative risk of NHL mortality associated with occupation as an aircraft mechanic, as described on the death certificate, equaled 2.5 (95% CI 1.1–6.0).[47] This definition of exposure is not specific to trichloroethylene.

There is no new evidence published since the IARC review[2] 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.[5] 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

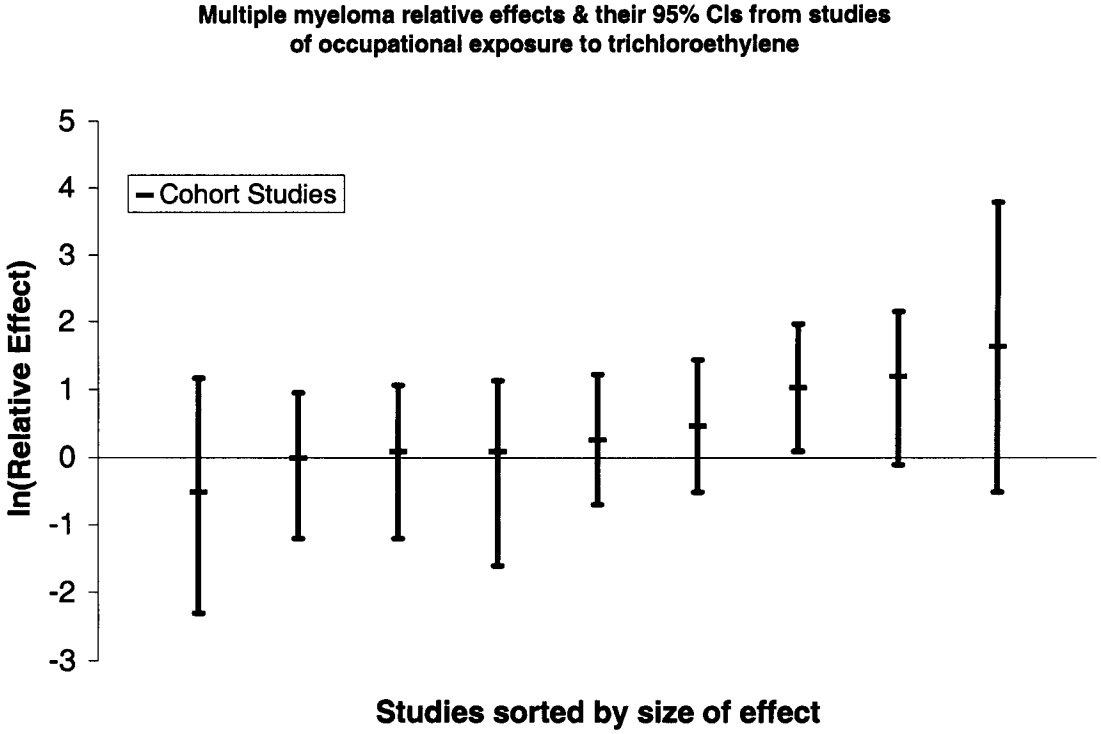
In its review of two studies with biologic monitoring to document trichloroethylene exposure, IARC[2] reported no SMRs for multiple myeloma. In its review of four cohort studies of miscellaneous manufacturing industries, IARC[2] made no mention of multiple myeloma findings. Findings were available for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

IARC[2] reviewed no case-control studies of the association between trichloroethylene exposure and the risk of multiple myeloma.

With no evidence reviewed, IARC[2] 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,[2] two cohort studies have examined the association between occupational exposure to trichloroethylene and the risk of multiple myeloma.[5] 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)[13] for mortality attributed to multiple myeloma, and an SMR of 5.1 (95% CI 0.6–43.7 for multiple myeloma incidence among men. [13] 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).[45] While the new evidence suggests a potential association, the accumulated evidence is too unstable to warrant a conclusion that the association is established as causal. This is particularly true in light of the evidence that preceded these recent results — evidence upon which that IARC[2] 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.[5] 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.

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 suggests 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[2] 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[2] 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[2] 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.

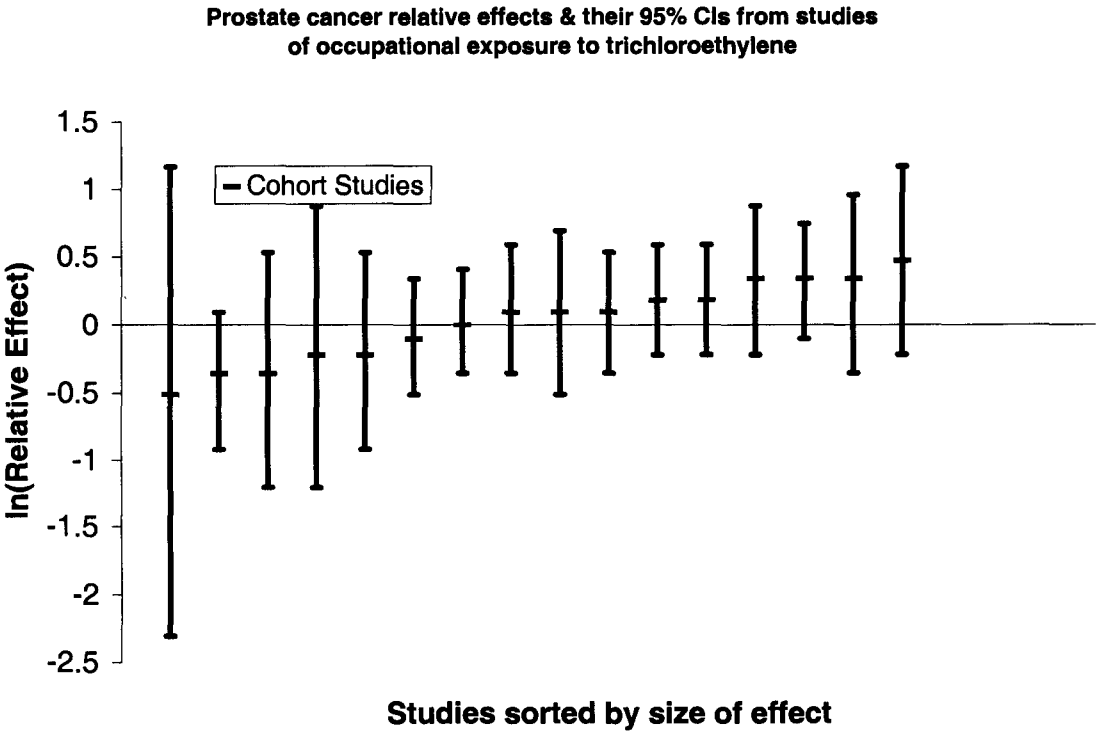
The prostate cancer associations were not mentioned in the summary section of IARC,[2] in which it was concluded that there was limited human evidence to suggest that trichloroethylene was carcinogenic.

3.5.2. Summary of new evidence

Since the IARC review,[2] four cohort studies have examined the association between occupational exposure to trichloroethylene and the risk of prostate cancer.[5] 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)[13] for prostate cancer mortality and an SMR of 1.2 (95% CI 0.8–1.8) for prostate cancer incidence among men.[13] Boice *et al.* reported an SMR for prostate cancer mortality of 1.0 (95% CI 0.7–1.5),[45] Morgan reported an SMR for prostate cancer mortality of 1.2 (95% CI 0.8–1.8),[46] and Ritz reported an SMR for prostate cancer mortality of 1.4 (95% CI 0.9–2.1).[12] The majority of evidence accumulated since the IARC review[2] supports the null hypothesis.

There is no new evidence published since the IARC review[2] 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.[5] 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.



3.5.3. Interpretation

Results published since the IARC review[2] 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. This is especially true given the marked qualitative and quantitative differences in metabolism, mutagenicity, and other central aspects of the compounds at issue.

- The *Draft* frequently cites papers indirectly – for example, "Jaffe *et al.*, 1985, Vamvakas *et al.*, 1992, both cited in Vamvakas *et al.*, 1993." Surely the *Draft* authors should have gathered and read the original papers, especially those published in readily available journals.

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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A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer

Timothy L Lash, Edmund A C Crouch, Laura C Green

Abstract

***Objectives*—To obtain summary measures of the relation between cumulative exposure to asbestos and relative risk of lung cancer from published studies of exposed cohorts, and to explore the sources of heterogeneity in the dose-response coefficient with data available in these publications.**

***Methods*—15 cohorts in which the dose-response relation between cumulative exposure to asbestos and relative risk of lung cancer has been reported were identified. Linear dose-response models were applied, with intercepts either specific to the cohort or constrained by a random effects model; and with slopes specific to the cohort, constrained to be identical between cohorts (fixed effect), or constrained by a random effects model. Maximum likelihood techniques were used for the fitting procedures and to investigate sources of heterogeneity in the cohort specific dose-response relations.**

***Results*—Estimates of the study specific dose-response coefficient ($k_{1,i}$) ranged from zero to 42 × 10^{-3} ml/fibre-year (ml/f-y). Under the fixed effect model, a maximum likelihood estimate of the summary measure of the coefficient ($\hat{\kappa}_1$) equal to 0·42 × 10^{-3} (95% confidence interval (95% CI) 0·22 to 0·69 × 10^{-3}) ml/f-y was obtained. Under the random effects model, implemented because there was substantial heterogeneity in the estimates of $k_{1,i}$ and the zero dose intercepts (A_i), a maximum likelihood estimate of $\hat{\kappa}_1$ equal to 2·6 × 10^{-3} (95% CI 0·65 to 7·4 × 10^{-3}) ml/f-y, and a maximum likelihood estimate of $\hat{A}$ equal to 1·36 (95% CI 1·05 to 1·76) were found. Industry category, dose measurements, tobacco habits, and standardisation procedures were identified as sources of heterogeneity.**

***Conclusions*—The appropriate summary measure of the relation between cumulative exposure to asbestos and relative risk of lung cancer depends on the context in which the measure will be applied and the prior beliefs of those applying the measure. In most situations, the summary measure of effect obtained under the random effects model is recommended. Under this model, potency, $\hat{\kappa}_1$, is fourfold lower than that calculated by the United States Occupational Safety and Health Administration.**

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Occupational exposure to asbestiform fibres causes lung cancer.[1] The relation between extent of exposure and risk of lung cancer influences (*a*) regulatory activity,[2] (*b*) estimates of risk from low level exposures to asbestos,[3] and (*c*) prediction of the impact of exposures on public health—such as lung cancer mortality among exposed workers in asbestos industries.[4] Overviews of the dose-response relation conducted to date have been semiquantitative and have not been examined in the light of updates of the cohort studies upon which they rely. We present a quantitative meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. We discuss potential sources of heterogeneity in the relation that was evident in the studies.

Methods

We identified published studies by reviewing an existing overview of the dose-response relation,[5] searching the Medline database from 1966 to December 1995, and by searching citations in the studies found by the first two methods. Any study reporting a measure of the relative risk for lung cancer associated with a quantitative measure of cumulative exposure was eligible for the meta-analysis. No such studies were intentionally excluded. Most studies identified, and all studies included in the meta-analysis, were retrospective cohort studies of mortality due to lung cancer. The diseases encompassed by the term lung cancer differed in the different studies. We abstracted and report, when available, the international classification of diseases (ICD) codes included under the definition of lung cancer in each study. We also extracted from each study the cohort entrance requirements; number, sex, and race of people studied; amount of person-time accumulated, noting exclusions; type of asbestos industry and of asbestos fibre; method of estimating cumulative exposure; characteristics of the referent population; method of ascertaining vital status and of classifying causes of death; number of total lung cancer deaths observed; number of observed and expected lung cancer deaths, and the corresponding standardised mortality ratio (SMR), within cumulative exposure strata; and any information on tobacco use by the cohort.

Cumulative exposure strata were usually defined by a range, often with an open end for the highest exposure stratum—for example, $\geqslant$ 100 fibre-year/ml (f-y/ml). We assigned fixed exposures to these ranges as the midpoint of the range, unless a mean or median was reported. For open ended categories, we assigned a fixed exposure by repeating the pattern found at lower exposures. We calculated 95% confidence intervals (95% CIs) about the SMR for each cumulative exposure with an approximation to a Poisson distribution.[6] For each study reporting SMRs for more than one cumulative exposure category, we fitted the following dose-response model:

$$E_{i,j} = A_i\,(1 + k_{1,i}\,d_{i,j})e_{i,j} \quad k_{1,i} \geqslant 0$$

where $E_{i,j}$ is the number of deaths from lung cancers expected under the model in study i at dose j, A_i is the fitted intercept corresponding to the relative risk of lung cancer among the cohort at zero exposure, $k_{1,i}$ (a measure of potency) is the coefficient relating cumulative exposure to asbestos to relative risk of lung cancer in study i under the linear dose-response model,[7] $d_{i,j}$ is the dose of asbestos assigned to cumulative exposure category j of study i, and $e_{i,j}$ is the population based expected number of deaths from lung cancer. The number of observed deaths from lung cancer in study i at dose j, which we denote $O_{i,j}$, was assumed to be a Poisson random variable with expectation $E_{i,j}$. To obtain estimates of A_i and $k_{1,i}$, we maximised the likelihood ($\mathcal{L}_i$) for each study:

$$\mathcal{L}_i = \prod_j \left(\frac{E_{i,j}^{\,O_{ij}}}{O_{i,j}!}\, e^{-E_{ij}} \right)$$

We estimated the 95% CI about each $k_{1,i}$ with the profile likelihood method.

We obtained a maximum likelihood summary measure of the dose-response coefficient ($\hat{\kappa}_1$) by substituting $\hat{\kappa}_1$ for each $k_{1,i}$ and maximising the sum of the $\ln\mathcal{L}_i$ with respect to $\hat{\kappa}_1$ and A_i, constraining i to the subset of studies chosen to represent unique cohorts. This constraint was necessary because some cohorts have been studied more than once. A 95% CI about $\hat{\kappa}_1$ was obtained by the profile likelihood method. The likelihood method weights each study by its precision.

We found substantial heterogeneity of the A_i and $k_{1,i}$, so the fixed effect summary estimate of the dose-response coefficient and its 95% CI may be inappropriate. We then calculated a random effects summary estimate of the dose-response coefficient by assuming that the A_i and $k_{1,i}$ derive from log normal distributions. Restating the likelihood under the random effects model, we have:

$$\mathcal{L} = \prod_i \left(\int_{-\infty}^{\infty} \frac{dz_i}{\Sigma\sqrt{2\pi}} \exp\left(-\frac{(z_i - \xi)^2}{2\Sigma^2} \right) \times \right.$$

$$\int_{-\infty}^{\infty} \frac{dw_i}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(w_i - \phi)^2}{2\sigma^2} \right) \times$$

$$\left. \prod_j \frac{\left(e^{wi}e_{ij}(1 + e^{zi}d_{ij})\right)^{Oij} \exp\left(-e^{wi}e_{ij}(1 + e^{zi}d_{ij})\right)}{O_{ij}!} \right)$$

where z_i is $\ln(k_{1,i})$, ξ is $\ln(\hat{\kappa}_1)$, and $z - \xi$ is normally distributed with SD Σ; and w_i is $\ln(A_i)$, ϕ is $\ln(\hat{A})$, and $w - \phi$ is normally distributed with SD σ.

We tested various hypotheses on sources of heterogeneity in estimates of $k_{1,i}$ under the model with likelihood techniques.

Results

We identified 15 cohorts in which the dose-response relation between cumulative exposure to asbestos and relative risk of lung cancer has been reported in 22 publications. The table contains a summary of each publication, including its $k_{1,i}$, A_i, and the 95% CI about $k_{1,i}$. Figure 1 shows the distribution of the individual $k_{1,i}$ plotted against the inverse normal of its rank, and fig 2 shows the distribution of the individual A_i plotted against the inverse normal

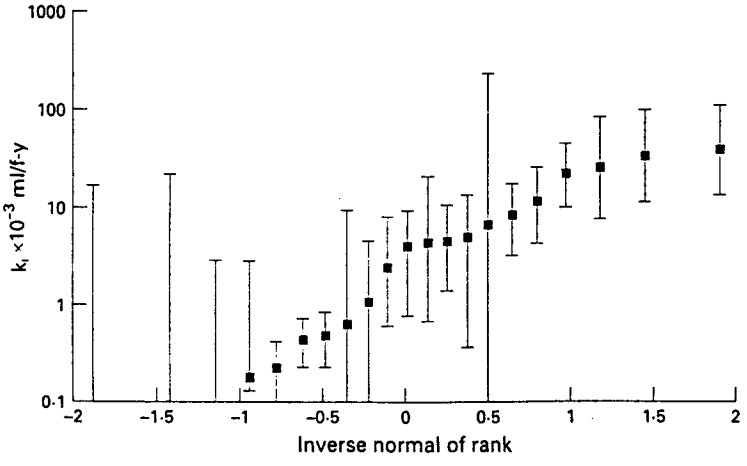

Figure 1 Distribution of maximum likelihood estimates of $k_{1,i}$ observed in 21 studies and 95% CIs about $k_{1,i}$. The lower bound on the CI about studies with error bars overlapping the abscissa equals 0. The maximum likelihood estimate for studies with no square marker equals 0. Two studies, in which only one dose group was reported, are not depicted. The shape of the distribution indicates that the $k_{1,i}$ is approximately log normally distributed.

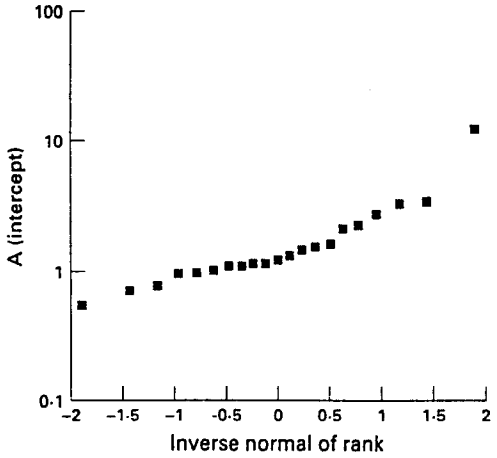

Figure 2 Distribution of maximum likelihood estimates of A_i observed in 21 studies. Two studies, in which only one dose group was reported, are not depicted. The shape of the distribution indicates that the A_i are approximately log normally distributed.

Summary of 23 investigations of the relation between cumulative exposure to asbestos and relative risk of lung cancer in 15 cohorts (the number in the first column indicates the cohorts and the letter indicates published studies of the cohort; cohort 1 was split into two, described under 1b and 1c)

1a Weill *et al* (1979).[8] 5645 men employed for at least one month between 1942 (first plant) or 1920 (second plant) and 1 January, 1955 at two asbestos cement building plants in new Orleans, Louisiana that used primarily chrysotile but also crocidolite, amosite, and silica. 51 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in 154 527 person-years of follow up accumulated to 31 December 1974. Expected lung cancer deaths (ICD-8 160–163) estimated from age, sex, race, and calendar year US rates. Cumulative exposure based on workplace air measurements beginning in 1950 and work histories including exposures only within 20 years of onset. Tobacco habits not available. $k_i = 4{\cdot}7 \times 10^{-3}$ (95% CI = $1{\cdot}5$ to 11×10^{-3}) ml/f-y. A = 0·69.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)‡*	*Lung cancer O/E*	*SMR*	*95% CI**
⩽ 10	7	19/24·7	0·77	(0·46 to 1·20)
11–50	42	8/11·4	0·70	(0·30 to 1·38)
51–100	105	1/3·8	0·26	(0·003 to 1·46)
101–200	210	9/3·1	2·90	(1·32 to 5·51)
> 200	560	14/6·2	2·26	(1·23 to 3·79)

1b †Hughes *et al* (1987).[9] 2565 men employed for at least one month between 1942 and 1 January 1970 at the first asbestos cement building materials plant in New Orleans, Louisiana that used primarily chrysotile but also crocidolite, amosite, and silica. 48 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local state, and federal records, were observed in an unreported number of total person-years of follow up accumulated to 31 December 1982 or age 80. Expected lung cancer deaths (ICD–8 162–163) estimated from age, sex, race, and calendar year Louisiana rates. Cumulative exposure based on workplace air measurements beginning in 1952 and work histories. Person-years were contributed to the cumulative exposure category attained 10 years previously. In 1969, 52% of workers were current smokers, 25% were ex-smokers, and 23% were never smokers. 55% of US men were current smokers in 1969 according to the authors. $k_i = 0{\cdot}66 \times 10^{-3}$ (95% CI = 0 to $9{\cdot}9 \times 10^{-3}$) ml/f-y. A = 0·93.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)§*	*Lung cancer O/E*	*SMR*	*95% CI**
< 6	5·6	3/2·9	1·04	(0·21 to 3·02)
6–24	18·2	9/8·0	1·12	(0·51 to 2·14)
25–49	49	2/3·7	0·55	(0·06 to 1·95)
50–99	103·6	3/3·8	0·78	(0·16 to 2·31)
⩾ 100	256·2	5/4·1	1·23	(0·39 to 2·85)

1c †Hughes *et al* (1987).[9] 4366 men employed for at least one month between 1937 and 1 January 1970 at the second asbestos cement building materials plant in New Orleans, Louisiana that used primarily chrysotile, some crocidolite, and silica. 107 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local state and federal records, were observed in an unreported number of total person-years of follow up accumulated to 31 December 1982 or age 80. Expected lung cancer deaths (ICD–8 162–163) estimated from age, sex, race, and calendar year Louisiana rates. Cumulative exposure based on workplace air measurements beginning in 1950 and work histories. Person-years were contributed to the cumulative exposure category attained 10 years previously. In 1969, 49% of workers were current smokers, 26% were ex-smokers, and 25% were never smokers. 55% of US men were current smokers in 1969 according to the authors. $k_i = 5{\cdot}2 \times 10^{-3}$ (95% CI = $0{\cdot}38$ to 14×10^{-3}) ml/f-y. A = 1·17.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)§*	*Lung cancer O/E*	*SMR*	*95% CI**
< 6	4·2	20/18·9	1·06	(0·65 to 1·63)
6–24	16·8	19/14·5	1·31	(0·79 to 2·05)
25–49	50·4	12/6·0	2·00	(1·03 to 3·49)
50–99	99·4	10/5·5	1·81	(0·87 to 3·34)
⩾ 100	229·6	12/5·2	2·31	(1·19 to 4·03)

2a †Finkelstein (1984).[10] 535 men employed for at least one year between 1948 and 1 January 1960 at an asbestos cement building materials plant in Ontario, Canada that used chrysotile, crocidolite, and silica. 26 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in 6328 person-years of follow up accumulated to 31 December 1977. Expected lung cancer rates (ICD–8 162) estimated from age and sex specific Ontario rates, 1970 to 1974, with only person-time more than 20 years after the onset of exposure contributing. Cumulative exposure based on personal and ambient workplace air measurements beginning in 1949 and work histories up to 18 years. Exposures longer than 18 years generally contributed less than 10% of the total. Person-years were contributed to the cumulative exposure category attained 10 years previously. 16 of 17 lung cancer cases queried were current or ex-smokers. $k_i = 6{\cdot}9 \times 10^{-3}$ (95% CI = 0 to 250×10^{-3}) ml/f-y. A = 3·46.

Range in study (f-y/ml)	*Value used in meta-analysis (f-y/ml)*	*Lung cancers*	*Relative rate*	*95% CI**
⩽ 30	15	3	2·31	(0·46 to 6·75)
30·1–75	52·5	6	6·15	(2·25 to 13·39)
75·1–105	90	5	12·07	(3·89 to 28·16)
105·1–150	127·5	5	9·00	(2·9 to 21·0)
> 150	165	2	2·69	(0·3 to 9·71)

of its rank. Figure 1 justifies the use of a log normal distribution for k_i in the random effects model. Figure 2 shows that a log normal distribution is appropriate for the A_i in the random effects model, as does the log normal distribution of SMRs for lung cancer found in 88 unexposed cohorts.[30] We considered using these unexposed cohorts to provide a prior estimate of the distribution of the A_i, but discovered that the distribution obtained from the asbestos cohorts differed significantly (P = 0·002).

Under the fixed effect model, from the 15 cohorts, we obtained a maximum likelihood estimate of $\hat{\kappa}_i$ equal to $0{\cdot}42 \times 10^{-3}$ (95% CI $0{\cdot}22$ to $0{\cdot}69 \times 10^{-3}$) ml/f-y. Under the random effects model, implemented because we found substantial heterogeneity in the estimates of $k_{i,i}$ and A_i, we found a maximum likelihood estimate of $\hat{\kappa}_i$ equal to $2{\cdot}6 \times 10^{-3}$ (95% CI $0{\cdot}65$ to $7{\cdot}4 \times 10^{-3}$) ml/f-y and a maximum likelihood estimate of $\hat{A}$ equal to 1·36 (95% CI 1·05 to 1·76). Our estimates of $k_{i,i}$ ranged from 0 ml/f-y[11 13 20] to 42×10^{-3} ml/f-y.[16] The dose-response model could not be fitted to two of the studies[12 25] because only one cumulative exposure category was reported. Given the substantial range of the $k_{i,i}$, we thought it imperative to measure possible causes for the heterogeneity found.

TOBACCO HABITS

The prevalence of tobacco use among asbestos workers in different cohorts, compared with their standard populations, provides a likely source of heterogeneity in the dose-response coefficient. To evaluate this source, we allowed the intercept of the dose-response curve to differ from 1·0. We then fitted a model that forced the effect of asbestos exposure to multiply the intercept. Positive interaction between occupational exposure to asbestos and tobacco use would cause higher values for $k_{i,i}$ to be found in studies in which the deviation between tobacco use in the cohort and the standard population is greatest. This required an assumption that the deviation of the intercept from 1·0 was constant across all dose groups. None the less, we expected some residual heterogeneity due to variation in relative tobacco habits. This expectation arose because cumulative tobacco use probably correlates with cumulative

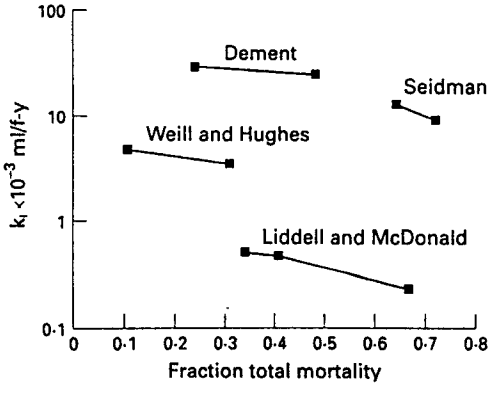

Figure 3 Fraction total mortality v $k_{i,i}$ at different stages of follow up in four cohorts.

2b Finkelstein (1938).[11] 339 men employed for at least nine years hired before 1960 at an asbestos cement building materials plant in Ontario, Canada that used chysotile, crocidolite, and silica. 20 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status, were observed in 2902 person-years of follow up accumulated to 31 October 1980. Expected lung cancer rates (ICD–8 162) estimated from age and sex specific Ontario rates, 1970–4, with only person-time 20 to 33 years after the onset of exposure contributing. Cumulative exposure based on personal and ambient workplace air measurements beginning in 1949 and work histories up to 18 years. Exposures longer than 18 years generally contributed less than 10% of the total. 16 of 17 lung cancer cases queried were current or ex-smokers. $k_i = 0$ (95% CI = 0 to 17×10^{-3}) ml/f–y. A = 12·6.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*¶	*Lung cancers*	*Relative rate*	*95% CI**
8–69	44	5	8·5	(2·7 to 19·8)
69–121	92	7	16·3	(6·5 to 33·6)
122–420	180	6	7·4	(2·7 to 16·4)

3 †Ohlson and Hogstedt (1985).[12] 1176 men employed for more than three months between 1943 and 1976 at an asbestos cement products plant in Sweden that used predominantly chrysotile, but also crocidolite and amosite. 11 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status, were observed in 26 931 person-years of follow up accumulated until age 79 from 1951 to 1982. Expected lung cancer deaths estimated from age, sex, and calendar year specific Swedish rates from 1951 to 1982. Cumulative exposure based on ambient workplace air measurements beginning in 1950s and work histories. 40% Of workers participating in a voluntary health survey in 1980 were smokers, 24% never smokers, and 36% ex-smokers. The investigators say this distribution is close to the national average. Dose-response model does not fit individual study because there was only one exposure group.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
Median = 10	10	11/9	1·23	(0·61 to 2·19)

4 †Neuberger and Kundi (1990).[13] 2816 people employed for at least three years between 1950 and 1981 at an asbestos cement products factory in Vöcklabruck, Austria that used primarily chrysotile, but also crocidolite. 49 Lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in national records, were observed in 51 218 person-years of follow up accumulated to the end of 1987. Expected lung cancer deaths (ICD–9 162) estimated from age, sex, and calendar year specific Upper Austrian rates. Cumulative exposure based on workplace air measurements beginning in 1950 and personal air samplers after 1975, both in combination with work histories. Lung cancer SMRs were 1·26 (95% CI 0·83 to 1·95) for ⩽ 25 f–y/ml and 0·96 (95% CI 0·64 to 1·43) for > 25 f–y/ml after adjustment for smoking history. $k_i = 0$ (95% CI = 0 to 22×10^{-3}) ml/f–y. A = 2·1.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
⩽ 25	12·5	25/12·8	1·95	(1·17 to 3·74)
> 25	37·5	24/15·04	1·60	(1·01 to 2·96)

5a †Dement *et al* (1994).[14] 1247 white men employed for at least one month between 1 January 1940 and 31 December 1965 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 74 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in national records, were observed in 44 131 person-years of follow up accumulated from 1 January, 1940 to 31 December 1990. Expected lung cancer deaths (ICD–9 162) estimated from age, sex, and calendar year specific US rates. Cumulative exposure based on workplace air measurements and work histories. 52·4% were current smokers, 22·3% were ex-smokers, and 25·3% were non-smokers, based on samples of the cohort. The prevalence of smokers among white men in the US population was 51·5% according to the authors. $k_i = 24 \times 10^{-3}$ (95% CI = 11 to 48×10^{-3}) ml/f–y. A = 1·32.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 2·7	1·35	11/12·3	0·89	(0·45 to 1·60)
2·7–6·8	4·75	15/5·8	2·59	(1·45 to 4·27)
6·8–27·4	17·1	10/5·1	1·96	(0·94 to 3·61)
27·4–109·5	68·45	16/5·2	3·08	(1·76 to 5·00)
> 109·5	215·4	20/2·4	8·33	(5·09 to 12·87)

5b Dement *et al* (1983).[15] 1261 white men employed for at least one month between 1 January 1940 and 31 December 1965 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 35 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in state and national records, were observed in 33 141 person-years follow up accumulated from 1 January 1940 to 31 December 1975. Expected lung cancer (ICD–7 162–163) estimated from age, sex, race, and calendar year specific US rates. Cumulative exposure based on workplace air measurements and work histories. 52·4% were current smokers, 22·3% were past smokers, and 25·3% were non-smokers, based on samples of the cohort. The prevalence of smokers among white men in the US population in 1965 was 51·5%, of ex-smokers 22·1%, and of non-smokers 26·4%, according to the authors. $k_i = 28 \times 10^{-3}$ (95% CI = 8·4 to 90×10^{-3}) ml/f–y. A = 1·56.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 2·7	1·4	5/3·58	1·40	(0·42 to 3·07)
2·7–27·4	15·1	9/3·23	2·79	(1·27 to 5·29)
27·4–109·5	68·5	7/1·99	3·52	(1·41 to 7·25)
109·5–274	191·8	10/0·91	10·99	(5·26 to 20·21)
> 274	411	2/0·11	18·18	(2·04 to 65·64)

asbestos exposure and because occupational exposure to asbestos and tobacco use interact positively to cause lung cancer.[31] A correlation between cumulative asbestos exposure and cumulative tobacco use would cause higher relative risks of lung cancer to be found in groups with a higher dose of asbestos, regardless of the effect of asbestos exposure (and therefore higher $k_{l,i}$) to be found in the studies of workers with higher cumulative asbestos exposures. To investigate the extent of the first source of heterogeneity, we plotted the A_i versus $k_{l,i}$. We found no correlation, suggesting that $k_{l,i}$ is unrelated to the extent of the deviation between tobacco use in the cohort and in the standard population. To investigate the influence of the second source of heterogeneity, we plotted the maximum dose studied in each cohort versus the cohort's $k_{l,i}$ and found the opposite of the expected correlation. The $\ln(k_{l,i})$ were negatively correlated with maximum dose ($P = 0{\cdot}001$, $r^2 = 0{\cdot}50$). We discuss this finding further in the section on dose measurement as a source of residual heterogeneity.

Two studies of one cohort reported dose-response information stratified by smoking status.[28 29] Fitting the dose-response model to each smoking stratum,[29] we found $A_{\text{non-smokers}} = 0{\cdot}19$ and $k_{l,\text{non-smokers}} = 4 \times 10^{-3}$ ml/f-y; $A_{\text{moderate smokers}} = 1{\cdot}16$ and $k_{l,\text{moderate smokers}} = 0{\cdot}7 \times 10^{-3}$ ml/f-y; and $A_{\text{heavy smokers}} = 2{\cdot}11$ and $k_{l,\text{heavy smokers}} = 0{\cdot}8 \times 10^{-3}$ ml/f-y. A test of the hypothesis of uniform k_l yielded $P = 0{\cdot}12$ and a uniform estimate of k_l in all smoker groups of $0{\cdot}8 \times 10^{-3}$ ml/f-y. Given the small number of lung cancers found among non-smokers, the test for homogeneity should not be considered particularly powerful. Pooling the observed and expected lung cancers across smoker strata within dose groups, and then implementing the dose-response model—that is, reaggregating the data into the form that they are usually reported—yielded $A_{\text{pooled}} = 0{\cdot}96$ and $k_{\text{pooled}} = 0{\cdot}9 \times 10^{-3}$ ml/f-y. Analyses of the first study of the cohort[28] yielded similar results. These data provide weak evidence that the dose-response coefficient is larger among non-smokers than among smokers and that the opposite is true for the intercept term. The pooled estimates of $k_{l,i}$ and A_i may depend, therefore, on the tobacco habits of the cohorts. The variability of tobacco habits in the cohorts included in the meta-analysis, compared with their respective standard populations, should be considered to be a source of heterogeneity.

INDUSTRY AND FIBRE TYPE

The United States Occupational Safety and Health Administration (OSHA)[2] postulated that the potency of asbestos exposure to cause lung cancer, measured on a relative scale, depends on the type of occupational exposure and type of asbestos fibre at issue. The notion is that mining and milling entails exposure to the least refined asbestos fibres, so is associated with the lowest potency per unit of cumulative exposure. Industries such as manufacturers of cement products that use asbestos of interme-

5c McDonald *et al* (1983).[16] 2543 men employed for at least one month between 1938 and 1958 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 66 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in an unreported number of person-years of follow up accumulated from 1 January 1938 to 31 December 1977. Expected lung cancer deaths (ICD-7 160–164) estimated from age, sex, race, and calendar year specific South Carolina rates. Cumulative exposure based on workplace air measurements and work histories. A lag time of 10 years before death or 1977 was imposed in determining exposure and only deaths 20 or more years after first employment were included. Cite Dement *et al* (1983)[15] for smoking habits. $k_i = 42 \times 10^{-3}$ (95% CI = 15 to 120×10^{-3}) ml/f-y. A = 1·09.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 10	7	31/21·66	1·43	(0·97 to 2·03)
10– < 20	21	5/2·74	1·83	(0·59 to 4·26)
20– < 40	42	8/2·63	3·04	(1·31 to 5·99)
40– < 80	84	7/1·67	4·20	(1·68 to 8·64)
⩾ 80	168	8/0·77	10·32	(4·47 to 20·47)

6 †Peto *et al* (1985).[17] 3211 men first employed between 1933 and 1974 at an asbestos textile factory in Rochdale, England that used principally chysotile, but also crocidolite. 132 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in company and national records, were observed in an unreported number of person-years of follow up accumulated over an unstated period. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for England and Wales. Cumulative exposure based on workplace air measurements and work histories. A lag time of 5 years was imposed in determining exposure and only deaths 20 or more years after first employment were included. No information on tobacco habits. $k_i = 4{\cdot}1 \times 10^{-3}$ (95% CI = 0·8 to $9{\cdot}8 \times 10^{-3}$) ml/f-y. A = 1·10.

Range in study (py/ml)	*Value used in meta-analysis (f-y/ml)‖*	*Lung cancer O/E*	*SMR*	*95% CI**
< 1000	6·0	34/29·53	1·15	(0·80 to 1·61)
1000–2000	40·3	8/7·66	1·04	(0·45 to 2·06)
2000–3000	71·7	11/6·60	1·67	(0·83 to 2·98)
3000–4000	99·3	6/5·66	1·06	(0·39 to 2·31)
4000–5000	130·0	10/4·29	2·33	(1·12 to 4·29)
⩾ 5000	258·8	24/10·83	2·22	(1·42 to 3·30)

7 †McDonald *et al* (1982).[18] 4137 men first employed between 1937 and 1 January 1959 for at least one calendar month at an asbestos textile factory in Pennsylvania that used principally chrysotile, but also crocidolite and amosite. 70 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in an unreported number of person-years of follow up accumulated to 31 December 1977. Expected lung cancer deaths (ICD–7 162–164) were estimated from age, sex, and calendar year specific rates for Pennsylvania. Cumulative exposure based on workplace air measurements beginning in 1956 and work histories. A lag time of 10 years was imposed in determining exposure and only deaths 20 or more years after first employment were included. Nine of 36 workers first employed between 1910 and 1919 had never smoked. $k_i = 36 \times 10^{-3}$ (95% CI = 13 to 110×10^{-3}) ml/f-y. A = 0·53.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 10	7	21/31·4	0·67	(0·41 to 1·02)
10– < 20	21	5/6·0	0·84	(0·27 to 1·94)
20– < 40	42	10/6·41	1·56	(0·75 to 2·87)
40– < 80	84	6/3·75	1·60	(0·58 to 3·48)
⩾ 80	168	11/2·64	4·16	(2·08 to 7·46)

8 †Henderson and Enterline (1979).[19] 1075 men age ⩾ 65 who retired between 1941 and 1967 from an asbestos products manufacturing factory in the United States that used chrysotile, crocidolite, and amosite. 63 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated through 31 December 1973. Expected lung cancer deaths (ICD–7 162–163) were estimated from white male rates for the United States. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_i = 2{\cdot}5 \times 10^{-3}$ (95% CI = 0·6 to $8{\cdot}4 \times 10^{-3}$) ml/f-y. A = 1·46.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)***	*Lung cancer O/E*	*SMR*	*95% CI**
< 125	86·8	19/9·6	1·98	(1·19 to 3·09)
125–249	254·8	9/5·0	1·80	(0·82 to 3·42)
250–499	492·8	19/5·8	3·28	(1·97 to 5·12)
500–749	848·4	9/2·0	4·50	(2·05 to 8·54)
⩾ 750	1366·4	7/0·9	7·78	(3·12 to 16·03)

diate refinement are associated with intermediate potency. Industries that use the most refined asbestos—the asbestos most enriched in long thin fibres—are associated with the highest potency. As for fibre type, it has been postulated that chrysotile asbestos is least potent and other forms more potent. We investigated these potential sources of heterogeneity by categorising each cohort by industry type (mining and milling, cement and cement products, or manufacturing and textile products) and by fibre type (predominantly chrysotile, chrysotile mixed with other, or other).

Under the fixed effect model, we found that these industry categories were a significant source of heterogeneity ($P < 0{\cdot}001$). The fixed effect dose-response coefficient for the mining and milling cohorts was $\hat{\kappa}_{i,mm} = 0{\cdot}3 \times 10^{-3}$ (95% CI 0·01 to $0{\cdot}5 \times 10^{-3}$) ml/f-y, for the cement products cohorts it was $\hat{\kappa}_{i,cem} = 3{\cdot}4 \times 10^{-3}$ (95% CI 0·1 to $8{\cdot}8 \times 10^{-3}$) ml/f-y, and for the manufacturing and textile cohorts it was $\hat{\kappa}_{i,man} = 7{\cdot}7 \times 10^{-3}$ (95% CI 4·7 to 12×10^{-3}) ml/f-y. Addition of a variable representing a uniform multiplicative modification to the industry specific dose-response coefficients for cohorts exposed to predominantly chrysotile fibres added no significant information ($P = 0{\cdot}58$), suggesting that after accounting for industry type, fibre type added no significant heterogeneity. Ignoring the industry specificity, the uniform multiplicative modification to the overall $\hat{\kappa}_i$ under the fixed effect model for cohorts exposed to predominantly chrysotile fibre equaled 0·05 (95% CI 0·02 to 0·14) with $\hat{\kappa}_i = 5{\cdot}4 \times 10^{-3}$ (95% CI 2·5 to 11×10^{-3}) ml/f-y.

Under the random effects model, applied to each of the three subsets of cohorts, we found insufficient evidence that industry category was a significant source of heterogeneity ($P = 0{\cdot}58$). The maximum likelihood estimates of the industry specific dose-response coefficients under the random effects model were similar to those estimated under the fixed effect model. The uniform multiplicative modification to the overall $\hat{\kappa}_i$ under the random effects model for cohorts exposed to predominantly chrysotile fibre equaled 0·19 (95% CI 0·02 to 1·6) with $\hat{\kappa}_i = 7{\cdot}9 \times 10^{-3}$ (95% CI 1·2 to 43×10^{-3}) ml/f-y. Fibre type, even independent of industry type, did not contribute significantly to the heterogeneity under the random effects model.

The disparity in the strength of the evidence supporting the hypothesis of industry specific dose-response coefficients under the fixed and random effects models probably arises from the treatment of the intercept terms. Under the fixed effect model, the A_i are fitted to their maximum likelihood value conditional on the dose-response coefficient, whether it be the summary or industry specific measure. The strength of the evidence supporting industry specific dose-response coefficients under the fixed effect model reflects both the goodness of fit of the dose-response and the additional freedom of fitting the intercept terms conditional on three, rather than

9 †McDonald *et al* (1984).[20] 3513 men employed for one month before 1 January 1959, and who had a social security number, at an asbestos friction products manufacturing factory in Connecticut that used chrysotile nearly exclusively. 89 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated to 31 December 1977. Expected lung cancer deaths (ICD–7 162–164) were estimated from age, sex, race, and calendar year specific rates for Connecticut. Cumulative exposure based on workplace air measurements and work histories. Only deaths 20 years or more years after first employment were included. No history of tobacco use reported. $k_i = 0$ (95% CI = 0 to 3×10^{-3}) ml/f-y. A = 1·6.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 10	7	55/32·9	1·67	(1·26 to 2·18)
10– < 20	21	6/5·9	1·02	(0·37 to 2·21)
20– < 40	42	5/4·7	1·05	(0·34 to 2·48)
40– < 80	84	6/3·7	1·63	(0·59 to 3·53)
⩾ 80	168	1/1·8	0·55	(0·01 to 3·09)

10a Seidman *et al* (1979).[21] 820 white men employed for between less than one month and 13 years beginning in June 1941 to December 1945 and ending in November 1954 at an asbestos insulation factory in Paterson, New Jersey that used amosite nearly exclusively. 83 lung cancer deaths, ascertained by coding of death certificates, were observed in an unreported number of person-years of follow up accumulated to the end of 1977. Expected lung cancer deaths (ICD-6 to ICD-8) were estimated from age, sex, race, and calendar year specific rates for New Jersey. Cumulative exposure based on duration of work and fibre concentrations observed in similar industries (Nicholson, 1983).[5] Only deaths five or more years after first employment were included. No history of tobacco use reported. $k_i = 12 \times 10^{-3}$ (95% CI = $4·6 \times 10^{-3}$ to 27×10^{-3}) ml/f-y. A = 2·80.

Range in study	*Value used in meta-analysis (f-y/ml)††*	*Lung cancer O/E‡‡*	*SMR*	*95% CI**
< 1 month	1·4	3/1·46	2·06	(0·41 to 6·00)
1 month	3·15	5/1·84	2·72	(0·88 to 6·34)
2 months	5·95	6/2·26	2·66	(0·97 to 5·78)
3–5 months	10·15	8/3·35	2·39	(1·03 to 4·71)
6–11 months	20·65	12/5·05	4·75	(1·23 to 4·15)
1 year	44·8	155/2·44	6·15	(3·44 to 10·14)
⩾ 2 years	166·95	34/4·30	7·91	(5·47 to 11·05)

10b †Seidman *et al* (1986).[22] 820 white men employed for between less than one month and 13 years beginning in June 1941 to December 1945 and ending in November 1954 at an asbestos insulation factory in Paterson, New Jersey that used amosite nearly exclusively. 102 lung cancer deaths, ascertained by coding of death certificates, were observed in an unreported number of person-years of follow up accumulated to 31 December 1982. Expected lung cancer deaths (ICD-6 to ICD-9) were estimated from age, sex, race, and calendar year specific rates for New Jersey. Cumulative exposure based on duration of work and fibre concentrations observed in similar industries (Nicholson, 1983).[5] Only deaths five or more years after first employment were included. No history of tobacco use reported. $k_i = 8·8 \times 10^{-3}$ (95% CI = $3·4$ to 18×10^{-3}) ml/f-y. A = 3·33.

Range in study (f-y/ml)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 6·0	3	14/5·31	2·64	(1·44 to 4·42)
6·0–11·9	9	12/2·89	4·15	(2·14 to 7·25)
12·0–24·9	18·5	15/3·39	4·42	(2·47 to 7·30)
25·0–49·9	37·5	12/2·78	4·32	(2·23 to 7·54)
50·0–99·9	75	17/2·38	7·14	(4·16 to 11·44)
100·0–149·9	125	9/1·49	6·04	(2·76 to 11·47)
150·0–249·9	200	12/1·32	9·09	(4·69 to 15·88)
⩾ 250·0	325	11/0·94	11·70	(5·83 to 20·94)

11a McDonald *et al* (1986).[23] 406 men employed for at least one year before 1 January 1963 at a vermiculite mine in Montana, at which the ore contained tremolite asbestos. 23 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with family, local, and Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated to 1 July 1983. Expected lung cancer deaths (ICD–8 160–163) were estimated from age and calendar year specific rates for US white men. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_i = 1·1 \times 10^{-3}$ (95% CI = 0 to $4·7 \times 10^{-3}$) ml/f-y. A = 2·32.

Range in study (f-y/ml)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
0– < 25	12·5	7/3·43	2·04	(0·82 to 4·21)
25– < 200	112·5	5/2·54	1·97	(0·63 to 4·59)
200– < 500	350	7/0·93	7·53	(3·02 to 15·51)
⩾ 500	2000	4/0·72	5·58	(1·49 to 14·22)

one, dose-response coefficients. Under the random effects model, the A_i are assumed to derive from a distribution of intercepts. We allowed the distribution to be fitted to each industry, thus providing the greatest power to detect differences in dose-response. None the less, constraining the intercept term to an industry specific distribution significantly reduced the strength of the evidence supporting the notion of industry specific dose-response coefficients. We conclude that industry type is a source of heterogeneity in these cohorts, but that the importance of its contribution to the heterogeneity of the dose-response coefficients is overstated under the fixed effect model.

DOSE MEASURE

Equivalent dose measures assigned to cumulative exposure categories in different cohorts likely reflect vastly different actual cumulative doses. We expect that differences in methods of measuring fibre concentrations and assigning cumulative exposures across studies introduce an important source of heterogeneity in dose-response coefficients. We explain with three lines of evidence. Firstly, for most cumulative exposure categories we assigned the midpoint of the range as the dose to be used in the dose-response analysis. For four cohorts[19 9 17] we used the mean cumulative exposure because it had been provided for each cumulative exposure category. Reanalysing these studies based on the midpoints rather than the means, we obtained ratios of $k_{l,i,\text{mean}}/k_{l,i,\text{midpoint}}$ of 1·0, 0·6, 0·7, and 1·5, respectively. Thus, substituting the midpoint for the mean, as we were forced to do for most cohorts, can artificially inflate or deflate the dose-response coefficient and must contribute to its heterogeneity. Secondly, some studies reported cumulative exposure categories in units other than f-y/ml. For those studies, we converted from the stated units to f-y/ml with the following conversion factors: f-y/ml = 1·4 × mppcf-y (million particles per cubic foot-year) for the cement and manufacturing industries[5]; f-y/ml = 3 × mppcf-y for the mining and milling industries[5]; and f-y/ml = 1/35 × py/ml (particles per millilitre–year) for the textile industry.[17] We parameterised these three conversion factors and maximised the likelihood under the fixed effect model with respect to k_l, A_i, and the conversion parameters. We obtained estimates of the conversion factors equal to f-y/ml = 0·6 × mppcf-y for the cement and manufacturing industry; f-y/ml = 0·07 × mppcf-y for the mining and milling industry; and f-y/ml = ppcf-y/80 for the textile industry. We cannot distinguish the extent to which the disparity between the published conversion factors and these maximum likelihood estimates depend on industry specific differences in fibre potency versus heterogeneity in estimating cumulative exposures between studies. We suspect that both factors play some part. Thirdly, we noted above a significant correlation between $k_{l,i}$ and the maximum cumulative exposure studied. This correlation provides the strongest evi-

11b †Amandus and Wheeler (1987).[24] 575 men employed before 1970 for at least one year at a vermiculite mine in Montana, at which the ore contained tremolite asbestos. 20 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with family, local, and Social Security Administration records, were observed in 13 502 person-years of follow up accumulated to 31 December 1981. Expected lung cancer deaths (ICD-8 162–163) were estimated from age and calendar year specific rates for US white men. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_i = 4{\cdot}5 \times 10^{-3}$ (95% CI = 0·7 to 21×10^{-3}) ml/f–y. A = 1·12.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI**
< 50	25	6/4·0	1·51	(0·55 to 3·26)
50–99	75	2/1·4	1·46	(0·16 to 5·16)
100–399	250	2/1·9	1·06	(0·12 to 3·80)
> 399	750	10/1·7	5·76	(2·82 to 10·82)

12 †Armstrong *et al* (1988).[25] 6506 men employed between 1943 and 1967 at a crocidolite mine in Western Australia. 91 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with local and national records, were observed in 95 264 person-years of follow up accumulated to 31 December 1980. Expected lung cancer deaths (ICD–9) were estimated from age, sex, and calendar year specific rates for Western Australia. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. Dose-response model does not fit individual study because there was only one exposure group.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI*
55·8% of workers < 10 29·1% 10–100 4·7% > 100 10·4% unknown	28·8 = (0·558 × 5+ 0·291 × 55+ 0·047 × 150)/ (0·558 + 0·291 +0·047)	91/34·5	2·64	(2·15 to 3·24)

13 †Piolatto *et al* (1990).[26] 1058 men employed for at least one year between 1946 and 1987 at a chrysotile mine in Balengero, Italy. 22 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with population registries, were observed in 27 010 person-years of follow up accumulated to 31 December 1987. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Italy. Cumulative exposure based on workplace air measurements and work histories, lagged one year. Deaths and person-years beyond age 80 were excluded. No history of tobacco use reported. $k_i = 0{\cdot}2 \times 10^{-3}$ (95% CI = 0 to $2{\cdot}9 \times 10^{-3}$) ml/f–y. A = 1·01.

Range in study (f–y/ml)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI*
< 100	50	4/5·1	0·8	(0·21 to 2·01)
100–400	250	8/6·1	1·3	(0·56 to 2·58)
> 400	1000	10/8·7	1·1	(0·55 to 2·11)

14a Liddell *et al* (1977).[27] 10 951 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 214 lung or trachea cancer deaths (ICD–7) were observed in an unreported number of person-years of follow up accumulated to 31 December 1973. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories. Person-time and deaths before 20 years after first employment were excluded. History of tobacco use known for a large portion of the cohort. $k_i = 0{\cdot}5 \times 10^{-1}$ (95% CI = 0·2 to $0{\cdot}9 \times 10^{-1}$) ml/f–y. A = 0·76.

Range in study (mppcf–y)	*Value used in meta-analysis (f–y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI*
< 3	4·5	28/31·93	0·88	(0·58 to 1·27)
3– < 10	19·5	11/19·09	0·58	(0·29 to 1·03)
10– < 30	60	17/18·76	0·91	(0·53 to 1·45)
30– < 100	195	37/40·08	0·92	(0·65 to 1·27)
100– < 300	600	34/45·02	0·76	(0·52 to 1·06)
300– < 600	1350	43/31·04	1·39	(1·00 to 1·87)
⩾ 600	3900	28/12·13	2·31	(1·51 to 3·29)

dence that equivalent cumulative exposures reported for different cohorts represent different effective doses.

DURATION VERSUS CONCENTRATION OF EXPOSURE

We considered the possibility that short exposure to high concentrations might confer different relative risk of lung cancer than long exposure to low concentrations, although both would entail similar cumulative exposures. Were this the case, then different patterns of exposure in different cohorts would contribute to heterogeneity. To test the hypothesis, we fitted the fixed effect model to the mean duration of exposure and mean concentration of exposure data provided in one study[28] and to the midpoint exposure and midpoint concentration data provided in a second.[8] We added to the relative risk model coefficients applied only to the concentration term and only to the duration term, while retaining the coefficient (k_i) applied to the product of the two. For both studies, the additional coefficients added no significant information to the relative risk model ($P = 0{\cdot}42$[28] and $P = 0{\cdot}43$[8]). We conclude that, within the cumulative dose ranges found in the studies at issue, the product of concentration and duration of exposure adequately measured dose. Thus, variation in patterns of exposure within cohorts is unlikely to be an important source of heterogeneity in the dose-response coefficient.

COHORT AGE

McDonald *et al*[29] argue that when comparing occupational cohorts, one must take account of "the stage reached in their evolution and the level of mortality observed." We tested for the stage of evolution as a source of heterogeneity by plotting the $k_{i,i}$ measured at different stages of follow up in four cohorts versus the fraction of the cohort that had died at that stage of follow up (fig 3). We noted that for all four cohorts, the $k_{i,i}$ was lowest for the latest follow up. This pattern may reflect declining relative risk due to increasing rates of lung cancer among the standard populations as the cohort ages. We noted no consistent pattern across cohorts in the relation of $k_{i,i}$ to the total mortality fraction, either in the four cohorts shown or in all cohorts (not shown). We conclude that the total mortality fraction is not an important source of heterogeneity of $k_{i,i}$. Our decision to include the latest follow up from each cohort, to maximise precision, may slightly bias the summary estimates of k_i toward the null.

CALENDAR PERIOD OF EXPOSURE

We considered the possibility that the calendar period of exposure of different cohorts might contribute to the heterogeneity of their $k_{i,i}$. For each cohort, we plotted its $k_{i,i}$ versus the date of first employment, date of last employment, and difference between date of last follow up and date of last employment. We discerned no patterns in any of these plots, so consider the calendar period of exposure to be a negligible source of heterogeneity.

14b McDonald *et al* (1980).[24] 10 939 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 250 lung cancer deaths (ICD-7 162–164) ascertained by coding of death certificates obtained after checking vital status, were observed in an unreported number of person-years of follow up accumulated to 31 December 1975. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories. Person-time and deaths before 20 years after first employment were excluded. History of tobacco use known for a large portion of the cohort, stratified by cumulative exposure. k_i = $0{\cdot}5 \times 10^{-3}$ (95% CI = $0{\cdot}2$ to $0{\cdot}8 \times 10^{-3}$) ml/f-y. A = 0·96.

Range in study (y, mppcf)	*Value used in meta-analysis (f-y/ml)§§*	*Lung cancer O/E*	*SMR*	*95% CI*
< 1,y 2·6 mppcf	1·6	19/16·2	1·17	(0·71 to 1·83)
< 1,4·3	5·2	12/13·2	0·91	(0·47 to 1·59)
< 1,14·4	17·3	9/10·2	0·88	(0·40 to 1·68)
< 1,78·0	117	7/8·8	0·80	(0·32 to 1·64)
1– < 5,2·5	9·8	5/7·6	0·66	(0·21 to 1·54)
1– < 5,6·2	40·9	13/13·7	0·95	(0·50 to 1·62)
1– < 52,3·6	177	6/7·32	0·82	(0·30 to 1·78)
1– < 58,2·6	693·8	5/6·4	0·78	(0·25 to 1·82)
5– < 20,2·5	48	13/9·2	1·41	(0·75 to 2·42)
5– < 20,5·6	174·7	14/11·5	1·22	(0·67 to 2·04)
5– < 20,17·0	535·5	7/8·4	0·83	(0·33 to 1·72)
5– < 20,62·3	2112·0	16/7·4	2·17	(1·24 to 3·51)
⩾ 20,4·2	313·7	28/23·1	1·21	(0·81 to 1·75)
⩾ 20,9·4	784·0	20/18·55	1·08	(0·66 to 1·67)
⩾ 20,19·2	1647·4	24/10·9	2·20	(1·41 to 3·28)
⩾ 20,46·8	4324·3	32/12·1	2·65	(1·81 to 3·73)

14c McDonald *et al* (1993).[25] 10 925 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 321 lung cancer deaths (ICD–8 or 9 162), ascertained by coding of death certificates obtained after checking vital status, were observed in an unreported number of person-years of follow up accumulated to 31 December 1989. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories accumulated to the age of 55. History of tobacco used known for a large portion of the cohort, stratified by cumulative exposure. $k_i = 0{\cdot}2 \times 10^{-3}$ (95% CI = $0{\cdot}1$ to $0{\cdot}4 \times 10^{-3}$) ml/f-y. A = 1·22.

Range in study (mppcf-y)	*Value used in meta-analysis (f-y/ml)*	*Lung cancer O/E*	*SMR*	*95% CI*
< 3	4·5	36/31·4	1·14	(0·80 to 1·58)
3– < 10	19·5	40/25·3	1·58	(1·13 to 2·15)
10– < 30	60	33/31·3	1·05	(0·73 to 1·48)
30– < 60	135	39/24·4	1·60	(1·14 to 2·19)
60– < 100	240	30/22·8	1·32	(0·89 to 1·88)
100– < 200	450	32/28·3	1·13	(0·77 to 1·60)
200– < 300	750	20/17·3	1·15	(0·71 to 1·78)
300– < 400	1050	16/10·7	1·50	(0·86 to 2·44)
400– < 1000	2100	42/25·4	1·65	(1·19 to 2·23)
⩾ 1000	4200	22/7·2	3·04	(1·90 to 4·60)

*95% CI calculated by an approximation to the Poisson[a] for our study, not by the original investigators.
†Represents the cohort in the calculation of the summary measures.
‡Unless otherwise noted, cumulative exposures assigned to ranges were calculated as the mid-point of the range, with application of a conversion factor of 3 f-y/ml per mppcf-y for mining and milling cohorts and 1·4 f-y/ml per mppcf-y for all other cohorts.[5] Values were assigned to open ended ranges by repeating the pattern observed at lower exposures.
§Assigned as the mean cumulative exposure reported by the authors, multiplied by 1·4 f-y/ml per mppcf-y.
¶Assigned the mean cumulative exposure reported by the authors.
‖Assigned the mean cumulative exposure reported by the authors, multiplied by 1/35 f-y/ml per py/ml.[17]
**Assigned the mean cumulative exposure reported by the authors, multiplied by 1·4 f-y/ml per mppcf-y.
††Assigned the values reported in another review.[5]
‡‡As reported in another review.[5]
§§Assigned the product of average duration of exposure and average exposure concentration reported by the authors, multiplied by 3 f-y/ml per mppcf-y.

STANDARDISED MORTALITY RATIOS AS MEASURES OF RELATIVE RISK

Rothman[32] emphasises that comparisons of SMRs across exposure categories can be misleading because each SMR is standardised to a different population. Consider, for example, that the relative risk of lung cancer associated with asbestos exposure is positively correlated with age. Assume further that the highest cumulative exposure groups contain the oldest men. Under these assumptions, the SMRs in different cumulative exposure categories within a cohort might differ systematically and appear as a dose-response relation. The systematic variation would arise because of the different age structures of the subpopulations in each cumulative exposure category, no matter whether the exposure categories exerted any influence. The extent of the modification of $k_{l,i}$ might differ for each cohort, so could be an important source of heterogeneity. Two lines of evidence indicate otherwise. Firstly, Nicholson *et al*[4] showed that, after accounting for duration of exposure to asbestos, age no longer affected the relative risk measure. The cumulative exposure categories within a study are essentially strata of durations of exposure. The potentially different underlying age structures should not substantially modify the SMRs. Secondly, one study[14] presented both SMRs and standardised rate ratios (SRRs) (relative effect measures standardised to a single population). We applied the fixed effect model to both sets of measures. With the SMRs, we obtained maximum likelihood estimates of $A_i = 1{\cdot}32$ and of $k_{l,i} = 24 \times 10^{-3}$ (95% CI = 11 to 48 $\times 10^{-3}$) ml/f-y. With the SRRs, we obtained maximum likelihood estimates of $A_i = 1{\cdot}49$ and of $k_{l,i} = 16 \times 10^{-3}$ (95% CI = 7 to 32 $\times 10^{-3}$) ml/f-y. The rates standardised to the same population gave a slightly lower estimate of the dose-response coefficient. We see no reason that standardisation to a single population across cumulative exposure categories within each cohort would have an effect of the same size or in the same direction for all cohorts. Standardisation to different populations, as is the norm in the cohorts included in the meta-analysis, may be a source of heterogeneity.

MISCLASSIFICATION OF MESOTHELIOMA

Misclassification of mesothelioma as lung cancer may be a significant source of heterogeneity because mesothelioma occurs predominantly among the subcohorts with high cumulative exposure to non-chrysotile asbestos and a long latency period.[21] Studies that include such subcohorts, if unduly influenced by misclassification of mesothelioma, should give the highest $k_{l,i}$. Recall, however, that we found both cohort age (a proxy for latency) and fibre type after controlling for industry type to be insubstantial sources of heterogeneity. Recall also that we found a negative correlation between the highest cumulative exposure category in a study and its $k_{l,i}$. These findings suggest that misclassification of mesothelioma as lung cancer is not a significant source of heterogeneity.

Discussion

Our analysis of this collection of occupational cohorts generated two summary measures, and one set of industry specific summary measures, of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Under the fixed effect model, we found the measure of potency of asbestos to cause lung cancer, $\hat{\kappa}_l$, to be $0{\cdot}42 \times 10^{-3}$ (95% CI $0{\cdot}22$ to $0{\cdot}69 \times 10^{-3}$) ml/f-y. Under the random effects model, we found that $\hat{\kappa}_l = 2{\cdot}6 \times 10^{-3}$ (95% CI $0{\cdot}65$ to $7{\cdot}4 \times 10^{-3}$) ml/f-y and $\hat{A} = 1{\cdot}36$ (95% CI 1·05 to 1·76). The

fixed effect dose-response coefficient for the mining and milling cohorts was $\hat{\kappa}_{l,mm} = 0{\cdot}25 \times 10^{-3}$ (95% CI 0·01 to 0·45 × 10^{-3}) ml/f-y, for the cement products cohorts was $\hat{\kappa}_{l,cem} = 3{\cdot}4$ (95% CI 0·1 to 8·8 × 10^{-3}) ml/f-y, and for the manufacturing and textile cohorts was $\hat{\kappa}_{l,man} = 7{\cdot}7$ (95% CI 4·7 to 12 × 10^{-3}) ml/f-y.

Given the variety of choices, the reader might ask "which summary measure is right?" At this time, no unique correct answer exists. The choice depends on the beliefs and assumptions implicit in the context of the question. If the context requires an analysis in which each cohort measures the same dose-response relation, with only random error introduced, then the summary measure found under the fixed effect model should be chosen. If the context allows for a distribution of dose-response relations, and allows for the distribution to derive largely from unknown or unimportant (for the question) sources of heterogeneity, then the summary measure found under the random effects model should be chosen.

If the question assumes that industry type is an important source of heterogeneity in the dose-response relation *and* that the intercept term representing background risk of lung cancer compared with the standard population should not be constrained, then the industry specific summary measures under the fixed effect model should be chosen. The second assumption is as important as the first, because under the random effects model, which constrains the intercept term to a reasonable distributional form, the industry specific dose-response relations explained an insignificant fraction of the heterogeneity.

An earlier, semiquantitative review by Nicholson for OSHA[5] of the relation between cumulative exposure to asbestos and relative risk of lung cancer gave a potency of $\hat{\kappa}_l = 10 \times 10^{-3}$ (range 3–30 × 10^{-3}) ml/f-y. The central tendency was selected as approximately the geometric mean of the individual $k_{l,i}$, and the range about the estimate derived primarily from consideration of uncertainties in the dose-measurements. The OSHA[2] adopted this estimate of $\hat{\kappa}_l$ in their 1986 rules. Our estimates for potency, $\hat{\kappa}_l$, are 24-fold lower than OSHA's under the fixed effect model and fourfold lower under the random effects model. Further, our 95% CIs exclude 10 × 10^{-3} ml/f-y under both models. Our study differs from the earlier review in the following respects. Firstly, we had available updates to many cohorts with additional cohort information that had not then been published. As shown above, updates have consistently yielded a lower estimate of $k_{l,i}$. Secondly, we allowed the intercept term to depart from a fixed value of 1·0 to allow for confounding, most likely by smoking, or the healthy worker effects. The earlier review, when calculating $k_{l,i}$ by regression methods, fixed the intercept at 1. Thirdly, we effectively weighted each measurement of relative risk within a cohort by the number of cases of lung cancer. The earlier review usually weighted all measurements of relative risk within a cohort equally. Fourthly, we weighted each study by the number of cases of lung cancer in the study to obtain our summary measures of effect. The earlier review, by choosing the approximate geometric mean, weighted each study uniformly. Fifthly, we calculated a summary measure under both a fixed effect model and a random effects model. The earlier review, by virtue of choosing the geometric mean of the individual study $k_{l,i}$, is more analogous to a random effects model.

The issue of publication bias must, by convention, be considered. We do not deny the possibility that unpublished studies, or published studies unknown to us, exist that may alter these findings, possibly toward the null. Given the well accepted role of occupational exposure to asbestos in causing lung cancer, we find it unlikely that the 95% CI about our summary measures would overlap the null if these absent studies were to be included. Publication bias of this sort in meta-analyses is analogous to the problem of unknown confounders in aetiological research. The role of unknown confounders in aetiological research or of publication bias in meta-analyses can never be rulled out. The extent to which a given aetiological association is confounded by unknown causes, or to which a given meta-analytical result is influenced by publication bias, is a matter of individual judgment; it cannot be subjected to the scientific method.

A second sort of publication bias is of more concern to this meta-analysis. It may be that only cohorts that, in aggregate, show a positive relation between asbestos exposure and relative risk of lung cancer are subjected to further analysis and expenditure of resources by disaggregation into cumulative exposure categories. Such a practice would bias the results of this meta-analysis away from the null. It may also be that investigators, upon obtaining a null result, would choose to disaggregate the cohort into cumulative exposure categories in the hopes of finding effects in the highest exposure groups or a positive dose-response trend. Apparent examples of both possibilities exist in the publications upon which we based our report. We cannot assess the extent to which the two possibilities balance within the larger body of scientific literature.

1 International Agency for Research on Cancer (IARC). *Overall evaluations of carcinogenicity: an updating of IARC monographs. Vols 1–42 (suppl 7).* Lyon: IARC, 1987.

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LETTER TO THE EDITORS

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Re: "Renal cell cancer correlated with occupational exposure to trichloroethylene"

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Vamvakas et al. (1998) conducted a case-control study of occupational exposure to trichloroethylene and risk of renal cell cancer. They report "an association of renal cell cancer with long-term exposure to C_2HCl_3 [trichloroethylene] (odds ratio 10.80: 95% CI: 3.36–34.75)." However, significant flaws in the selection of controls and inadequate description of the means of gathering crucial information render the study's results unreliable.

Cases were 58 of 73 patients with renal cell cancer diagnosed between 1 December 1987 and 31 May 1992 in a country hospital in North Rhine–Westphalia. Controls were 84 of 112 people who in 1993 were patients in the accident wards of three hospitals *other* than the hospital whence the cases were drawn, but within approximately 20 km of the case hospital.

Controls should be a sample of the population whence the cases arose – they should be the subjects' peers in place and time. Instead, Vamvakas and colleagues explicitly excluded as controls individuals who would have presented to the cases' "country hospital in North Rhine–Westphalia," and used different, non-overlapping time periods for case and control identification. These procedures violate the tenets for case-control studies set forth in the methodologic paper referenced by Vamvakas et al. (Wacholder et al. 1992).[1]

Vamvakas et al. found a startling 33% prevalence of history of occupational exposure to trichloroethylene among cases, leading the reader to wonder whether there isn't something quite peculiar about the immediate area served by the cases' hospital. If the cases' hospital served an area with more opportunities for significant exposure to trichloroethylene than areas served by the control hospitals, then an irreparable bias was introduced. Of course, if controls had been selected from the cases' hospital, we might have learned whether *their* exposure prevalence was also extraordinary. As it is, we know (from Table 4 of Vamvakas et al.) only that 38% both of cases and of controls had occupations *potentially* involving exposure to trichloroethylene (as judged by the authors) yet, oddly, a 5.5-fold difference in *actual* trichloroethylene exposure (33% of cases versus 6% of controls) was reported.

Controls were significantly younger in 1993 than were the cases in 1987–1992; and these differences in years, in both senses, likely indicate differences in opportunities for exposure to high levels of trichloroethylene. Occupational exposure to trichloroethylene has declined dramatically in recent years: production of trichloroethylene in Western Europe declined from 205,000 tonnes in 1985 to 131,000 tonnes in 1990 (IARC 1995). Fully 26% of the controls (22 of 84) were younger than age 40 in 1993, and only 3% of the cases (2 of 58) were younger than age 40 in 1987–1992. In general, one would expect opportunities for substantial trichloroethylene exposure to be lower among the young, and lower as time progresses. In fact, only one of the 22 young controls was classified as exposed; even as both of the two young cases were classified as exposed, generating a remarkable odds ratio of 72. Further, these two young cases were likely in their mid- to late thirties (given the rarity of kidney cancer among people in their teens or twenties), whereas a substantial fraction of the young controls, being accident victims, may well have been only in their teens or twenties, and so quite unlikely to have had occupational exposure to trichloroethylene during their short and recent working lives. Clearly, the "adjustment for age" performed by the authors has not accounted for these systematic differences.

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[1] These tenets also mean that the abdominal sonography required of the controls was needless and inappropriate. This requirement likely dissuaded some, and perhaps many, of the 25% of controls who declined to participate in the study. Whether a bias was thus introduced is not known

The authors do not describe adequately how exposure information was obtained. For example, there is no description of when or where interviews were done, or of how many interviews were with "former colleagues and relatives" as opposed to with subjects themselves. Exposure information obtained from cases' next-of-kin interviewed "by physicians of the area" several years after case diagnosis or death, for example, might not be comparable to information gathered by different physicians from controls interviewed while in the accident ward of a hospital.

What quantitative impact did the invalid selection of controls, and possible biases in ascertainment of exposure information, have on the study's estimate of effect? One cannot answer precisely, but there is good evidence that the effect estimate is strongly biased upward. Using data in the Vamvakas et al. report and kidney cancer incidence data from the Cancer Registry of Saarland, Germany (Parkin et al., 1992), we constructed Table 1. The table compares kidney cancer incidence among those *not* exposed to trichloroethylene in the Vamvakas et al. (1998) study with kidney cancer incidence in a sample of the general German population. The apparent effect of aging alone in Vamvakas et al. (1998) dramatically overestimates the effect observed in the general population.

Since the apparent effect of aging is dramatically overestimated, likely because of the invalid selection of controls, the effect of trichloroethylene may well be overestimated also. Further, age and trichloroethylene exposure in the study of Vamvakas et al. appear to be strongly interdependent. Using data in Table 6 of Vamvakas et al. (1998), we calculated the synergy index (Rothman 1974) – a relative measure of the excess effect due to co-action of age and trichloroethylene exposure. For those aged 50–60, compared with those < 50, the synergy index equals 4.1. For those > 60, compared with those < 50, the synergy index equals 4.9. Thus, one cannot separate the bias evident in the apparent effect of aging from the bias one suspects in the estimated effect of trichloroethylene exposure.

More broadly, the magnitude of the result – that occupational exposure to trichloroethylene increases by 11-fold a person's risk of renal cancer – is so large as to invite wonder. As the authors note, this solvent "has been used on a large scale ... for more than eight decades." This wide-scale usage has been accompanied by considerable epidemiologic study focusing on risk of cancer. The four major cohort studies of trichloroethylene provide no evidence that occupational exposure increases risk of renal cancer: (1) Axelson et al. (1994) studied 1,421 men using trichloroethylene in Sweden and obtained a standardized incidence ratio (SIR) for kidney cancer of 1.2 (95% CI: 0.4–2.0); (2) Anttila et al. (1995) studied 3,089 men and women using trichloroethylene in Finland and obtained an SIR for kidney cancer of 0.87 (95% CI: 0.32–1.9); (3) Spirtas et al. (1991) studied 7,282 men using trichloroethylene in the United States and obtained a standardized mortality ratio (SMR) for kidney cancer of 1.1 (95% CI: 0.46–2.1); and (4) Garabrant et al. (1988) studied 14,067 men and women employed in aircraft manufacture in the United States and obtained an SMR for kidney cancer of 0.93 (95% CI: 0.48–1.6). Further, three published case-control studies have evaluated the specific hypothesis of interest: odds ratios of 1.7 (95% CI: 0.7–3.8), 3.4 (95% CI: 0.92–12.66), and 0.8 (95% CI: 0.4–2.0), have been reported (by Asal et al. 1988, Sharpe et al. 1989, and Siemiatycki 1991, respectively). These results are consistent with at most a weak association, and no result is as striking as that reported by the present study.

Of course, discrepancies in results between the present work and past work are not themselves damning. Perhaps occupational exposures to trichloroethylene were much higher in the present study than they have been in any prior investigation. Perhaps differences in stabilizers or impurities among different brands of trichloroethylene result in marked differences in carcinogenic risk. But given the serious methodologic flaws noted above, it is premature to conclude that high-level exposure to trichloroethylene is a genuine and substantial risk factor for development of renal cancer – whether for working men and women apparently highly exposed to it in North Rhine–Westphalia, or for workers farther afield.

Table 1 Kidney cancer incidence in a sample of the general German population and among those not exposed to trichloroethylene in the Vamvakas et al. (1998) study

	Ages 30 to < 50	Ages 50 to < 60	Ages 60 to < 85
Kidney cancer incidence in Germany (/100,000)[a]	5.3	25.1	48.2
Relative risk (population)	1. (reference)	4.8	9.1
Relative risk (Vamvakas et al. 1998)[b]	1.	15.4	42
Excess apparent effect in Vamvakas et al. (1998)	Not Applicable	10.6	32.9

[a] Incidence from the Cancer Registry of Saarland, Germany, 1983–1987, reported in Parkin et al. (1992), averaged over the given age range within sexes and then weighted 2/3 male and 1/3 female, per the proportion of sexes in Vamvakas et al. (1998)
[b] Relative risk of ages calculated for the group unexposed to trichloroethylene and estimated from data in Table 6 of Vamvakas et al. (1998)

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