Comments on the Weight-of-Evidence Analysis of Epidemiology Data in the May 22, 2008 NTP Report on Carcinogens Draft Background Document for Styrene

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1 Introduction

In chapter 3 of the 2008 Report on Carcinogens: Draft Background Document for Styrene (Draft Document), the National Toxicology Program (NTP) conducts a weight-of-evidence analysis of several key styrene epidemiology studies. They mostly focus on 10 cohorts of workers in the reinforced plastics and composites (RPC), styrene-butadiene latex rubber (SBR) and styrene/polystyrene (PS) industries, an occupational cohort in Finland reporting urinary concentrations of a styrene metabolite (Anttila *et al.*, 1998) and a cohort of students who attended high school adjacent to facilities that produced synthetic styrene-butadiene (Loughlin *et al.*, 1999). These are shown here in Figures 1 to 4, which graphically trace the history of the examination of particular cohorts in studies over time.

Although the NTP report is a background document and is not by itself intended to provide interpretations or conclusions, in order to support a sound process of interpretation, the available studies should be laid out objectively, with the appropriate information and analyses. Below we discuss NTP's description and analysis of the weight-of-evidence as to whether styrene should be considered carcinogenic. After discussing NTP's weight-of-evidence analysis, we describe an alternative weight-of-evidence analysis for each cancer type noted by NTP, comparing risk estimates across exposure categories and studies, and systematically evaluating consistency and coherence.

2 Assembling Evidence Across Studies

Epidemiology data can have a key role in evaluating potential human risk. Systematic reviews and quantitative meta-analyses of available epidemiology studies are important tools for synthesizing data to develop overall risk conclusions, but it is important for the evaluation process to be methodical, unbiased, and transparent (von Elm *et al.*, 2007; WHO, 2000; Stroup *et al.*, 2000; ILSI, 1995). A working group of the World Health Organization (WHO) has identified five steps, in an attempt to develop "a set of processes and general approaches to assess available epidemiological in a clear, consistent and explicit manner" (WHO, 2000). These steps include:

- Developing a review protocol;
- Identifying relevant studies;
- Systematically assessing epidemiological study validity;
- Conducting systemic overviews and/or meta-analyses; and
- Drawing conclusions from epidemiological evidence.

In the first step, researchers must design a protocol to locate studies. In order to minimize bias and provide a foundation for an informative analysis, the literature review must be comprehensive and methodical, identifying well-defined inclusion/exclusion criteria at the outset (Pai *et al.*, 2004; Stroup *et al.*, 2000). When developing rules for study inclusion criteria, several experts have asserted that it is better to be inclusive than exclusive, and that the sensitivity of the results to various inclusion criteria can be explored in a subsequent sensitivity analysis (ILSI, 1995; WHO, 2000). To achieve a meaningful evaluation, it is not enough to simply gather studies and synthesize material giving equal weight to each study. It is important to give more weight to studies with small variances because these studies give more precise outcome information (Cochrane Collaboration, 2002).

Also warranting consideration within a given study is the accuracy of exposure quantification, assessment of an appropriate latency period, proper treatment of confounders, and use of appropriate statistical analyses (Swaen, 2006; Stroup *et al.*, 2000). Evaluating consistency in outcomes for individual endpoints across studies should also be examined, keeping in mind that limitations in study design, power, statistical methods, and study population may lead to different outcomes. The variability in the results should be considered in the overall strength of the data, preferably quantitatively, through a formal heterogeneity analysis (WHO, 2000; ILSI, 1995). Alternative explanations for observed results, such as

the influence of co-exposures and other confounders, should also be considered (Wong *et al.*, 1994). Because so many of these steps involve expert judgments, sensitivity analyses can be useful for testing how various types of judgments influence overall conclusions (WHO, 2000). Finally, whether an exposure is associated with a disease should be evaluated using a scheme such as the Bradford Hill criteria, which give consideration to the strength of association, temporal relationship, biological plausibility, evidence of a dose response relationship, coherence, consistency, and specificity (Hill, 1965).

Using quantitative techniques to combine results of individual studies can increase the power of the data and the precision of conclusions (Cochrane Collaboration, 2002), but much like a more qualitative systematic review, certain steps are necessary to achieve a reliable evaluation. A straightforward pooling of participants is not a reliable approach for data synthesis, nor is averaging the results across studies (Egger *et al.*, 1997; Cochrane Collaboration, 2002, module 12, p. 1). Instead, results should be combined to account for variance among studies using a fixed or random effect model (a fixed model is commonly used in occupational studies) (Wong *et al.*, 1994). The International Life Science Institute (ILSI) has recommended conducting meta-analyses under a variety of circumstances, including the following situations: when examining heterogeneity is important; when the relationship between exposure and health effects is not clear; and when multiple studies have no consensus on the exposure-disease relationship (ILSI, 1995).

When conducting a qualitative or a quantitative analysis, thought and care must be exercised when considering whether the results for an endpoint across studies of different cohorts support the conclusion that an agent causes an increased risk of that endpoint. On the one hand, there are many factors, some known but others unknown, which differ among studies, and these hamper the comparability of the various examinations of the causality question. The populations, their age distributions, and their background exposures are different; the exposure levels and patterns are different; the methods for assessing exposure and outcomes and the follow-up period may be different; and different sets of potential confounders apply. The power of studies to detect effects differs depending on these factors, study size, and the degree of exposure. An uncritical arraying of study results as though they were repeated measurements of exactly the same phenomenon risks confusing effects of these extraneous factors with properties of the agent being studied.

On the other hand, the hallmark of a true causative effect is that it appears consistently from setting to setting. Assessing the degree of consistency of results across studies is a critical tool for distinguishing between a true effect of the chemical being studied and a spurious or apparent one that

arises in some studies (for study-specific reasons not attributable to the agent in question) but not in others. Considering studies together can increase their collective statistical power by revealing a common tendency for all outcomes to deviate from the null in a similar way, even if the outcomes in studies of lesser power are not by themselves significant. Intelligible patterns of increasing risk with increasing exposure constitute a sign that the varying levels of the agent are a consequential factor. That is, comparing outcomes across studies, assessing their consistency or lack thereof and the factors that are or are not reliably associated with apparent effect – in other words, a weight-of-evidence analysis – is an essential aspect of the critical assessment of a body of studies and their bearing on conclusions about the agent's ability to influence disease probabilities.

In short, a simplistic or naïve comparison of results across studies is to be discouraged, but a careful and insightful one, done with appropriate skepticism and bearing in mind the pitfalls, is essential. Such a comparison can be accomplished by a critical review in which consistency and lack of consistency are examined and the patterns evaluated by noting the differences among studies and evaluating whether a common causal pattern attributable to the chemical in question constitutes a strongly supported explanation of the patterns in view of the evidence for the role of extraneous factors, differences in exposure levels or co-exposures, differing confounding factors, differences in study power, and so on. It may also be possible to treat these questions quantitatively in a formal meta-analysis, in which the patterns of commonality are assessed vis-à-vis the degrees of study-by-study heterogeneity evident when analyzing the whole body of data.

Synthesizing several epidemiological studies to come to a conclusion regarding human risk can be a formidable task given heterogeneity in study design and conflicting results across studies. There is no prescribed methodology for this type of evaluation, but is clear that certain steps will help increase the strength of the analysis. The WHO working group has stated, "The method of choice [for data synthesis] is critical scientific thinking; there are no formulas or checklists that will suffice." Because drawing conclusions from systematic reviews and meta-analyses involves scientific judgment, the process of evaluation, and the transparency of the process, is critical for gaining acceptance of the evaluation.

2.1 NTP Analysis

NTP appears to have conducted some type of weight-of-evidence analysis in the Draft Document, although they are not explicit regarding the details. They do not describe how they conducted their literature search or how they chose endpoints (*i.e.*, specific cancer types) for further study. They

emphasize and conduct limited quantitative analyses on risk estimates from the highest-exposed RPC industry and their highest exposed workers, but they do not quantitatively analyze risk estimates based on other workers in this industry, on other exposure metrics in this industry, or on other industries. Only a subset of these other risk estimates is mentioned in the discussion of each endpoint[1] and it is not clear how each risk estimate was chosen or how well each represented the cohort from which it was calculated. There also is an inappropriate emphasis on positive risk estimates, with insinuations that non-significant positive findings are indicative of an increased risk (although there are no such insinuations about non-significant or significant negative findings indicating a decreased risk). In addition, NTP does not discuss how they classify evidence. That is, they do not state what they consider to be strong, weak, or limited evidence, nor do they explicitly set criteria for determining whether the weight of evidence supports a causal association between styrene and cancer risk.

After describing individual styrene epidemiology studies and cohorts, in their Table 3-6, NTP tabulates the major cancer sites analyzed in the 12 cohorts described in the bold-bordered boxes in Figures 1 to 4, here. For each cohort and for each cancer type, there is a + if a risk estimate was positive and statistically significant, and a (+) if a finding was positive but not significant. Likewise, there is a - if a risk estimate was negative and statistically significant, and a (-) if a risk estimate was negative but not significant.

There are many advantages, but also some shortcomings, to this table. It shows which cancer endpoints were examined in specific cohorts. The cohorts are divided by industry, and cohorts with the highest exposures are on the left of the table, going towards cohorts with the lowest exposures on the right. The symbols on the table are indicative of the overall finding in a cohort. They give a general overall impression of the results and are informative regarding whether risk estimates tended to be in the same direction across cohorts. The table is not informative, however, regarding the magnitude of association for either significant or non-significant findings. If a group of cohorts have small positive non-significant findings for an endpoint, this is not necessarily indicative of risk. Also, this table is not informative regarding exposure-response, or whether risk estimates based on different exposure metrics in a cohort are consistent.

Although NTP adequately describes how they chose which cohorts/studies to include and exclude in Table 3-6, they do not provide accompanying text to describe how one is to interpret the table. More

[1] More details are given earlier in the NTP Draft Document in the description of styrene cohorts.

specifically, they do not explain how they chose which cancer types to examine in more detail. NTP focuses on cancers of the esophagus, pancreas, larynx, and lung, all lymphohematopoietic cancers combined, lymphoma, Hodgkin's disease, multiple myeloma, and leukemia. For each cancer type, they describe some findings in the text and, for the cohorts in the RPC industry, they show SMRs/SIRs for the entire cohort (Table 3-7) and for the high exposure group (Table 3-8). Because a high proportion of individuals in the Danish cohort are included in the European cohort, those individuals are excluded from the SMRs in Tables 3-7 and 3-8 (although they are not excluded in discussions of the risk estimates in the text). NTP adds the observed and expected individuals across cohorts for each cancer type (without double-counting the Danish cohort because they are excluded from the European cohort) and shows the ratio of total observed to total expected individuals.[2] They do not, however, consistently describe any statistics for this ratio.

Based on the ratio of the total observed/total expected individuals in Tables 3-7 and 3-8, we calculated risk estimates and 95% confidence intervals (CIs), as shown in Table 2.[3] We found that, based on the 95% CI excluding 1, the overall risk was statistically significantly increased for lung cancer in all RPC workers and for esophageal and pancreatic cancer in highly exposed RPC workers.[4]

We also conducted Fisher's tests on these risk estimates. Fisher's method (Sokal and Rohlf, 1981) is a useful method for assessing whether several disparate studies that have all examined the same underlying question are jointly finding a consistent deviation in outcome from the null expectation, even when no single study finds a deviation big enough to be ruled statistically significant. The method is based on the idea that, if there is truly no effect, the p-values for the various studies, presuming that they are unbiased, should follow a uniform distribution, even if each study is evaluated by a different statistical test. If -2 times the sum of the natural logarithms of n p-values exceeds the critical value of a chi-squared distribution with 2n degrees of freedom, this constitutes evidence that the p-values as a set are significantly skewed toward indication of an effect compared to the expectation of uniformity if there were no effect. This works best when the p-values are one-sided, since any common effect across studies, if it exists, ought to be in the same direction.

[2] It should be noted that, although it might not have a large influence on the results, bias can be introduced when comparing SMRs.

[3] NTP reported the SMR and 95% CI for pancreatic cancer in the highly exposed workers (SMR = 1.77, 95% CI = 1.23-2.47), but neglected to do so for any other ratio shown in Tables 3-7 and 3-8.

[4] The expected number of highly-exposed individuals with esophageal cancer was ≥ 7.2. It is not possible to determine what the association would have been were the actual number of expected cases of esophageal cancer known.

Using the Fisher's test on one-sided p-values for an increase in SMR/SIR, the aforementioned associations (statistically significantly increased risk for lung cancer in all RPC workers and for esophageal and pancreatic cancer in "highly-exposed" RPC workers) remained significant, and that between styrene and esophageal cancer in all RPC workers was also statistically significant. None of the other associations with these cancers or laryngeal cancer, all lymphohematopoietic cancers combined, lymphoma, Hodgkin's disease, multiple myeloma, or leukemia were statistically significant.

The Fisher's test and the 95% CI on the risk estimate are more appropriate than simply adding the observed and expected numbers of individuals with specific cancers. The advantage of the Fisher method, in addition to its simplicity, is that it adjusts for differences among studies in statistical power, since it attends not to the effect size but rather to the degree that each study's outcome is unexpected under the null, given that study's power. The significant disadvantage of both approaches for epidemiological data, however, is that they depend on the lack of bias and heterogeneity among the combined studies and have no way to detect or adjust for any such heterogeneity or bias. Since these problems arise dependably in epidemiology, these approaches are best thought of as simple initial approaches to be followed up with more rigorous methods, such as a formal meta-analysis. As our more detailed discussions of esophageal, pancreatic, and lung cancers show (Sections 2.2.1, 2.2.2, and 2.4.4, respectively), when examined in detail, the case for effects on these cancer types by styrene exposure is quite weak.

If there is truly an association between styrene and a specific cancer type, it should be seen in the industries with high exposures, and within these industries, in the highest exposed individuals. It is not clear, however, whether NTP's "high-exposure" group necessarily represents the highest exposed individuals (for example, the Danish cohort is not actually based on an exposure measure, but rather on how many employees were engaged in some aspect of reinforced plastic manufacture). In addition, these tables only represent the total cohort (Table 3-7) and the "laminators and others" (Table 3-8), when there were many exposure metrics used for estimating risks in each study. Furthermore, these tables completely omit cohorts not in the RPC industry. Although these cohorts had lower exposures than did those in the RPC industry, they were still exposed, and a weight-of-evidence analysis should consider *all* available data.

The inclusion of all available data does not mean that all data will be weighted equally. On the contrary, it is crucial to consider the utility of each individual study and weight it accordingly. Factors to consider include, for example, study population, sample size, exposure metrics, statistical methodology,

and confounders. While NTP discusses most of these factors to some degree throughout Chapter 3 of the Draft Document, the factors are not put in context of the endpoint-by-endpoint analysis.

NTP concludes that the "the most consistent findings were for increases in lymphohematopoietic malignancies and pancreatic cancer." They discuss that findings for lymphohematopoietic malignancies were strongest in the SBR industry, and limited to the Danish workers in the RPC industry. They do not discuss whether the findings for either cancer, in light of the strengths and limitations of individual studies and cohorts, are supportive of a causal association with styrene. Furthermore, they do not discuss anywhere in the report the biological plausibility of one chemical causing lymphohematopoietic and pancreatic cancers, which differ in their modes of action.

We have conducted an independent weight-of-evidence analysis of the cancer types on which NTP focuses: esophagus, pancreas, larynx, and lung; all lymphohematopoietic cancers combined, lymphoma, Hodgkin's disease, multiple myeloma, and leukemia. These analyses are discussed in Section 2.2, below.

2.2 Endpoint-by-Endpoint Analysis

We conducted a weight-of-evidence analysis of the association between styrene exposure and the risks of each of the cancer types on which NTP focused, which included cancers of the esophagus, pancreas, larynx, and lung, all lymphohematopoietic cancers combined, as well as lymphoma, Hodgkin's disease, multiple myeloma, and leukemia. We did not examine the process of selecting these particular cancers for further study by NTP, and it would be difficult to do so because they provide no discussion of their rationale. In a final analysis, it would be important to set out the criteria that are used to identify endpoints that are considered serious candidates for effects of styrene exposure.

After reviewing the exposure metrics examined in each study (our Table 1), we tabulated the risk estimates separately for each cancer type from the most recent studies of each of the 12 cohorts in Table 3-6 of the Draft Document. The first risk table for each cancer type (*e.g.*, our Table 3.1a for esophageal cancer) presents risk estimates for each job category that is presented in each study (similar to Table 3-8 of the Draft Document but including all job categories and all cohorts). The second table for each cancer type (*e.g.*, our Table 3.1b for esophageal cancer) presents risk estimates for each exposure group in each exposure metric, as they are presented in the studies. P-values for trend tests are included if available.

In some studies, subcategory analyses were conducted using two or more exposure metrics. For example, Kogevinas *et al.* (1994) examines SMRs for certain cancers by time since first exposure (< 10, 10-19, ≥ 20 years, and total), length of exposure (< 2, ≥ 2 years, total), and also with all each combination of these. This leads to 4 x 3 = 12 SMRs for each cancer type for these analyses alone. These sub-analyses are not shown in the tables, but they are discussed in the accompanying text.

We next assessed the consistency of risk estimates within and among studies for each cancer type. For each study, we considered factors that could affect study results – such as study power, inclusion criteria, methodologies, exposure metrics, confounders, *etc.* – and discuss their bearing on the results. We assessed exposure-response relationships within and across studies, with an emphasis on comparing estimates that based on the same exposure metric. We also assessed associations across industries. Because RPC workers have the highest exposures, one would expect higher risks in these individuals if an association between styrene and a specific cancer type exists.

Our analyses discussed below are all qualitative in nature, except for the statistical analysis we conducted based on the meta-analysis performed by NTP in Tables 3-7 and 3-8. We note that it is unclear whether these calculations are appropriate given that tests for heterogeneity among studies have not been conducted. A more complete meta-analysis may prove to be informative, but much can be ascertained from the qualitative analyses discussed below.

2.2.1 Esophageal Cancer

Among four cohorts of RPC workers, NTP reports that significant increases in esophageal cancer were observed among all workers in the Washington state (SMR = 2.3, 95% CI = 1.19-4.02, Ruder *et al.*, 2004) and US (SMR = 1.92, 95% CI = 1.05-3.22, Wong *et al.*, 1994) cohorts, although these associations were not statistically significant in highly-exposed workers (Draft Document Tables 3-7 and 3-8). NTP also discusses several statistically non-significant findings from sub-analyses of these cohorts in the text. NTP reports that mortality was increased among workers from Washington state who had high exposure for over a year, citing a highly non-significant of SMR of 2.74 (95% CI = 0.004-22.3) based on 1 death. In contrast, they report that "no statistically significant association between esophageal cancer and styrene exposure was observed" in the Gerin *et al.* (1998) study, based on an equally non-significant OR of 1.4 (95% CI = 0.5-3.8) and 5 cases. NTP also states that the SMR is "close to unity" in the SBR industry (SMR = 0.94, 95% CI = 0.68-1.26, Sathiakumar *et al.*, 1998) and that a total of 4 cases were identified compared to 5.1 expected in the PS industry (Bond *et al.*, 1992; Hodgson and Jones, 1985). This case

illustrates how selective citation of "elevated" SMRs without regard to statistical significance or stated standards for what is to be considered evidence of elevation can be misleading about the true nature of the evidence regarding association of exposure and risk.

In all RPC cohorts, there are no trends of increased risks with employment duration, exposure duration, cumulative exposure, or time since first hire, nor are there any statistically significant associations in any exposure group in any of these exposure metrics, except for two in the US cohort: men with 10-19 years time since their first exposure ($p < 0.05$), but not < 10 or ≥ 20 years since first exposure, and men with a cumulative exposure of 30.0-99.9 ppm-years ($p < 0.05$), but not with < 10.0, 10-29.9 or ≥ 100 ppm-years cumulative exposure (our Tables 3.1a and 3.1b). Nor are there significantly increased risks associated with any job category in RPC workers except for the low, but not the high, exposure Washington-state workers (SMR = 1.23; 95 % CI = 1.02-1.47, Ruder *et al.*, 2004).

NTP sums the observed and expected number of individuals with esophageal incidence or mortality among the RPC studies, reporting a total observed/expected ratio of 51/42.7 overall and 14/ ≥ 7.2 in the high exposure groups (their Tables 3-7 and 3-8). Although we determined that these values are statistically significant based on their confidence intervals and the Fisher's test (our Table 2), it is not clear whether it is appropriate to pool these values because no tests of heterogeneity were conducted among the studies. In addition, because the expected number of cases is reported as ≥ 7.2 among the high exposure groups (reflecting the lack of stated expected numbers in the Danish cohort), using the actual number might lead to a non-significant finding. Based on this, and on the lack of consistent findings of effect within and across exposure metrics, studies, and industries, the data do not support a causal association between styrene and esophageal cancer.

2.2.2 Pancreatic Cancer

Pancreatic cancer incidence and mortality is not statistically significantly increased overall in any the RPC cohorts (Table 3-7 of the Draft Document), but it is increased among the "high exposure" group in the Danish cohort (SMR = 2.2, 95% CI = 1.1-4.5). NTP also reports an SMR of 0.87 (95% CI = 0.68-1.08, Sathiakumar *et al.*, 2005) in the SBR industry and "divergent" findings in the PS industry based on *non-significant* decreased mortality in two studies (Bond *et al.*, 1992 and Frentzel-Beyme *et al.*, 1978)[5] and *non-significant* increased mortality in another study (Anttila *et al.*, 1998). In actually, these risks are

[5] Frentzel-Beyme *et al.* (1978) actually reported 2 observed and either 0.721 or 0.705 expected pancreatic cancers ($p > 0.15$ for both), depending on the comparison group. This is correctly noted in Table 3-6 of the Draft Document.

non-divergent – they are consistently null. Also, the statement by NTP, "The biomonitored workers (Anttila *et al.*, 1998) showed a 3-fold increased risk of pancreatic cancer (SIR = 3.64, 95% CI = 0.75 to 10.6) 10 years or more after the first measurement," is misleading, particularly in light of the wide confidence interval. This risk estimate supports anywhere from a 25% decreased risk to a 1,060% increased risk of pancreatic cancer – in essence, it is not informative.

Although Kogevinas *et al.* (1994) found a near-significant trend (p = 0.068) with cumulative exposure in the European cohort, no such trend was evident based on cumulative exposure by Wong *et al.* (1994) in a US cohort. There were also no trends of increased risks with job/exposure category, employment duration, exposure duration, cumulative exposure, or time since first hire, nor are there any statistically significant associations in any exposure group in any of these exposure metrics for workers in any of the styrene industries, except the "high-exposure" Danish workers (our Tables 3.2a and 3.2b).

In their summary in Section 3.9, NTP states:

> The risk of pancreatic cancer was increased across five studies of workers (three studies of the reinforced plastics industry, one study of the styrene monomer and polymer industry, and the cohort of biomonitored workers) exposed to high levels of styrene. Moreover, among the highest styrene-exposure group in the reinforced plastics industry, there was an excess (1.77 fold) in the total number of observed cases across the four cohort studies compared to the total number of expected cases. There were also indications of an exposure-response relationship in the two of the four studies that assessed cumulative exposure or duration of exposure. However, no increased risk of pancreatic cancer was reported among styrene-butadiene workers.

We find the NTP's discussion to be highly misleading. Only one risk estimate was actually statistically significant, and this was in the Danish "high exposure" group, who may not actually have had higher exposures because they are defined by the percentage of employees in a company involved in some aspect of reinforced plastic manufacture (Kolstad *et al.*, 1994; 1995). Although the 1.77-fold excess in pancreatic cancer risk in the high exposure group (NTP's Table 3-8) was statistically significant based on a Fisher's test and the confidence interval (see Table 2), it was primarily based on this Danish cohort (17 of 34 observed, 7.7 of 19.2 expected cases), which drove up the numerator and drove down the denominator of the risk estimate, and, because no tests of heterogeneity were conducted, it is not evident that this analysis was appropriate. Given the crudeness of this meta-analysis, and a lack of consistent increased risks across studies, the data do not support an association between styrene exposure and pancreatic cancer.

2.2.3 Laryngeal Cancer

There were no statistically significant associations between styrene and laryngeal cancer in any study of RPC workers overall or in any exposure group based on job category, employment duration, exposure duration, cumulative exposure, or time since first hire (Tables 3.3a and 3.3b). NTP reports that among all RPC workers, 36 laryngeal cancers were observed *vs*. 32.7 expected, and among the high-styrene-exposure RPC workers, 3 were observed *vs*. 1.9 expected. We found that these differences are not statistically significant (Table 2), but note that we do not necessarily agree that this analysis is appropriate. NTP also reports a non-significant decreased laryngeal cancer mortality in the SBR industry[6] (SMR = 0.71, 95% CI = 0.41-1.13) and 1 death *vs*. 2.9 expected in the PS industry (Bond *et al.*, 1992). NTP states that Hodgson and Jones (1985) found an excess of incident cases, but this appears to be an error, as laryngeal cancer is not addressed in this study.

The number of observed laryngeal cancers was small in every study, and even lower in specific exposure categories. Overall, these studies are non-informative regarding laryngeal cancer risk owing to low power. One should not interpret low power as meaning an association would be seen if the power were only high enough. Rather, it means the data currently do not support an association between styrene and laryngeal cancer, and only a study with more power could address whether a small association likely exists.

2.2.4 Lung Cancer

NTP reported that, of the four RPC cohorts, lung cancer risk was statistically significantly increased in only one (US RPC workers overall: SMR = 1.41, 95% CI = 1.20–1.64; Wong *et al.*, 1994). There were no significant risks associated with any job category in these subjects, nor were there any trends of increased risks with employment duration, exposure duration, cumulative exposure, or time since first exposure. Although there were a few significant associations in certain exposure groups in these exposure metrics, but there was no consistent pattern in the US cohort (Tables 3.4a and 3.4b). There was actually a slightly *inverse* relation ($\beta = -0.046059$, $p = 0.0054$) with duration of exposure based on a proportional hazards model (Wong *et al.*, 1994). Among other studies of RPC workers, there were no statistically significant associations between styrene and increased lung cancer risk, although Kolstad *et al.* (1994; 1995) found an increased risk in Danish workers categorized as *not* having worked with

[6] Sathiakumar *et al.* (2005) also reported an SMR of 0.96 with a confidence interval of 0.56 to 0.54 based on follow-up from 1944-1991, but this is clearly an error.

reinforced plastics (SMR = 1.23, 95 % CI = 1.02-1.47), particularly those whose year of first employment was 1970 or earlier (SMR = 1.8, 95% CI = 1.1-3.0).

In the SBR industry, the only significant association was a *decreased* risk in North American workers over the entire follow-up period (1944-1998; SMR = 0.91, 95% CI = 0.84-0.99, Sathiakumar *et al.*, 2005). No significant excesses was observed in the PS industry (Bond *et al.*, 1992; Nicholson *et al.*, 1978; Hodgson and Jones, 1985; Frentzel-Beyme *et al.*, 1978), in styrene-monitored workers (Anttila *et al.*, 1998), or in individuals with potential environmental exposures (Loughlin *et al.*, 1999), although Bond *et al.* (1992) noted a statistically significant decreased risk of respiratory cancers in US product research and development workers (SMR = 0.60, $p < 0.05$). As discussed by NTP, "no significant association with lung cancer was observed among potentially styrene-exposed cases in a population-based, case-control study by Scelo *et al.* (2004) or the population-based study of Gerin *et al.* (1998)…"

NTP sums the observed and expected number of individuals with lung cancer incidence or mortality among the RPC studies, reporting a total observed/expected ratio of 654/579.3 overall and 158/151.5 in the high exposure groups (their Tables 3-7 and 3-8). We determined that the ratio for the overall cohort is statistically significant based on the ratio's confidence intervals and the Fisher's test (our Table 2), but the ratio for the "high-exposure" groups is not statistically significant. Were there increasing risk with increasing dose, one would expect a stronger association among the "highly-exposed" workers, and this is clearly not the case. It should be noted, however, that it is not clear whether it is appropriate to pool these numbers across studies because no tests of heterogeneity were conducted among the studies. Based on this, and despite some decreased risks in certain populations, the lack of consistent findings of effect within and across exposure metrics, studies, and industries, suggest no association, with either increased or decreased risk, between styrene and lung cancer.

2.2.5 All Lymphohematopoietic Cancers

NTP shows SMRs/SIRs for all lymphohematopoietic cancers combined and specific lymphohematopoietic cancers (*i.e.*, lymphoma, Hodgkin's disease, multiple myeloma, and leukemia) separately in Tables 3-7 and 3-8. In Section 3.8.5 of the Draft Document, however, they are all discussed together, with an emphasis on positive (significant and non-significant) results. This is inappropriate for several reasons. Each of the specific lymphohematopoietic cancers is a different disease, with a different mode of action, and an association with one type is not necessarily indicative of risk of another. In addition, if one study reports a significant finding for one cancer type, and another reports a significant

finding for another cancer type, these results are discussed without an indication of whether results for the *same* cancer type were consistent across these two studies. This makes it very difficult for the reader to appreciate the weight-of-evidence for each cancer type. To assess whether styrene is associated with each individual lymphohematopoietic cancer, or all of them combined, one should systematically examine them one-by-one, as we have done here, starting with all-combined.

As shown in Tables 3-7 and 3-8 of the Draft Document, there were no statistically significant associations between styrene exposure and all lymphohematopoietic cancers combined in "highly-exposed" or all RPC workers, and non-significant associations were in both directions (*i.e.*, positive and negative). The ratio of observed to expected cases among cohorts calculated by NTP was less than 1 for the "highly-exposed" workers and for all workers, and we calculated that these were not statistically significant (Table 2).

In the RPC cohorts, lymphohematopoietic cancers were examined by job category, employment duration, exposure duration, cumulative exposure, employment start date, and time since first hire or first exposure (Tables 3.5a and 3.5b). When examined this way, the overwhelming majority of associations was not statistically significant and included both non-significant positive and negative findings. Kolstad *et al.* (1994) reported an increased risk in Danish men who started working between 1964 and 1970 (SMR = 1.32, 95% CI = 1.02-1.67). This association was not observed in men who started working between 1971 and 1975 or between 1976 and 1998. No other study examined this association by employment start date. Kolstad *et al.* (1994) also observed an increased risk in men who were employed < 1 year with a time since first employment ≥ 10 years prior (SMR = 1.65, 95% CI = 1.18-2.26), but not in men employed ≥ 1 year or with a time since first employment < 10 years prior. In the European cohort, one-third of whom were in the Danish cohort, Kogevinas *et al.* (1994) found an increased risk in Europeans who had < 2 years exposure and 10-19 years since the first exposure (SMR = 1.83, 95% CI = 1.12-2.83), but not in men with ≥ 2 years exposure or < 10 or ≥ 20 years since the first exposure. Using Poisson models, Kogevinas *et al.* (1994) reported a significant trend with time since first exposure (p_{trend} = 0.012) and average exposure (p_{trend} = 0.019), but not with cumulative exposure (p_{trend} = 0.65). In Europeans whose time since first exposure was < 10 years, however, the risk, although non-significant, was < 1, (SMR=0.6, 95% CI = 0.32-1.03), and the observed trend may be more a product of unusually low risks in the lowest latency group (time since first exposure was < 10 years) rather than elevated risks in the higher latency groups (10-19 and ≥ 20 years since the first exposure). In addition, Ruder *et al.* (2004) and Wong *et al.* (1994) examined the association between styrene and lymphohematopoietic cancers in the Washington state and US cohorts, respectively, and found no association in any group, including those in

the US cohort hired < 10 years before. Thus, there is no consistent finding of increased risk for all lymphohematopoietic cancers from styrene exposure within or among studies of RPC workers.

NTP noted, "In the cohort of styrene-butadiene rubber workers established by Delzell and colleagues, a slightly increased mortality from all lymphohematopoietic malignancies (SMR = 1.06, 95% CI = 0.90 to 1.23, 162 observed deaths)… was observed in the follow-up by (Sathiakumar *et al.* 1998)." They go on to say, "A nested case-control study from this cohort of 58 lymphohematopoietic cases and 1,242 controls found two- to three-fold increased risks for lymphohematopoietic cancers, lymphoma, lymphosarcoma, and myeloma and styrene exposure (increase of 1 ppm in TWA) after controlling for butadiene exposure (Matanoski *et al.* 1997)" and "Risk of lymphohematopoietic cancer and myeloma also increased with increasing cumulative exposure to styrene in a model controlling for butadiene exposure in the cohort established by Matanoski and colleagues and using a measurement based exposure assessment (Matanoski *et al.* 1997)." This is misleading, as it implies that these studies found increased risks, when they are clearly null in the Sathiakumar *et al*. (1998) study and no confidence intervals are given for the Matanoski *et al*. (1997) study. These are also studies of the same cohort, and NTP does not discuss the findings for this endpoint in the most recent studies of the cohort, by Sathiakumar *et al*. (2005) and Graff *et al*. (2005), both of which reported no association between styrene exposure and risk of all lymphohematopoietic cancers combined. NTP does mention co-exposures to 1,3-butadiene could affect risk estimates, but they appear to dismiss the possibility that it could have significantly affected the results.

One other study of synthetic rubber workers examined risk from lymphohematopoietic cancer. McMichael *et al*. (1976) reported that workers with at least 5 years' employment in the synthetic plant had a risk ratio of 6.2 (99.9% CI = 4.1 to 12.5). There was no adjustment made for other exposures, however, so one cannot attribute this risk to styrene with any certainty.

NTP said, "Among all workers at the four styrene monomer and polymer plants studied, there were 34 deaths due to lymphohematopoietic malignancies, compared with 23.1 expected (Bond *et al.* 1992, Frentzel-Beyme *et al.* 1978, Hodgson and Jones 1985, Nicholson *et al.* 1978)." Hodgson and Jones (1985) reported a significant increase in deaths from any lymphohematopoietic cancer (3 observed *vs.* 0.56 expected, p = 0.02) and a near-significant excess of lymphohematopoietic cancer incidence (SIR = 2.50, 4 observed vs. 1.6 expected, p = 0.079). NTP also said, "The risk of all lymphohematopoietic malignancies increased with increasing duration of employment but not with increasing styrene exposure level (Bond *et al.* 1992)." Actually, there were no analyses by duration of employment reported by Bond

et al. (1992). These investigators reported a significant association with a minimum 15-year latency (SMR = 1.60, 95% CI = 1.02-2.38), but there was no trend of increasing risk across three categories of time since first exposure (< 15, 15-34 ≥ 35 years). Bond *et al*. (1992) also reported no association with all-lymphohematopoietic cancers in styrene-exposed workers in Michigan (compared to US mortality rates for white males or to unexposed workers from the Michigan manufacturing location). In workers exposed to styrene and ethylbenzene, they reported no trend with increased duration of exposure (< 1, 1-4, ≥ 5 years), but there was an increased risk over the three exposure categories (SMR = 2.36, 95% CI = 1.22-4.11) in workers exposed to a TWA of 1-4 ppm styrene and ethylbenzene, but not to ≥ 5 ppm styrene and ethylbenzene. There is not only a lack of dose-response, but one cannot determine whether the association is with styrene, ethylbenzene, or both.

No associations between styrene and all lymphohematopoietic cancers were reported by Anttila *et al*. (1998) in their biomonitoring study or by Loughlin *et al*. (1999) in their environmental exposure study.

It should be noted that examining associations by exposure metric for the lymphohematopoietic cancers is particularly challenging because several studies examined associations using several combinations of exposure metrics, leading to slightly different results. For example, Kogevinas *et al.* (1994) show a total of 13, 26, and 10 observed cases of lymphohematopoietic cancer in the time-since-first-exposure categories of < 10, 10-19, and ≥ 20 years, respectively, in Table 3, but in Table 4, there are 13, 25, and 9 observed cases and in Table 3 of the Kogevinas *et al.* (1993) publication, there are 15, 24, and 11 observed cases, respectively. The reason for the discrepancies is usually that the data are divided up into analyses by more than one metric (*e.g.*, time since first exposure and number of years exposed). Individuals missing data for either endpoint were likely omitted from that particular analysis. This makes it even more important for one to examine the consistency of results across a cohort. If an association is only significant by breaking up the data a certain way, it is more likely a chance finding than indicative of risk.

Although there were some findings of increased risk with average exposure, time since first exposure, and an earlier start date of employment (when exposures were highest) in the European cohort, these associations were primarily seen in short-term workers, and there was no association with cumulative exposure in this cohort. Given the overwhelming majority of null findings among all cohorts,

the weight of evidence does not support an association between styrene exposure and lymphohematopoietic cancer.

2.2.6 Non-Hodgkin's Lymphoma

NTP tabulates SMRs/SIRs for lymphoma in the RPC industry Tables 3-7 and 3-8. NTP calculated 58 observed and 53.8 expected cases overall and 14 observed and ≥ 15.1 expected in "highly-exposed" RPC workers. Neither of these differences is statistically significant. As stated by NTP, "In the reinforced plastics industry… the risk of lymphoma… did not increase with increasing cumulative styrene exposure (Kogevinas *et al.* 1994a) or duration of employment (Kolstad *et al.* 1994, Ruder *et al.* 2004, Wong *et al.* 1994)."

Kolstad *et al.* (1994) reported an increase in non-Hodgkin's lymphoma in Danish men if the time since first hire was < 10 years prior (SMR = 1.68, 95% CI = 1.03-2.53), but this was limited to companies in which 1-49% of employees were in reinforced plastics production (SMR = 2.35, 95% CI = 1.42-3.67) or if production company was unclassified (SMR = 3.86, 95% CI = 1.05-9.85). No associations were seen in companies with 50-100% of employees working in reinforced plastics. Also, no associations were found based on the first year of employment or in men working ≥ 1 year.

Although Kogevinas *et al*. (1994) reported no association between all malignant lymphomas (*including* non-Hodgkin's lymphoma), and the number of years exposed or cumulative exposure, they found near-significant trends for time since first exposure (p = 0.072) and average exposure (p = 0.052). The only statistically significant risk estimate among these two metrics was in men exposed to an average of 120-199 ppm (SMR = 7.15, 95% CI = 1.21-42.11). This is a very unstable estimate, with a large confidence interval and no other associations were statistically significant. Furthermore, Kogevinas *et al*. (1994) did not report these results for non-Hodgkin's lymphoma alone.

In a US cohort, Wong *et al*. (1994) examined associations between lymphosarcoma and reticulosarcoma and time since first exposure, duration of employment, duration of exposure, cumulative exposure, and job category, and found no trends or significant association in any exposure group. In addition, they found no association with non-Hodgkin's lymphoma based on proportional hazards model, although the number of cases was small (n = 10). In the Washington state cohort, Ruder *et al*. (2004) reported one case in the low exposure group of lymphosarcoma or reticulosarcoma, and this was also not

statistically significant. The findings in the RPC industry overall do not support an association between styrene exposure and lymphoma risk.

Non-Hodgkin's lymphoma was assessed in one SBR cohort. NTP stated, "Matanoski *et al.* (1997) and colleagues presented updated analyses that relied on non-matched controls and measurement-derived estimates of styrene exposure. Analyses based on average styrene exposure level (calculated across all exposed years) adjusted for butadiene exposure, showed that a 1-ppm increase in average styrene exposure level increased the [OR] for… non-Hodgkin's lymphoma (OR = 2.67, 95% CI = 1.22 to 5.84, 12 deaths)." Regarding the same cohort, they also stated:

> The rate of non-Hodgkin's lymphoma was slightly higher at higher cumulative styrene exposure levels than at lower levels. The RRs, with adjustment for age and latency, were as follows: 0 ppm-years (reference), RR = 1.0; < 8.3 ppm-years, RR = 1.4 (95% CI = 0.5 to 3.6, 16 observed deaths); 8.3 to < 31.8 ppm-years, RR = 1.1 (95% CI = 0.4 to 2.9, 11 observed deaths); 31.8 to < 61.1 ppm-years, RR = 1.5 (95% CI = 0.5 to 4.2, 9 observed deaths); ≥ 61.1 ppm-years, RR = 2.3 (95% CI = 0.9 to 5.9, 16 observed deaths). (Graff *et al.* 2005)

These statements are misleading. Although Matanoski *et al*. (1997) reported an association even after adjusting for 1,3-butadiene, in a study of the same cohort, Graff *et al*. (2005) did not. Also, the Graff *et al*. (2005) results presented by NTP are not significant and are not adjusted for 1,3-butadiene. Furthermore, Sathiakumar *et al.* (2005) examined non-Hodgkin's lymphoma based on job category, being an hourly employee, years since hire, and years worked, and also found no significant associations in this cohort.

In the PS industry, no significant associations were noted by Nicholson *et al.* (1978) (Hodgkin's and non-Hodgkin's) or Bond *et al*. (1992) (non-Hodgkin's lymphoma), but Hodgson and Jones (1985) noted observed 3 deaths from lymphoma (Hodgkin's and non-Hodgkin's), when 0.56 were expected (p = 0.02). They found no trends with age, and this was only significant in individuals who were 15-44 years of age at death (2 observed, 0.27 expected). The incidence of all lymphomas (Hodgkin's and non-Hodgkin's) was also increased in this study (SRR = 3.75, p = 0.047, 3 observed, 0.8 expected). With regard to environmental exposures, Loughlin *et al*. (1999) reported no increased risks with non-Hodgkin's. Although some significant and non-significant findings were reported in all styrene industries, the majority of findings were null and do not support an association between styrene exposure and non-Hodgkin's lymphoma.

2.2.7 Hodgkin's Disease

Hodgkin's disease was examined in many studies of all styrene industries, although there were generally few observed cases (Tables 3.7a and 3.7b). NTP reported 27 observed cases (26.8 expected) in all four RPC cohorts combined, and 11 observed (≥ 4.7 expected) in "highly-exposed" workers in these cohorts. We found these differences not to be statistically significantly different (Table 2). There were no statistically significant associations in any exposure group in the four cohorts (Wong *et al*., 1994; Ruder *et al*., 2004; Kolstad *et al*., 1995; Kogevinas *et al*., 1994).

NTP reported non-significant risk estimates for the RBC industry and for styrene-monitored workers. They stated, "Matanoski *et al.* (1990) observed increased mortality from Hodgkin's disease (SMR = 1.20, 95% CI = 0.52 to 2.37, 8 observed deaths)" and "Among workers biomonitored for styrene exposure, the incidence of Hodgkin's disease was slightly increased (SIR = 1.89, 95% CI = 0.23 to 6.84, 2 cases) (Anttila *et al.*, 1998)." These associations are both null and highly non-significant. Furthermore, the Matanoski *et al*. (1990) cohort was included in the Sathiakumar *et al*. (2005) study, which also reported no association between styrene exposure and Hodgkin's disease.

In the PS industry, Hodgson and Jones (1985) reported no incident cases of Hodgkin's disease and Bond *et al*. (1992) reported no association in exposed workers in Michigan (compared to US mortality rates for white males or to unexposed workers from the Michigan manufacturing location). Loughlin *et al*. (1999) reported no increased risk with environmental exposure. As no studies reported an increased risk with Hodgkin's disease, these data clearly do not support an association with styrene exposure.

2.2.8 Multiple Myeloma

Risk estimates for multiple myeloma, generally based on few observed cases, are shown in Tables 3.8a and 3.8b. In their Tables 3-7 and 3-8, NTP shows no multiple myeloma cases in the Washington and US styrene cohorts, and a total of 17 (19.6 expected) in the Danish and European cohorts combined and 4 (≥ 3.4 expected) among "highly-exposed" workers in these cohorts. We calculated that these differences are not statistically significant (Table 2), and there were no significant risk estimates for any exposure category in these cohorts (Kolstad *et al*., 1994; Kogevinas *et al*., 1995). Despite the absence of US cases in Tables 3-7 and 3-8, there was an analysis of multiple myeloma in the US cohort, as NTP states earlier in Chapter 3 that Wong *et al.* (1994) found "Cox regression analyses (internal analysis) of cumulative

styrene exposure or duration of styrene exposure showed no indications of exposure-response relationships for… multiple myeloma." NTP also states, "Lower SMRs were observed for long-term workers (≥ 2 years) for… multiple myeloma" in the European cohort. These observations were not discussed in Section 3.8.5, even though they contribute to the weight-of-evidence for determining whether an association exists between styrene exposure and multiple myeloma.

Sathiakumar *et al.* (2005) examined multiple myeloma in SBR workers based on job category and various combinations of the years since hire and years worked, and found no significant associations with styrene exposure (Tables 3.8a and 3.8b). In addition, Graff *et al.* (2005) examined this cohort and, as reported by NTP, found that "[n]o increased risk was suggested by the results for multiple myeloma." This is particularly important, because this is the same cohort from which Matanoski *et al.* (1997) conducted a nested case-control analysis. NTP states, "Risk of lymphohematopoietic cancer and myeloma also increased with increasing cumulative exposure to styrene in a model controlling for butadiene exposure in the cohort established by Matanoski and colleagues and using a measurement based exposure assessment (Matanoski *et al.* 1997)." Thus, NTP stresses a significant finding in an early study of a cohort, but do not discuss the results in the context of those based on the same cohort by Sathiakumar *et al.* (2005) or Graff *et al.* (2005), which were not consistent with those of Matanoski *et al.* (1997).

As shown in Tables 3.8a and 3.8b, no statistically significant associations were observed overall in the PS industry (Bond *et al.*, 1992, Hodgson and Jones, 1985). Bond *et al*. (1992) reported no association in exposed workers in Michigan compared to US mortality rates for white males (SMR = 1.84, 95% CI = 0.74-3.80), but found a significant increase when these men were compared to unexposed workers from the Michigan manufacturing location (RR = 2.45, 95% CI = 1.07-5.65). Based on all the data, the weight-of-evidence does not support and association between styrene exposure and multiple myeloma.

2.2.9 Leukemia

Leukemia is the most-studied cancer endpoint among the styrene epidemiology studies (Tables 3.9a and 3.9b). With respect to the RPC industry, which has the highest styrene exposures, NTP states:

> Increased risks were mainly limited to the Danish workers, which reported higher risks of leukemia among workers with high probable exposure, earlier first date of exposure, and who had worked at least 10 years since first employment, but not for workers employed for 1 year or more.

In Tables 3-7 and 3-8, NTP shows the total number of leukemia cases was *less* than expected in RPC workers (overall: 73 observed, 76.1 expected; "highly-exposed": 19 observed, 19.6 expected, neither statistically significant [our Table 2]). Also, while Kolstad *et al.* (1994) reported an increased risk in Danish men who started working between 1964 and 1970 (SMR = 1.54, 95% CI = 1.04-2.19), this association was not observed in men who started working between 1971 and 1975 or between 1976 and 1998. No other study examined this association by employment start date. Kolstad *et al.* (1994) also observed an increased risk in men whose time since first employment ≥ 10 years prior (SMR = 1.57, 95% CI = 1.07-2.22; for those also employed < 1 year, SMR = 2.34, 95% CI = 1.43-3.61), but not in men employed ≥ 1 year or with a time since first employment < 10 years prior. Kogevinas *et al.* (1994) found an increased risk in Europeans who had < 2 years exposure and 10-19 years since the first exposure (SMR = 2.15, 95% CI = 1.03-3.95), but not in men with ≥ 2 years exposure or < 10 or ≥ 20 years since the first exposure. Using Poisson models, Kogevinas *et al.* (1994) reported a near-significant trend with time since first exposure (p_{trend} = 0.094), but not with average exposure (p_{trend} = 0.47) or cumulative exposure (p_{trend} = 0.65). It should be noted, however, Kogevinas *et al*. (1994) reported that if time since first exposure was < 10 years, the SMR was < 1, (0.52, 95% CI: 0.17-1.22), and the observed trend may be more a product of unusually low risks in the lowest latency group (time since first exposure was < 10 years) rather than elevated risks in the higher latency groups (10-19 and ≥ 20 years since the first exposure). In light of no significant findings in either US cohort (Wong *et al*., 1994; Ruder *et al*., 2004, see Tables 3.9a and 3.9b), and the few but inconsistent positive findings in the Danish and European cohorts, the data do not support an association between styrene exposure and leukemia in RPC workers.

With regard to the SBR industry, in their executive summary, NTP states:

> The evidence for lymphohematopoietic malignancies appears to be the strongest in the styrene-butadiene industry. Significantly increased risk estimates were found for (1) leukemia and all lymphohematopoietic malignancies in the Texas cohort study, (2) leukemia among specific job groups in the multi-plant cohort, and (3) lymphohematopoietic malignancies (combined), lymphoma, lymphosarcoma, and myeloma in a nested case control study of the 8-plant cohort (which overlapped substantially with the multi-cohort study) after controlling for butadiene exposure. The risk of leukemia increased with increasing cumulative exposure to styrene, although the trend was attenuated somewhat after controlling for butadiene. The increased risk of leukemia among styrene-butadiene rubber workers also exposed to butadiene could indicate a synergistic effect of these two exposures.

NTP also discussed leukemia risk in the SBR industry in two other ways:

> In the styrene-butadiene rubber industry, the risk of leukemia increased with increasing cumulative exposure to styrene (Delzell *et al.* 2001, Matanoski *et al.* 1997). [Note that this observation was reported in the nested case-control study from the Matanoski cohort that used a measurement based exposure assessment, and the studies from the Delzell cohort that used a revised exposure assessment (Delzell *et al.* 2001), which gave significantly higher estimates than documented by measurement.] This trend remained but was dampened when analyses were adjusted for exposure to butadiene. Results indicated a positive interaction between styrene exposure and high-level butadiene exposure (Delzell *et al.* 2001), but this observation was sensitive to the exposure assessment strategy (Macaluso *et al.* 1996).
>
> In the cohort of styrene-butadiene rubber workers established by Delzell and colleagues, a slightly increased mortality from… leukemia (SMR = 1.16, 95% CI = 0.91 to 1.47, 71 observed deaths) was observed in the follow-up by (Sathiakumar *et al.* 1998). Statistically significant increased risks or leukemia (SMR ranging from 2.58 to 4.31) were observed among workers involved in production (polymerization and coagulation job groups) and labor (maintenance and laboratories job groups) (Sathiakumar *et al.* 2005). (Note that production and maintenance workers had high exposure to both styrene and butadiene, and coagulation workers had low to moderate exposure to styrene, but only background exposure to butadiene.)

These statements are all true but, as presented, they are highly misleading. Although findings were significant in the Texas cohort, these individuals were included in larger cohort studies, and citing the Texas studies alone is essentially "double-counting." NTP also stated that Sathiakumar *et al.* (2005) found increased leukemia risks in four of nine job categories that were evaluated. NTP neglected to state that there were no increased risks when Sathiakumar *et al.* (2005) examined associations based on being an hourly employee, years since hired, or years worked, with one exception (see Tables 3.9a and 3.9b). In addition, NTP cites earlier studies of this cohort that found associations with cumulative exposure to styrene, but did not cite the findings of Graff *et al.* (2005). These investigators found no trends with increasing cumulative exposure or increasing total styrene peaks > 50 ppm when they were adjusted for 1,3-butadiene. Although there are some findings of effect in the SBR industry, if one objectively examines *all* the data, and not just select studies, it is evident that there is no clear pattern of effect.

Regarding the PS industry, NTP states:

> In the styrene monomer and polymer industries, the risk of lymphohematopoietic malignancies was also increased in three of the four cohort studies (as well as the total number of observed cases across studies), but these workers might have been exposed to benzene.

Again, this is misleading. McMichael *et al.* (1976) reported that for workers with at least 5 years' employment in the synthetic plant, the risk ratio for lymphatic leukemia was 3.9 (99.9% CI = 2.6 to 8.0).

Yet these authors did not examine any possible co-exposures. Nicholson *et al*. (1978) reported 1 leukemia case where 0.79 was expected and Hodgson and Jones (1985) reported 1 observed incident case, when 0.6 were expected. Bond *et al*. (1992) found no association overall in exposed workers in Michigan (compared to US mortality rates for white males or to unexposed workers from the Michigan manufacturing location) or in any job category. It is more appropriate to categorize three of the four studies as having no association, and to discuss the possibility of confounding by co-exposures.

Loughlin *et al*. (1999) found that people who attended high school adjacent to an SBR plant had an increased risk of leukemia if they attended the school for ≤ 2 years (SMR = 5.29, 95% CI = 1.09-15.46), but not ≥ 3 years. Although significant, this is a highly unstable estimate with a large confidence interval, and there is no increase in risk with increase time attending school, if students were even exposed at all.

In sum, the weight of evidence suggests if there are any associations between styrene exposure and leukemia, they are not evident in the high exposure industry (RPC). There are no consistent associations seen across studies of the same cohort in the SBR industry, and co-exposure to 1,3-butadiene likely confounded results. There were few reported cases in the PS industry, and three of four studies reported no statistically significant increase. Overall, the weight of evidence does not support an association between styrene and leukemia.

2.3 Combining Evidence Across Cancer Types

True carcinogens tend to be specific in the particular organs and tissues for which they induce increased cancer risk (Cole *et al.*, 2003). As noted above, the process of weighing evidence for the existence of any such causative effect stresses whether consistent and mutually supportive results are found for particular endpoints when one looks within studies (say, for trends in response with increasing dose) and across studies. When examined in this way, for no particular endpoint is there a consistent pattern in accord with what one would expect from a true causative effect.

There is the further question of whether outcomes across different cancers – those in different organs and tissues – should be combined into an overall assessment of a compound's potential carcinogenicity. Again, consistency and interpretability of patterns is key to differentiating between a case when such results are to be deemed mutually supporting and one in which the disparate outcomes are more properly ascribable to sporadic results that do not support a common, causal interpretation. Agents

that truly cause several different types of cancer usually have an intelligible pattern of commonality across responses, based on plausibly common mode of action, on sensitivity of particular tissue or cell types, or on pharmacokinetic and dose-delivery considerations. The overall weight of evidence for carcinogenicity is increased when there is sound and consistent evidence for the individual types of cancer and when there is an interpretable and plausible pattern among responses that points to the basis of commonality among them. The overall evidence is weaker when the individual cancer types are weakly supported, when they collectively form no particular syndrome or pattern, and when the apparent positive outcomes appear in different studies. In the case of styrene, the case for the ability of the chemical to cause any particular one of the cancers that have been examined is weak and inconsistent, and moreover, there is no pattern in outcomes for different cancer types that would point to a common causal process.

3 Conclusions

The 2008 NTP Report on Carcinogens: Draft Background Document for Styrene is not intended to provide interpretations or conclusions based on the epidemiology literature regarding styrene and cancer risk, but it is intended to be useful for such a process. As it stands, the data are not presented in a way that is conducive to applying a weight-of-evidence analysis across studies. We have laid out our view of how these data should be presented and the main elements of this type of analysis. NTP concludes that "the most consistent findings were for increases in lymphohematopoietic malignancies and pancreatic cancer." Had NTP conducted a complete weight-of-evidence analysis, their conclusions may have been different.

We conducted a weight-of-evidence analysis of the association between styrene exposure and the risks of each of the cancer types on which NTP focused in the Draft Document, including esophageal, pancreatic, laryngeal, and lung cancer, all lymphohematopoietic cancers combined, lymphoma, Hodgkin's disease, multiple myeloma, and leukemia. If styrene were a causal factor for any of these cancers, one would expect to see associations in the RPC industry, which has the highest exposures to styrene and the fewest likely confounding exposures, and particularly in the highest-exposed RPC workers. Although some positive associations were reported in certain exposure groups of some cohorts in some studies, so, too, were null and negative effects. There were no *consistent* findings of effect for any cancer type in the RPC, SBR, or PS industries.

Although no formal meta-analyses were conducted, NTP calculated risk estimates for these cancers based on the total observed and expected individuals with these cancers in the RPC industry overall and in "highly-exposed" RPC workers. Despite the limitations of these analyses with respect to heterogeneity among studies, based on the 95% CI and the Fisher's method, we found that none of the lymphohematopoietic cancers were associated with styrene exposure, although some associations with lung, esophageal, and pancreatic cancer were statistically significant. These associations, however, are not supported by a critical weight-of-evidence review of the data.

In the end, NTP will use the Background Document to come to a judgment about whether styrene should be listed in the Report on Carcinogens, and if so, the level of evidence by which it should be characterized. In the current (11th) Report on Carcinogens, NTP (2006) states, "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration

given to all relevant information." With respect to epidemiologic data, a determination has to be made as to whether the evidence is "sufficient" or "limited." A "sufficient" classification indicates that the data support concluding that a causal relationship between exposure to the agent and human cancer exists, while "limited" evidence "indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded." There are no precisely defined standards for when the "limited" criterion is to be deemed satisfied.

It is important to realize that "limited" evidence still requires a positive finding that a causal explanation is credible; it is not simply applied when the data are inconsistent or inconclusive, and the mere presence of some positive evidence in some studies is not by itself grounds to conclude that a causal explanation is credible. Instead, when results are mixed or inconsistent, an evaluation of all of the data must consider whether it is credible to hold that a truly causal relationship exists (and the studies failing to show it do so because of chance and low power or because the true responses are somehow obscured by extraneous factors) or whether it is more credible that there is no causal effect (and the studies appearing to show an effect of exposure are in fact only showing chance findings or the effects of biases or confounding factors). Making such a judgment requires a thorough and systematic evaluation of the evidence and an evaluation of the relative plausibility of the competing explanations – actual causality partially obscured by chance or bias on the one hand versus bias and confounding creating the spurious appearance of apparent effects on the other. That is, the "limited" evidence category does not simply consist of cases for which there are some positive and some negative results; it is only when a case for a credible (albeit unproven) causative effect can be made that the "limited" evidence characterization should be applied.

In our view, when all the evidence is evaluated, the low numbers of observed cases and the lack of consistent patterns in outcomes within cohorts and across cohorts, combined with the real concerns about co-exposures and confounding, one comes to the conclusion that a causal relation of styrene exposure and human cancer is not credible, and the standards of "limited" evidence are not met.

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Tables

Table 1
Cohorts Included in Quantitative Analyses in the NTP Report on Carcinogens Draft Background Document for Styrene

Reference	Job/Exposure Category	Subjects (n)	Total Follow-up (person-years)	Period of Follow-up	Minimum Employment Duration	Employment Duration (Years)	Exposure Duration (Years)	Average Exposure (ppm)	Cumulative Exposure (ppm-yr)	Employment Start Date	Time Since Hire/First Exposure (Years)	Hourly Employee	Co-Exposures/ Confounders Discussed in Study	Notes
Reinforced Plastic Industry (RP)														
Kolstad *et al.* (1994, 1995) Workers from Denmark.	Exposed: Ever worked in company producing reinforced plastic Low: 1-49% of employees in RP production High: 50-100% of employees in RP production Unexposed: Never worked in company producing reinforced plastic Exposure unknown	50,903	584,556	1970-1989	< 1 ≥ 1	< 1 ≥ 1				1964-1970 1971-1975 1976-1988 ≤ 1970 > 1970	< 10 ≥ 10			Exposure classification based on opinions of two dealers of plastic raw materials. These differed from employers' classifications. Mean styrene levels were 180 ppm (1964-1970), 88 ppm (1971-1975), and 43 ppm (1976-1988).
Kogevinas *et al.* (1993, 1994) Workers from Denmark, Finland, Italy, Norway, Sweden and the United Kingdom	Laminators Unspecified Tasks Other exposed Jobs Unexposed	40,688	539,479	1945-1991 (varies by country)			< 2 ≥ 2	< 60 60-99 100-119 120-199 > 200	< 75 75-199 200-499 ≥ 500		< 10 10-19 ≥ 20		Peroxides Styrene oxide Acetone Methylene chloride Other aromatic hydrocarbons Fibers Dust	Study examines decreasing exposure over time. Study uses part of Danish cohort described in Kolstad *et al.* (1994, 1995).
Wong *et al.* (1994). Workers in the US.	Open mould processing Mixing and closed mould processing Finishing operations Plant supports Maintenance and preparation Supervisory and professional	15,826	307,932	1948-1989	≥ 6 months	< 1 1-1.9 2-4.9 5-9.9 ≥ 10 up to 1977	< 1 1-1.9 2-4.9 5-9.9 ≥ 10 up to 1977		< 10.0 10.0-29.9 30.0-99.9 ≥ 100.0		< 10 10-19 ≥ 20			Job category analysis - all cohort members employed > 2 yr
Ruder *et al.* (2004). Workers at two boatbuilding plants in the U.S.	High exposure: Fiber glass (TWA = 42.5 ppm) or Lamination (TWA = 71.7 ppm) Low exposure: Never worked in high-exposure departments	5,204	135,588	1959-1998	> 1 d	< 1 > 1							Fiberglass Solvents Wood dust Wood finishing agents	
Styrene-Butadiene Rubber Industry (SBR)														
McMichael *et al.* (1976). Male workers at a tire plant in the US (OH).	SBR Plant 15 other work areas	6,678	--	1964-1973	> 10 yr (99%)	>2 >5							Gases or liquids that are ingredients for the particular synthetic rubber being made	
Sathiakumar *et al.* (2005). Male workers at 8 U.S. and Canadian synthetic rubber plants.	Production (polymerization, coagulation, finishing) Maintenance (shop, field) Labor (production, manintence) Laboratories Other	17,924	--	1944-1991 1992-1998 1944-1998	≥ 1yr	< 10 ≥ 10					< 20 20-29 ≥ 30	Ever Never	1,3-Butadiene DMDTC Benzene	Graff *et al.* (2005) examined cumulative exposure and freqeuency of peak exposure > 50 ppm in same cohort
Polystyrene/Styrene Production Industry (PS)														
Frentzel-Beyme *et al.* (1978). Workers at BASF Ludwigshafen, Germany.	All employees engaged in the manufacture of styrene or polystyrene	1,960	20,138	1931-1976	> 1 month									
Bond *et al.* (1992). Male workers at Dow Chemical plants in the US.	Styrene monomer and finishing Styrene-butadiene latex production Product research and development Polymerization, coloring, extrusion All styrene-based products cohort Workers unexposed to styrene Styrene/ethylbenzene only Mixed exposures to styrene, ethyl benzene, benzene, alkylbenzenes, acrylonitrile Extrusion fumes; indrenct colorants; styrene, ethylbenzene, or acrylonitrile Extrusion fumes; drenct colorants; styrene, ethylbenzene, or acrylonitrile Polymer dusts plus styrene/ethylbenzene Several other categories 1-4 ppm and ≥ 5 styrene 8-hr TWA.	2,904	89,825	1937-1986	≥ 1 yr	< 1 1-4 ≥ 5							Ethylbenzene Alkylbenzene compounds Benzene Acrylontrile Polymer dusts Styrene oligomers Mineral Oil Direct colorants Indirect colorants	
Hodgson and Jones (1985). Male workers at a plant in England.	Laboratory and manual workers (styrene production, polymerization, and processing) Manual workers with no specific occupational styrene exposure	622	8,654	1945-1978	≥ 1 yr					1945-1958 1959-1968 1969-1974			Acrylonitrile Pitch Polyvinyl chlorinde fumes Benzene Dyestuffs Antioxidants Polyolefines Ethylene Oxide	Exposure substantially < 100 ppm. Also conducted analyses stratified by age.
Nicholson *et al.* (1978). Male workers at a plant in the US (TX).	Production and polymerization Maintenance Utilities service	560	--	1960-1975	≥ 5 yr						10-19 20-29 ≥ 30		Benzene	Exposures: 5 – 20 ppm or < 1 ppm
Styrene Monitored Workers														
Anttila *et al.* (1998). Male and female workers biologically monitored by the Finnish Institute of Occupational Health.	Workers monitored by Finnish Institute of Occupational Health	2,580	34,288	1973-1983	--						0-9 ≥ 10			Time since measurement of styrene metabolite in urine.
Environmental Exposure														
Loughlin *et al.* (1999). Former students of an Eastern TX high school, located adjacent to styrene mfg facilities.	Students attending high school adjacent to SBR facility	15,403	310,254	1963/4-1992/3	≥ 3 consec. months attendance in a school year	≤ 2 ≥ 3								

Table 2
Summary Statistics for Analyses in the NTP Report on Carcinogens Draft Background Document for Styrene Tables 3-7 and 3-8

Cancer	Observed	Expected	SMR	95% CI	p-value (Fisher's test)
All Workers					
Esophagus	51	42.7	1.19	0.89-1.57	0.003
Pancreas	95	87.3	1.09	0.88-1.33	0.12
Larynx	36	32.7	1.10	0.77-1.52	0.30
Lung	654	579.3	1.13	1.04-1.22	0.00005
All LH	196	199.2	0.98	0.85-1.13	0.44
Lymphoma	58	53.8	1.08	0.82-1.39	0.33
Hodgkin's	27	26.8	1.01	0.66-1.47	0.51
MM	17	19.6	0.87	0.51-1.39	0.70
Leukemia	73	76.1	0.96	0.75-1.21	0.62
High-Styrene-Exposure Groups (Laminators and Others)					
Esophagus	14	≥ 7.2	1.94	1.06-3.26	0.003
Pancreas	34	19.2	1.77	1.23-2.47	0.001
Larynx	3	≥ 1.9	1.58	0.33-4.61	0.13
Lung	158	151.5	1.04	0.89-1.22	0.30
All LH	52	52.8	0.98	0.74-1.29	0.45
Lymphoma	14	≥ 15.1	0.93	0.51-1.56	0.13
Hodgkin's	11	≥ 7.9	1.39	0.7-2.49	0.08
MM	4	≥ 3.4	1.18	0.32-3.01	0.26
Leukemia	19	19.6	0.97	0.58-1.51	0.39

Table 3.1a
Esophageal Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	Reinforced plastics	13	0.92	0.50-1.57
	No reinforced plastics	7	1.13	0.45-2.32
Kogevinas *et al.* (1993, 1994)	Laminators	10	1.81	0.87-3.34
	Unspecified Tasks	5	0.83	0.27-1.93
	Other exposed Jobs	1	0.24	0.01-1.31
	Unexposed	**0**	**--**	**0-0.93**
	Total	17	0.82	0.47-1.31
Wong *et al.* (1994) [c]	Open mould processing	2	3.57	
	Mixing and closed mould processing	0	--	
	Finishing operations	4	3.01	
	Plant supports	1	0.98	
	Maintenance and preparation	3	2.30	
	Supervisory and professional	1	1.99	
	Total	**14**	**1.92**	**1.05-3.22**
Ruder *et al.* (2004)	High Exposure	2	1.65[d]	0.20-5.94
	Low Exposure	10	2.34[d]	**1.12-4.31**
	Total	**12**	**2.19[d]**	**1.13-3.83**
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992)	Total	3	0.63	0.13-1.85
Hodgson and Jones (1985) [c]	Exposed workers	1	--[e]	
	Unexposed workers	0	--[e]	

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in the study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) SMR not calculated by authors if observed <10

Table 3.1b
Esophageal Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]											
	Kogevinas *et al.* (1993, 1994)				Wong *et al.* (1994)			Ruder *et al.* (2004) [d]			
	Category	**Obs**	**RR**	**95% CI**	**Category**	**Obs**	**SMR [b, c]**	**Category**	**Obs**	**SMR**	**95% CI**
Employment Duration (Years)					< 1	2	1.60	> 1	3	1.26	0.26-3.69
					1-1.9	3	2.39				
					2-4.9	4	2.48				
					5-9.9	1	0.77				
					≥ 10	4	2.13				
Exposure Duration (Years)					< 1	2	1.55				
					1-1.9	3	2.37				
					2-4.9	4	2.41				
					5-9.9	1	0.73				
					≥ 10	4	2.34				
Cumulative Exposure (ppm-yr)	< 75	5	1.0		< 10.0	4	2.51				
	100-199	2	1.01	0.20-5.23	10.0-29.9	2	1.24				
	200-499	3	1.67	0.39-7.18	30.0-99.9	**6**	**2.95**				
	≥ 500	4	1.76	0.42-7.30	≥ 100.0	2	0.97				
	p_{trend}		0.31								
Time Since First Exposure (Years)					< 10	2	1.43				
					10-19	**8**	**2.66**				
					≥ 20	4	1.38				

Styrene-Butadiene Rubber Industry (SBR) [a]				
	Sathiakumar *et al.* (2005) [b]			
	Category	**Obs**	**SMR**	**95% CI**
Period of Follow-up (Years)	1944-1991	25	0.77	0.50-1.14
	1992-1998	19	1.33	0.80-2.08
	1944-1998	44	0.94	0.68-1.26

a) Statistically significant findings indicated in bold.

b) Values were divided by 100 for comparison.

c) 95% Confidence Interval was not provided, but statistical significance was indicated in study.

d) Compared to the US population. Similar results when compared to Washington state population.

Table 3.2a
Pancreatic Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR [b]	95% CI [b]
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	1-49% employees in reinforced plastics	24	1.1	0.6-2.2
	50-100 % employees in reinforced plastics	**17**	**2.2**	**1.1-4.5**
	Total Reinforced plastics	41	1.2	0.86-1.63
	No reinforced plastics	14	0.9	0.49-1.51
Kogevinas *et al.* (1993, 1994)	Laminators	12	1.48	0.76-2.58
	Unspecified Tasks	17	1.17	0.68-1.88
	Other exposed Jobs	2	0.30	0.04-1.10
	Unexposed	5	0.79	0.26-1.86
	Total	37	1.00	0.71-1.38
Wong *et al.* (1994) [c]	Open mould processing	1	0.80	
	Mixing and closed mould processing	2	1.57	
	Finishing operations	3	0.93	
	Plant supports	1	0.44	
	Maintenance and preparation	1	0.34	
	Supervisory and professional	0	--	
	Total	19	1.13	0.68-1.77
Ruder *et al.* (2004)	High Exposure	4	1.81[d]	0.49-4.64
	Low Exposure	10	1.26[d]	0.61-2.33
	Total	14	1.38[d]	0.76-2.32
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992)	Total	5	0.49	0.16-1.13
Frentzel-Beyme *et al.* (1978) [e]	Total	2	2/0.7	p = 0.16
Styrene Monitored Workers				
Anttila *et al.* (1998)	Total	3	1.66	0.34-4.85

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in the study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) Values based on two comparison groups.

Table 3.2b
Pancreatic Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994) [b]				Wong *et al.* (1994) [b, c]			Ruder *et al.* (2004) [d]			
	Category	**Obs**	**IRR**	**95% CI**	**Category**	**Obs**	**RR**	**95% CI**	**Category**	**Obs**	**SMR**	**Category**	**Obs**	**SMR**	**95% CI**
Employment Duration (Years)	< 1	20	2.5	0.8-7.2					< 1	6	2.09	> 1	7	1.49	0.60-3.08
	≥ 1	21	1.8	0.6-7.4					1-1.9	3	1.05				
									2-4.9	5	1.33				
									5-9.9	0	--				
									≥ 10	5	1.18				
Exposure Duration (Years)									< 1	6	2.03				
									1-1.9	3	1.04				
									2-4.9	5	1.29				
									5-9.9	0	--				
									≥ 10	5	1.30				
Cumulative Exposure (ppm-yr)					< 75	9	1.0		< 10.0	5	1.40				
					100-199	5	1.44	0.48-4.34	10.0-29.9	6	1.61				
					200-499	6	1.90	0.65-5.53	30.0-99.9	3	0.63				
					≥ 500	10	2.56	0.90-7.31	≥ 100.0	5	1.06				
					p_{trend}		0.068								
Employment Start Date	> 1970	14	1.1	0.4-3.5											
	≤ 1970	27	1.1	0.4-3.4											
Time Since Hire/First Exposure (Years)	< 10	15	1.3	0.5-3.5					< 10	5	1.45				
	≥ 10	26	1.5	0.5-4.3					10-19	6	0.87				
									≥ 20	8	1.25				

Styrene-Butadiene Rubber Industry (SBR) [a]

	Sathiakumar *et al.* (2005) [b]			
	Category	**Obs**	**SMR**	**95% CI**
Period of Follow-up (Years)	1944-1991	49	0.76	0.56-1.01
	1992-1998	27	1.16	0.76-1.68
	1944-1998	76	0.87	0.68-1.08

Styrene Monitored Workers [a]

	Anttila *et al.* (1998)			
	Category	**Obs**	**SIR**	**95% CI**
Time Since First Measurement (Years)	0-9	0	0.00	0.00-3.76
	≥ 10	3	3.64	0.75-10.6

a) Statistically significant findings indicated in bold.

b) Ratios and confidence intervals were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in the study.

d) Compared to the US population. Similar results when compared to Washington state population.

Table 3.3a
Laryngeal Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR [b]	95% CI [b]
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	Reinforced plastics	25	1.1	0.71-1.63
	No reinforced plastics	14	1.45	0.79-2.43
Kogevinas *et al.* (1993, 1994)	Laminators	3	1.55	0.32-4.52
	Unspecified Tasks	4	1.18	0.32-3.02
	Other exposed Jobs	1	0.59	0.01-3.28
	Unexposed	2	1.32	0.16-4.75
	Total	10	1.11	0.53-2.05
Wong *et al.* (1994) [c]	Open mould processing	0	--	
	Mixing and closed mould processing	0	--	
	Finishing operations	0	--	
	Plant supports	0	--	
	Maintenance and preparation	0	--	
	Supervisory and professional	0	--	
	Total [d]	4	1.02	0.28-2.61
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992)	Total	1	--[e]	0-1.95

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) The total includes the entire study cohort, it is not the sum of all the observed cases by job category.

e) SMR not calculated by authors when observed <3.

Table 3.3b
Laryngeal Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]				
	Wong *et al.* (1994)			
	Category	**Obs**	**SMR [b, c]**	
Employment Duration (Years)	< 1	3	4.53	
	1-1.9	1	1.49	
	2-4.9	0	--	
	5-9.9	0	--	
	≥ 10	0	--	
Exposure Duration (Years)	< 1	3	4.39	
	1-1.9	1	1.47	
	2-4.9	0	--	
	5-9.9	0	--	
	≥ 10	0	--	
Cumulative Exposure (ppm-yr)	< 10.0	1	1.16	
	10.0-29.9	1	1.15	
	30.0-99.9	1	0.91	
	≥ 100.0	1	0.91	
Time Since Hire/First Exposure (Years)	< 10	2	2.32	
	10-19	1	0.62	
	≥ 20	1	0.69	
Styrene-Butadiene Rubber Industry (SBR) [a]				
	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR[b]**	**95% CI**
Period of Follow-up (Years)	1944-1991	17	0.96	**-- [d]**
	1992-1998	**0**	**--**	**0-0.57**
	1944-1998	17	0.71	0.41-1.13

a) Statistically significant findings indicated in bold.

b) Values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) The authors reported a 95% CI of 0.56 to 0.54 but this is clearly a typo. We assume it was likely 0.56 to 1.54 but cannot be certain.

Table 3.4a
Lung Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI [b]
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	1-49% employees in reinforced plastics	176	0.9	0.7-1.1
	50-100 % employees in reinforced plastics	72	1	0.7-1.3
	Total	248	1.12	0.98-1.26
	No reinforced plastics	**123**	**1.23**	**1.02-1.47**
Kogevinas *et al.* (1993, 1994)	Laminators	60	1.06	0.81-1.36
	Unspecified Tasks	78	0.99	0.78-1.24
	Other exposed Jobs	42	0.89	0.65-1.21
	Unexposed	37	0.84	0.58-1.16
Wong *et al.* (1994) [c,e]	Open mould processing	8	0.9	
	Mixing and closed mould processing	10	1.24	
	Finishing operations	31	1.43	
	Plant supports	17	1.07	
	Maintenance and preparation	**30**	**1.49**	
	Supervisory and professional	5	0.66	
Ruder *et al.* (2004) [e]	High Exposure	18	1.16[d]	0.69-1.84
	Low Exposure	58	1.01[d]	0.77-1.31
	Total	76	1.04[d]	0.82-1.31
Polystyrene/Styrene Production Industry (PS) [a]				
Frentzel-Beyme *et al.* (1978) [f]	Total	3	3/5.6	--
Bond et al. (1992)	Total	56	0.81	0.61-1.05
Hodgson and Jones (1985) [c,e]	Exposed population	5	--	
	Unexposed population	24	0.9	
Nicholson *et al.* (1978)	Total	6	6/6.99	
Styrene Monitored Workers [a]				
Anttila *et al.* (1998)	Total	5	0.59	0.19-1.38
Environmental Exposure [a]				
Loughlin *et al.* (1999) [e]	Men	5	1.46	0.47-3.40
	Women	1	0.44	0.01-2.48

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) Includes lung, trachea, and bronchus.

f) Values based on two comparison groups.

Table 3.4b
Lung Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994)				Wong *et al.* (1994) [e]			Ruder *et al.* (2004) [e]			
	Category	**Obs**	**IRR**	**95% CI**	**Category**	**Obs**	**RR**	**95% CI**	**Category**	**Obs**	**SMR [b, c]**	**Category**	**Obs**	**SMR**	**95% CI**
Employment Duration (Years)	< 1 ≥ 1	122 126	1.2 0.9	0.8-1.6 0.7-1.3					< 1 1-1.9 2-4.9 5-9.9 ≥ 10	**36** 25 **45** 28 28	**1.83** 1.26 **1.77** 1.35 0.95	> 1	31	0.93[d]	0.63-1.31
Exposure Duration (Years)									< 1 1-1.9 2-4.9 5-9.9 ≥ 10	**37** 25 **44** 30 26	**1.83** 1.24 **1.68** 1.37 0.97				
Cumulative Exposure (ppm-yr)					< 75 100-199 200-499 ≥ 500 p_{trend}	73 25 26 37	1.0 0.75 0.74 0.90 <0.43	 0.47-1.19 0.47-1.16 0.58-1.38	< 10.0 10.0-29.9 30.0-99.9 ≥ 100.0	**37** **48** 43 34	**1.50** **1.88** 1.32 1.04				
Employment Start Date	> 1970 ≤ 1970	86 162	1.1 1.6	0.7-1.7 0.9-2.5											
Time Since Hire/First Exposure (Years)	< 10 ≥ 10	78 170	0.8 0.9	0.6-1.2 0.6-1.5					< 10 10-19 ≥ 20	23 **70** **69**	1.07 **1.46** **1.51**				

Styrene-Butadiene Rubber Industry (SBR)[a]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR[b]**	**95% CI**
Period of Follow-up (Years)	1944-1991	406	0.93	0.84-1.02
	1992-1998	157	0.87	0.74-1.02
	1944-1998	**563**	**0.91**	**0.84-0.99**

Polystyrene/Styrene Production Industry (PS) [a]

	Nicholson *et al.* (1978) [b]		
	Category	**Obs**	**Obs/Exp**
Time Since Hire/First Exposure (Years)	≥ 10	6	6/6.99

Styrene Monitored Workers[a]

	Anttila *et al.* (1998) [e]			
	Category	**Obs**	**SIR**	**95% CI**
Time Since First Measurement (Years)	0-9	1	0.21	0.01-1.16
	≥ 10	4	1.11	0.30-2.84

Table 3.5a
All Lymphohematopoietic Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI
Reinforced Plastic Industry (RPC) [a]				
Kolstad et al. (1994, 1995)	1-49% employees in reinforced plastics	81	1.24	0.99-1.54
	50-100 % employees in reinforced plastics	31	1.09	0.74-1.55
	Total Reinforced plastics	112	1.2	0.98-1.44
	No reinforced plastics	37	0.92	0.65-1.27
	Production unclassified	12	1.71	0.89-2.99
Kogevinas *et al.* (1993, 1994)	Laminators	13	0.81	0.43-1.39
	Unspecified Tasks	30	1.19	0.80-1.70
	Other exposed Jobs	7	0.65	0.26-1.34
	Unexposed	9	0.91	0.41-1.72
	Total	60	0.93	0.71-1.20
Wong *et al.* (1994) [c]	Open mould processing	4	1.41	
	Mixing and closed mould processing	2	0.71	
	Finishing operations	4	0.62	
	Plant supports	3	0.65	
	Maintenance and preparation	5	0.93	
	Supervisory and professional	2	1.02	
	Total	31'	0.82	0.56-1.17
Ruder *et al.* (2004)	High Exposure	4	0.71[d]	0.19-1.81
	Low Exposure	12	0.74[d]	0.38-1.29
	Total	16	0.73[d]	0.42-1.19
Styrene-Butadiene Rubber Industry (SBR) [a]				
McMichael *et al.* (1976) [e]	Receiving and shipping		**1.8**	**1.3-2.7**
	Compounding, mixing: cement mixing		**1.4**	**1.1-2.0**
	Inspection, finishing, repair		**2**	**1.5-2.9**
	Synthetic plant		**6.2**	**4.1-12.5**
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992) [c]	Styrene monomer and finishing	5	1.28	
	Styrene-butadiene latex production	1	--[g]	
	Product research and development	6	0.95	
	Polymerization, coloring, extrusion	16	1.72	
	Total	28	1.44	0.95-2.08
Hodgson and Jones (1985)	Total	4	2.5	
Styrene Monitored Workers [a]				
Anttila *et al.* (1998)	Total	2	0.39	0.05-1.40
Environmental Exposure [a]				
Loughlin *et al.* (1999)	Men	12	1.64	0.85-2.87
	Women	2	0.47	0.06-1.70

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in the study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) McMichael et al. (1976) calculated 99.9% Confidence Intervals and did not report non-significant associations.

f) The total includes the entire study cohort, it is not the sum of all the observed cases by exposure category.

g) SMR not calculated by authors when observed <3.

Table 3.5b
All Lymphohematopoietic Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994)				Wong *et al.* (1994)			Ruder *et al.* (2004)			
	Category	**Obs**	**SIR**	**95% CI**	**Category**	**Obs**	**SMR/RR**	**95% CI**	**Category**	**Obs**	**SMR** [b, c]	**Category**	**Obs**	**SMR**	**95% CI**
Employment Duration (Years)									< 1 1-1.9 2-4.9 5-9.9 ≥ 10	3 7 10 4 7	0.39 0.97 1.12 0.63 0.94	> 1	5	0.53[d]	0.17-1.25
Exposure Duration (Years)					< 1[e] ≥ 1[e] < 2[e] ≥ 2[e]	16 34 29 20	0.84 1.02 1.02 0.93	0.48-1.37 0.71-1.43 0.68-1.47 0.57-1.43	< 1 1-1.9 2-4.9 5-9.9 ≥ 10	4 7 9 4 7	0.51 0.96 0.99 0.61 1.03				
Cumulative Exposure (ppm-yr)					< 75 100-199 200-499 ≥ 500 p_{trend}	20 8 10 9	0.01 0.98 1.24 0.84 0.65	0.43-2.26 0.57-2.72 0.35-2.02	< 10.0 10.0-29.9 30.0-99.9 ≥ 100.0	9 5 8 9	1.05 0.56 0.76 0.94				
Employment Start Date	1964-1970 1971-1975 1976-1988	**6** 28 18	**1.32** 1.12 0.97	**1.02-1.67** 0.75-1.62 0.57-1.53											
Time Since Hire/First Exposure (Years)	< 10 ≥ 10	48 64	1.19 1.20	0.88-1.58 0.92-1.53	*1994* < 10 10-19 ≥ 20 *1994* < 10 10-19 ≥ 20 p_{trend} *1993* < 10 10-19 ≥ 20	*(Table 3)* 13 26 10 *(Table 4)* 13 **25** **9** *1993* 15 24 11	*(Table 3)* 0.60 1.25 1.32 *(Table 4)* 0.01 **2.90** **3.97** **0.012** *(Table 3)* 0.67 1.09 1.40	0.32-1.03 0.82-1.83 0.64-2.44 **1.29-6.48** **1.30-12.13** 0.38-1.11 0.70-1.62 0.70-2.51	< 10 10-19 ≥ 20	9 10 12	0.81 0.66 1.04				
Average Exposure (ppm)					< 60 60-99 100-119 120-199 ≥ 200 p_{trend}	7 9 **10** **13** 8	0.01 1.68 **3.11** **3.08** 3.59 **0.019**	0.59-4.79 **1.07-9.06** **1.04-9.08** 0.98-13.14							

Styrene-Butadiene Rubber Industry (SBR) [a]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR**[b]	**95% CI**
Period of Follow-up (Years)	1944-1991	115	1.07	0.88-1.28
	1992-1998	47	1.04	0.77-1.39
	1944-1998	162	1.06	0.90-1.23

Styrene Monitored Workers [a]

	Anttila *et al.* (1998)			
	Category	**Obs**	**SIR**	**95% CI**
Time Since First Measurement (Years)	0-9	2	0.61	0.07-2.20
	≥ 10	0	--	0.00-1.97

Environmental Exposure [a]

	Loughlin *et al.* (1999)			
	Category	**Obs**	**SMR**	**95% CI**
High School Attendance (Years)	≤ 2	4	3.2	0.87-8.20
	≥ 3	8	1.32	0.57-2.60

a) Statistically significant findings indicated in bold.
b) Values were divided by 100 for comparison.
c) If 95% Confidence Interval was not provided, statistical significance was indicated in the study.
d) Compared to the US population. Similar results when compared to Washington state population.
e) The 1 year cutoff was used in the 1993 study; the 2 year cutoff was used in the 1994 study

Table 3.6a
Non-Hodgkin's Lymphoma Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI
Reinforced Plastic Industry (RP) [a]				
Kolstad *et al.* (1994, 1995)	1-49% employees in reinforced plastics	**36**	**1.65**	**1.15-2.28**
	50-100 % employees in reinforced plastics	6	0.62	0.23-1.35
	Total reinforced plastics	42	1.33	0.96-1.80
	No reinforced plastics	15	1.13	0.63-1.86
	Production unclassified	4	1.68	0.46-4.30
Kogevinas *et al.* (1993, 1994)	Laminators	7	1.40	0.56-2.88
	Unspecified Tasks	4	0.55	0.15-1.39
	Other exposed Jobs	1	0.30	0.01-1.67
	Unexposed	3	1.01	0.21-2.94
	Total	15	0.77	0.43-1.28
Wong *et al.* (1994) [c]	Open mould processing	1	2.55	
	Mixing and closed mould processing	0	--	
	Finishing operations	0	--	
	Plant supports	0	--	
	Maintenance and preparation	1	1.24	
	Supervisory and professional	1	3.44	
	Total	4	0.72	0.19-1.85
Ruder *et al.* (2004) [e]	Total	1	0.51 [d]	0.01-2.86
Styrene-Butadiene Rubber Industry (SBR) [a]				
Sathiakumar *et al.* (2005)	Production, polymerisation	11	1.37	0.69-2.46
	Production, coagulation	4	1.00	0.27-2.56
	Production, finishing	16	1.43	0.82-2.33
	Maintenance, shop	4	1.05	0.29-2.68
	Maintenance, field	11	1.04	0.52-1.86
	Labour, production	4	1.57	0.43-4.03
	Labour, maintenance	7	1.15	0.46-2.37
	Laboratories	5	1.17	0.38-2.74
	Other operations	4	0.51	0.14-1.31
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992) [c]	Styrene monomer and finishing	1	--	
	Styrene-butadiene latex production	--	--	
	Product research and development	2	--	
	Polymerization, coloring, extrusion	4	1.38	
	Total	7	1.17	0.47-2.40
Hodgson and Jones (1985)	Total	2	-- [e]	
Nicholson *et al.* (1978)	Total	1	1/1.25	

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated.

d) Compared to the US population. Similar results when compared to Washington state population.

e) SMR not calculated by authors if observed <10

Table 3.6b
Non-Hodgkin's Lymphoma Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994) [e]				Wong *et al.* (1994) *		
	Category	**Obs**	**SIR**	**95% CI**	**Category**	**Obs**	**SMR/RR**	**95% CI**	**Category**	**Obs**	**SMR** [b, c]
Employment Duration (Years)									< 1	1	0.89
									1-1.9	0	--
									2-4.9	1	0.75
									5-9.9	0	--
									≥ 10	2	1.86
Exposure Duration (Years)					< 1 [e]	3	0.54	0.11-1.57	< 1	1	0.87
					≥ 1	9	0.89	0.41-1.69	1-1.9	0	--
					< 2 [e]	5	0.60	0.19-1.40	2-4.9	1	0.73
					≥ 2	7	1.05	0.42-2.17	5-9.9	0	--
									≥ 10	2	2.09
Cumulative Exposure (ppm-yr)					< 75 [f]	5	0.01		< 10.0	1	0.78
					100-199	5	2.63	0.74-9.32	10.0-29.9	0	--
					200-499	5	2.99	0.82-10.91	30.0-99.9	2	1.29
					≥ 500	3	1.64	0.34-7.82	≥ 100.0	1	0.74
					p_{trend}		0.52				
Employment Start Date	1964-1970	21	1.28	0.79-1.96							
	1971-1975	10	1.19	0.57-2.18							
	1976-1988	11	1.64	0.82-2.94							
Time Since Hire/First Exposure (Years)	< 10	**21**	**1.68**	**1.03-2.53**		*1994*	*(Table 3)*		< 10	1	0.47
	≥ 10	21	1.12	0.69-1.70	< 10	3	0.51	0.11-1.49	10-19	1	0.46
					10-19	5	0.76	0.25-1.78	≥ 20	2	1.63
					≥ 20	4	1.55	0.42-3.97			
						1994 [f]	*(Table 4)*				
					< 10	6	0.01				
					10-19	8	2.43	0.69-8.49			
					≥ 20	4	5.16	0.90-29.47			
					p_{trend}		0.072				
						1993	*(Table 3)*				
					< 10	3	0.49	0.10-1.43			
					10-19	5	0.72	0.23-1.69			
					≥ 20	4	1.50	0.41-3.85			
Average Exposure (ppm) [f]					< 60	3	0.01				
					60-99	4	2.51	0.49-12.87			
					100-119	1	1.65	0.15-18.57			
					120-199	8	7.15	1.21-42.11			
					≥ 200	2	4.40	0.42-45.99			
					p_{trend}		0.052				

Styrene-Butadiene Rubber Industry (SBR) [d]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR** [b]	**95% CI**
Period of Follow-up (Years)	1944-1991	33	0.93	0.64-1.31
	1992-1998	20	1.12	0.68-1.73
	1944-1998	53	1.00	0.75-1.30
Hourly Employee	Ever	49	1.11	0.82-1.47
	Never	4	0.44	0.12-1.12
Years Since Hire (ysh) and Years Worked (yrs)	< 20 ysh, < 10 yrs	0	0	0-0.76
	< 20 ysh, 10+ yrs	1	0.28	0.01-1.55
	20-29 ysh, < 10 yrs	5	1.43	0.46-3.33
	20-29 ysh, 10+ yrs	11	1.70	0.85-3.05
	30+ ysh, < 10 yrs	7	0.87	0.35-1.79
	30+ ysh, 10+ yrs	25	1.41	0.91-2.08

Environmental Exposure

	Loughlin *et al.* (1999)			
	Category	**Obs**	**SMR**	**95% CI**
High School Attendance (Years)	≤ 2	0	0.00	0-31.89
	≥ 3	0	0.00	0-6.43

a) Statistically significant findings indicated in bold.
b) Values were divided by 100 for comparison.
c) If 95% Confidence Interval was not provided, statistical significance was indicated.
d) Compared to the US population. Similar results when compared to Washington state population.
e) The 1 year cutoff was used in the 1993 study; the 2 year cutoff was used in the 1994 study.
f) Values include all lymphomas, and are also presented in Table 3.7b

Table 3.7a
Hodgkin's Lymphoma Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI
Reinforced Plastic Industry (RPC) [a]				
Kolstad et al. (1994, 1995)	1-49% employees in reinforced plastics	9	0.92	0.42-1.74
	50-100 % employees in reinforced plastics	7	1.41	0.57-2.91
	Total Reinforced plastics	16	1.08	0.62-1.76
	No reinforced plastics	6	1.00	0.37-2.17
	Production unclassified	2	1.71	0.21-6.17
Kogevinas *et al.* (1993, 1994)	Laminators	3	1.33	0.27-3.88
	Unspecified Tasks	3	1.07	0.22-3.12
	Other exposed Jobs	1	0.80	0.02-4.46
	Unexposed	0	--	0-3.18
	Total	7	0.90	0.36-1.84
Wong *et al.* (1994) [c]	Open mould processing	0	--	
	Mixing and closed mould processing	0	--	
	Finishing operations	1	1.71	
	Plant supports	0	--	
	Maintenance and preparation	0	--	
	Supervisory and professional	0	--	
	Total	4	0.90	0.25-2.30
Ruder *et al.* (2004)	High Exposure	1	1.66 [d]	0.04-9.24
	Low Exposure	0	--	--
	Total	1	0.57 [d]	0.01-3.15
Styrene-Butadiene Rubber Industry (SBR) [a]				
Sathiakumar *et al.* (2005)	Production, polymerisation	0	--	0-2.60
	Production, coagulation	0	--	0-5.69
	Production, finishing	2	0.88	0.11-3.19
	Maintenance, shop	0	--	0-5.30
	Maintenance, field	1	0.53	0.01-2.96
	Labour, production	0	--	0-5.47
	Labour, maintenance	1	0.74	0.02-4.11
	Laboratories	0	--	0-4.45
	Other operations	2	1.41	0.17-5.08
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992) [c]	Styrene monomer and finishing	2	-- [e]	
	Styrene-butadiene latex production	0	--	
	Product research and development	2	-- [e]	
	Polymerization, coloring, extrusion	1	-- [e]	
	Total	5	2.22	0.71-5.18
Hodgson and Jones (1985)	Total	0	--	
Styrene Monitored Workers [a]				
Anttila *et al.* (1998)	Total	2	1.89	0.23-6.84
Environmental Exposure [a]				
Loughlin *et al.* (1999)	Men	2	1.46	0.18-5.28
	Women	1	1.2	0.03-6.68

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) SMR not calculated by authors if observed <3.

Table 3.7b
Hodgkin's Lymphoma Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994)				Wong *et al.* (1994)		
	Category	**Obs**	**SIR**	**95% CI**	**Category**	**Obs**	**SMR**	**95% CI**	**Category**	**Obs**	**SMR** [b, c]
Employment Duration (Years)									< 1	2	1.75
									1-1.9	1	1.00
									2-4.9	1	0.87
									5-9.9	0	--
									≥ 10	0	--
Exposure Duration (Years)					< 1[e]	2	0.77	0.09-2.79	< 1	2	1.72
					≥ 1[e]	5	1.33	0.43-3.10	1-1.9	1	0.99
					< 2[e]	5	1.34	0.44-3.13	2-4.9	1	0.85
					≥ 2[e]	2	0.87	0.11-3.14	5-9.9	0	--
									≥ 10	0	--
Cumulative Exposure (ppm-yr)									< 10.0	2	1.74
									10.0-29.9	1	0.85
									30.0-99.9	1	0.83
									≥ 100.0	0	--
Employment Start Date	1964-1970	9	1.45	0.66-2.76							
	1971-1975	3	0.71	0.15-2.07							
	1976-1988	4	0.92	0.25-2.37							
Time Since Hire/First Exposure (Years)	< 10	11	1.21	0.61-2.17		*1994*	*(Table 3)*		< 10	3	1.29
	≥ 10	5	0.87	0.28-2.04	< 10	3	0.82	0.17-2.41	10-19	1	0.64
					10-19	3	1.53	0.32-4.47	≥ 20	0	--
					≥ 20	1	2.44	0.06-13.59			
						1994 [f]	*(Table 4)*				
					< 10	6	0.01				
					10-19	8	2.43	0.69-8.49			
					≥ 20	4	5.16	0.90-29.47			
					p_{trend}		0.072				
						1993	*(Table 3)*				
					< 10	3	0.79	0.16-2.32			
					10-19	3	1.43	0.29-4.17			
					≥ 20	1	2.38	0.06-13.27			

Styrene-Butadiene Rubber Industry (SBR) [a]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR**[b]	**95% CI**
Period of Follow-up (Years)	1944-1991	11	1.13	0.56-2.02
	1992-1998	1	0.98	0.02-5.45
	1944-1998	12	1.11	0.58-1.95
Hourly Employee	Ever	7	0.77	0.31-1.58
	Never	5	3.05	0.99-7.11
Years Since Hire (ysh) and Years Worked (yrs)	< 20 ysh, < 10 yrs	2	0.61	0.07-2.21
	< 20 ysh, 10+ yrs	3	1.78	0.37-5.19
	20-29 ysh, < 10 yrs	1	1.29	0.03-7.20
	20-29 ysh, 10+ yrs	1	0.70	0.02-3.92
	30+ ysh, < 10 yrs	0	--	0-5.91
	30+ ysh, 10+ yrs	0	--	0-2.71

Styrene Monitored Workers [a]

	Anttila *et al.* (1998)			
	Category	**Obs**	**SIR**	**95% CI**
Time Since First Measurement (Years)	0-9	2	2.53	0.31-9.15
	≥ 10	0	--	0-13.7

Environmental Exposure [a]

	Loughlin *et al.* (1999)			
	Category	**Obs**	**SMR**	**95% CI**
Exposure Duration (Years)	≤ 2	0	--	0-15.75
	≥ 3	2	1.77	0.21-6.38

a) Statistically significant findings indicated in bold.
b) Values were divided by 100 for comparison.
c) 95% Confidence Interval was not provided, but statistical significance was indicated in study.
d) Compared to the US population. Similar results when compared to Washington state population.
e) The 1 year cutoff was used in the 1993 study; the 2 year cutoff was used in the 1994 study.
f) Values include all lymphomas, and are also presented in Table 3.6b

Table 3.8a
Multiple Myeloma Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI [b]
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	1-49% employees in reinforced plastics	8	0.92	0.40-1.81
	50-100 % employees in reinforced plastics	4	1.18	0.32-3.02
	Total Reinforced plastics	12	0.99	0.51-1.73
	No reinforced plastics	3	0.55	0.11-1.61
	Production unclassified	0	--	0-4.29
Kogevinas *et al.* (1993, 1994)	Laminators	--	0.00	0-1.55
	Unspecified Tasks	7	1.93	0.78-3.98
	Other exposed Jobs	1	0.53	0.01-2.95
	Unexposed	2	1.13	0.14-4.08
	Total	10	0.99	0.48-1.83
Styrene-Butadiene Rubber Industry (SBR) [a]				
Sathiakumar *et al.* (2005)	Production, polymerisation	1	0.26	0.01-1.46
	Production, coagulation	0	--	0-1.83
	Production, finishing	2	0.38	0.05-1.37
	Maintenance, shop	1	0.57	0.01-3.20
	Maintenance, field	3	0.60	0.12-1.75
	Labour, production	4	1.89	0.52-4.83
	Labour, maintenance	7	1.50	0.60-3.10
	Laboratories	0	--	0-2.00
	Other operations	4	1.02	0.28-2.61
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992) [c]	Styrene monomer and finishing	1	-- [d]	
	Styrene-butadiene latex production	0	--	
	Product research and development	1	-- [d]	
	Polymerization, coloring, extrusion	5	2.94	
	Total	7	1.84	0.74-3.80
Hodgson and Jones (1985)	Total	0	-- [e]	

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated.

d) SMR not calculated by authors if observed <3.

e) SMR not calculated by authors if observed <10

Table 3.8b
Multiple Myeloma Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RPC) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994)			
	Category	**Obs**	**SIR**	**95% CI**	**Category**	**Obs**	**SMR**	**95% CI**
Exposure Duration (Years)					< 1[e]	4	0.15	0.43-4.06
					≥ 1[e]	4	0.74	0.20-1.89
					< 2[e]	5	1.29	0.42-3.02
					> 2[e]	3	0.80	0.16-2.33
Employment Start Date	1964-1970	6	0.80	0.29-1.74				
	1971-1975	6	1.99	0.73-4.34				
	1976-1988	0	--	0.02-3.50				
Time Since Hire/First Exposure (Years)	< 10	6	1.41	0.52-3.07		*1994*	*(Table 3)*	
	≥ 10	6	0.76	0.28-1.66	< 10	2	0.83	0.10-2.99
					10-19	5	1.40	0.45-3.26
					≥ 20	1	0.62	0.02-3.44
						1993	*(Table 3)*	
					< 10	2	0.81	0.10-2.94
					10-19	5	1.33	0.43-3.10
					≥ 20	1	0.60	0.02-3.34

Styrene-Butadiene Rubber Industry (SBR) [a]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR**[b]	**95% CI**
Period of Follow-up (Years)	1944-1991	20	1.10	0.67-1.70
	1992-1998	6	0.66	0.24-1.43
	1944-1998	26	0.95	0.62-1.40
Hourly Employee	Ever	20	0.86	0.53-1.33
	Never	6	1.46	0.54-3.17
Years Since Hire (ysh) and Years Worked (yrs)	< 20 ysh, < 10 yrs	0	--	0-2.36
	< 20 ysh, 10+ yrs	3	2.07	0.43-6.05
	20-29 ysh, < 10 yrs	2	1.17	0.14-4.23
	20-29 ysh, 10+ yrs	6	1.75	0.64-3.80
	30+ ysh, < 10 yrs	3	0.65	0.13-1.89
	30+ ysh, 10+ yrs	6	0.58	0.21-1.26

a) Statistically significant findings indicated in bold.

b) Values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated.

d) Compared to the US population. Similar results when compared to Washington state population.

e) The 1 year cutoff was used in the 1993 study; the 2 year cutoff was used in the 1994 study

Table 3.9a
Leukemia Cancer Risk in Job/Exposure Categories in Styrene Cohorts

Study	Job/Exposure Category	Observed	SMR/SIR/RR/SRR [b]	95% CI
Reinforced Plastic Industry (RPC) [a]				
Kolstad *et al.* (1994, 1995)	1-49% employees in reinforced plastics	28	1.15	0.77-1.67
	50-100% employees in reinforced plastics	14	1.38	0.75-2.32
	Total Reinforced plastics	42	1.22	0.88-1.65
	No reinforced plastics	13	0.86	0.46-1.47
	Production unclassified	6	2.37	0.87-5.16
Kogevinas *et al.* (1993, 1994)	Laminators	3	0.48	0.10-1.39
	Unspecified Tasks	16	1.4	0.79-2.28
	Other exposed Jobs	4	0.94	0.26-2.40
	Unexposed	4	0.99	0.27-2.54
	Total	28	1.04	0.69-1.50
Wong *et al.* (1994) [c]	Open mould processing	1	0.9	
	Mixing and closed mould processing	0	--	
	Finishing operations	2	0.8	
	Plant supports	1	0.56	
	Maintenance and preparation	1	0.48	
	Supervisory and professional	1	1.33	
	Total	11 [f]	0.74	0.37-1.32
Ruder *et al.* (2004)	High Exposure	1	0.46 [d]	0.01-2.58
	Low Exposure	4	0.64 [d]	0.17-1.63
	Total	5	0.59 [d]	0.19-1.38
Styrene-Butadiene Rubber Industry (SBR) [a]				
Sathiakumar *et al.* (2005)	Production, polymerisation	**18**	**2.04**	**1.21-3.22**
	Production, coagulation	**10**	**2.31**	**1.11-4.25**
	Production, finishing	19	1.56	0.94-2.44
	Maintenance, shop	4	0.93	0.25-2.38
	Maintenance, field	10	0.84	0.40-1.55
	Labour, production	4	1.23	0.34-3.15
	Labour, maintenance	**15**	**2.03**	**1.14-3.35**
	Laboratories	**14**	**3.26**	**1.78-5.46**
	Other operations	6	0.69	0.25-1.50
McMichael *et al.* (1976) [e]	Compounding, mixing: cement mixing		1.3	1.0-1.8
	Extrusion, tread cementing		**3.2**	**2.4-5.0**
	Inspection, finishing, repair		**3.7**	**2.8-5.3**
	Synthetic plant		**3.9**	**2.6-8.0**
Polystyrene/Styrene Production Industry (PS) [a]				
Bond *et al.* (1992) [c]	Styrene monomer and finishing	1	-- [g]	
	Styrene-butadiene latex production	1	-- [g]	
	Product research and development	1	-- [g]	
	Polymerization, coloring, extrusion	6	1.65	
	Total	9	1.18	0.54-2.24
Hodgson and Jones (1985)	Exposed workers	0	--	
	Unexposed workers	0	--	
	Total	1 [f]	-- [g]	
Nicholson *et al.* (1978)	Total	1	1/0.79	
Environmental Exposure [a]				
Loughlin *et al.* (1999)	Men	6	1.82	0.67-3.96
	Women	1	0.45	0.01-2.48

a) Statistically significant findings indicated in bold.

b) Some values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) McMichael et al. (1976) calculated 99.9% Confidence Intervals and did not report non-significant associations.

f) The total includes the entire study cohort, it is not the sum of all the observed cases by exposure category.

g) SMR not calculated by authors if observed <3.

Table 3.9b
Leukemia Cancer Risk Based on Several Exposure Measures in Styrene Cohorts

Reinforced Plastic Industry (RP) [a]

	Kolstad *et al.* (1994, 1995)				Kogevinas *et al.* (1993, 1994)				Wong *et al.* (1994)		
	Category	**Obs**	**SIR**	**95% CI**	**Category**	**Obs**	**SMR/RR**	**95% CI**	**Category**	**Obs**	**SMR** [b, c]
Employment Duration (Years)									< 1	0	--
									1-1.9	3	1.04
									2-4.9	4	1.13
									5-9.9	3	1.23
									≥ 10	1	0.35
Exposure Duration (Years)					< 1[e]	7	0.85	0.34-1.75	< 1	0	--
					≥ 1[e]	16	1.15	0.66-1.87	1-1.9	3	1.04
					< 2[e]	14	1.13	0.62-1.89	2-4.9	4	1.11
					≥ 2[e]	8	0.91	0.39-1.79	5-9.9	3	1.18
									≥ 10	1	0.39
Cumulative Exposure (ppm-yr)					< 75	11	0.01		< 10.0	1	0.29
					100-199	2	0.46	0.10-2.09	10.0-29.9	4	1.12
					200-499	3	0.69	0.19-2.53	30.0-99.9	3	0.72
					≥ 500	5	0.86	0.26-2.83	≥ 100.0	3	0.80
					p_{trend}		> 0.52				
Employment Start Date	1964-1970	**30**	**1.54**	**1.04-2.19**							
	1971-1975	9	1.00	0.46-1.90							
	1976-1988	3	0.51	0.11-1.50							
Time Since Hire/First Exposure (Years)	< 10	10	0.71	0.34-1.31		*Table 3*	*(1994)*		< 10	5	1.11
	≥ 10	**32**	**1.57**	**1.07-2.22**	< 10	5	0.52	0.17-1.22	10-19	4	0.68
					10-19	13	1.50	0.80-2.57	≥ 20	2	0.46
					≥ 20	4	1.36	0.37-3.47			
						Table 4	*(1994)*				
					< 10	5	0.01				
					10-19	12	3.01	0.90-10.08			
					≥ 20	4	3.79	0.70-20.59			
					p_{trend}		0.094				
						Table 3	*(1993)*				
					< 10	7	0.70	0.28-1.45			
					10-19	11	1.20	0.60-2.15			
					≥ 20	5	1.63	0.53-3.81			
Average Exposure (ppm)					< 60	3	0.01				
					60-99	4	1.58	0.32-7.79			
					100-119	8	4.43	0.98-20.03			
					120-199	3	1.36	0.22-8.48			
					≥ 200	3	2.16	0.29-16.24			
					p_{trend}		0.47				

Styrene-Butadiene Rubber Industry (SBR) [a]

	Sathiakumar *et al.* (2005)			
	Category	**Obs**	**SMR**[b]	**95% CI**
Period of Follow-up (Years)	1944-1991	51	1.16	0.86-1.53
	1992-1998	20	1.17	0.71-1.81
	1944-1998	71	1.16	0.91-1.47
Hourly Employee	Ever	63	1.23	0.94-1.57
	Never	8	0.82	0.35-1.61
Years Since Hire (ysh) and Years Worked (yrs)	< 20 ysh, < 10 yrs	4	0.57	0.16-1.46
	< 20 ysh, 10+ yrs	6	1.36	0.50-2.96
	20-29 ysh, < 10 yrs	4	0.98	0.27-2.51
	20-29 ysh, 10+ yrs	**19**	**2.58**	**1.56-4.03**
	30+ ysh, < 10 yrs	10	1.13	0.54-2.07
	30+ ysh, 10+ yrs	20	1.02	0.62-1.58

Environmental Exposure

	Loughlin *et al.* (1999)			
	Category	**Obs**	**SMR**	**95% CI**
High School Attendance (Years)	≤ 2	**3**	**5.29**	**1.09-15.46**
	≥ 3	3	1.10	0.23-3.21

a) Statistically significant findings indicated in bold.

b) Values were divided by 100 for comparison.

c) If 95% Confidence Interval was not provided, statistical significance was indicated in study.

d) Compared to the US population. Similar results when compared to Washington state population.

e) The 1 year cutoff was used in the 1993 study; the 2 year cutoff was used in the 1994 study.

Figures

Figure 1. The Reinforced Plastics and Composites Industry. Adapted from Cohen *et al*. (2002). *Studies with bold border included in NTP Draft Document Table 3-6.*

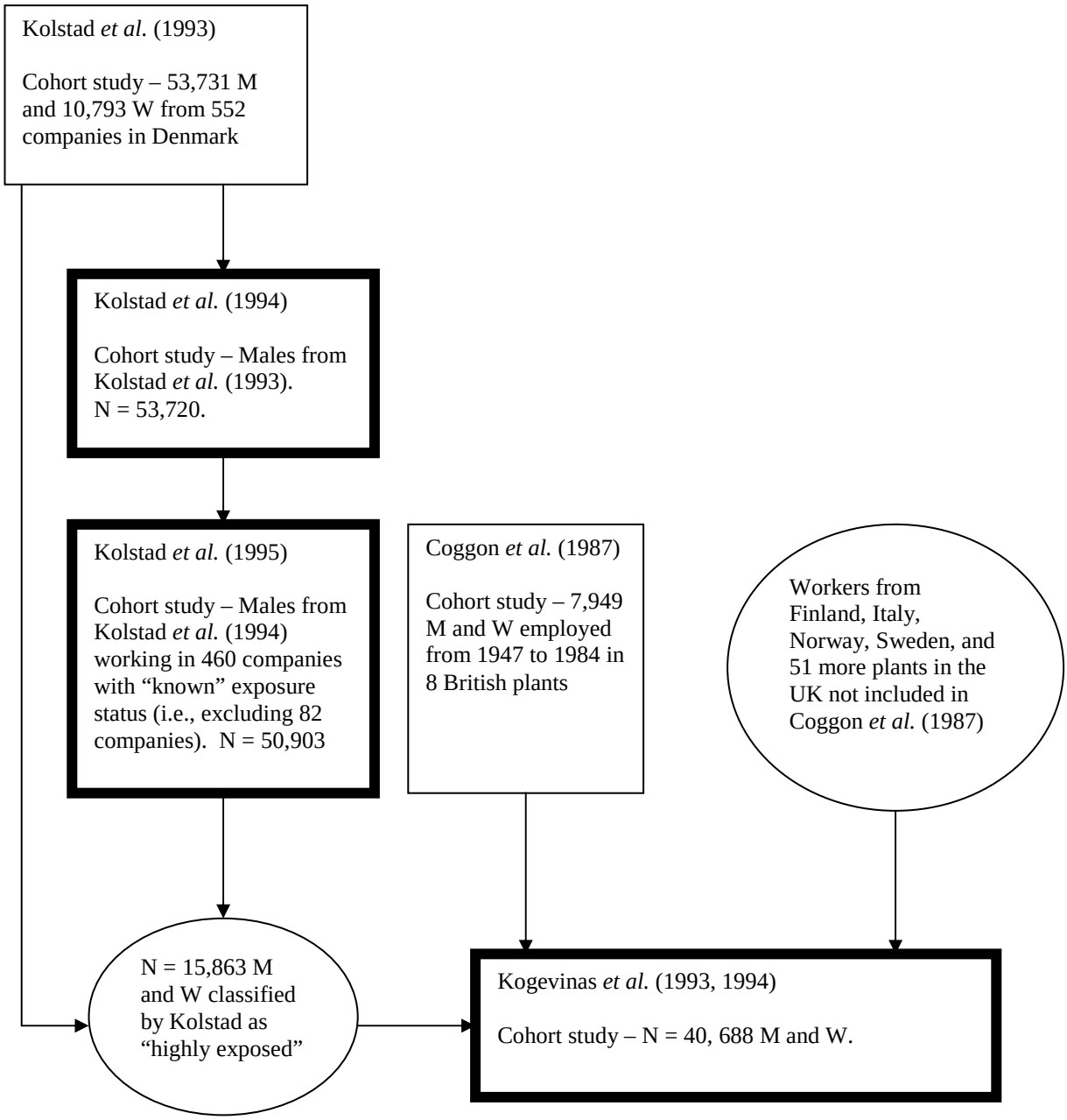

Figure 1 (Continued). The Reinforced Plastics and Composites Industry. Adapted from Cohen *et al*. (2002). *Studies with bold border included in NTP Draft Document Table 3-6.*

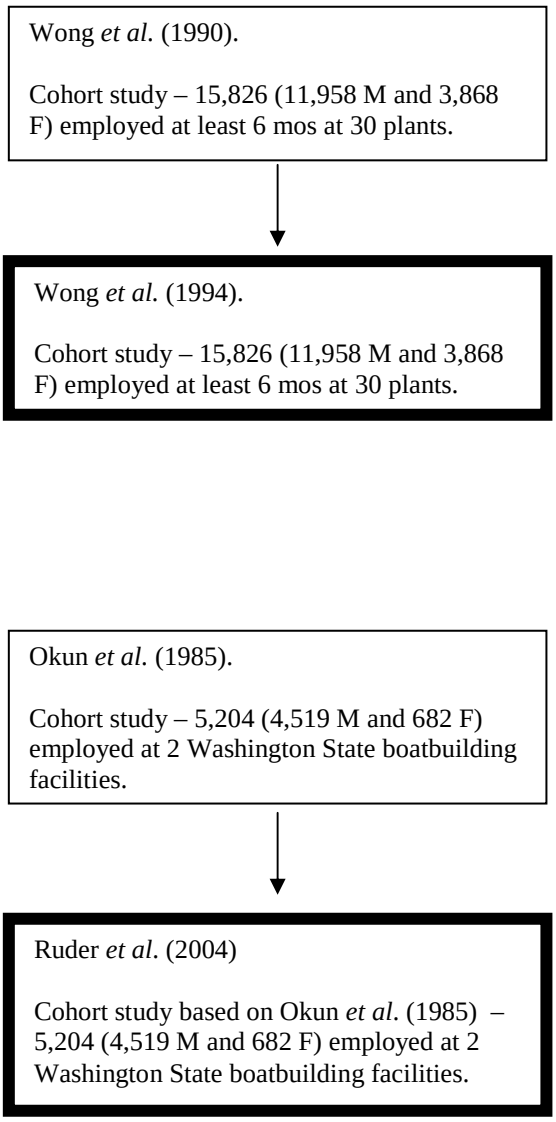

Figure 2. Major Epidemiologic Studies of the SBR Industry. Adapted from Cohen *et al*. (2002). *Studies with bold border included in NTP Draft Document Table 3-6.*

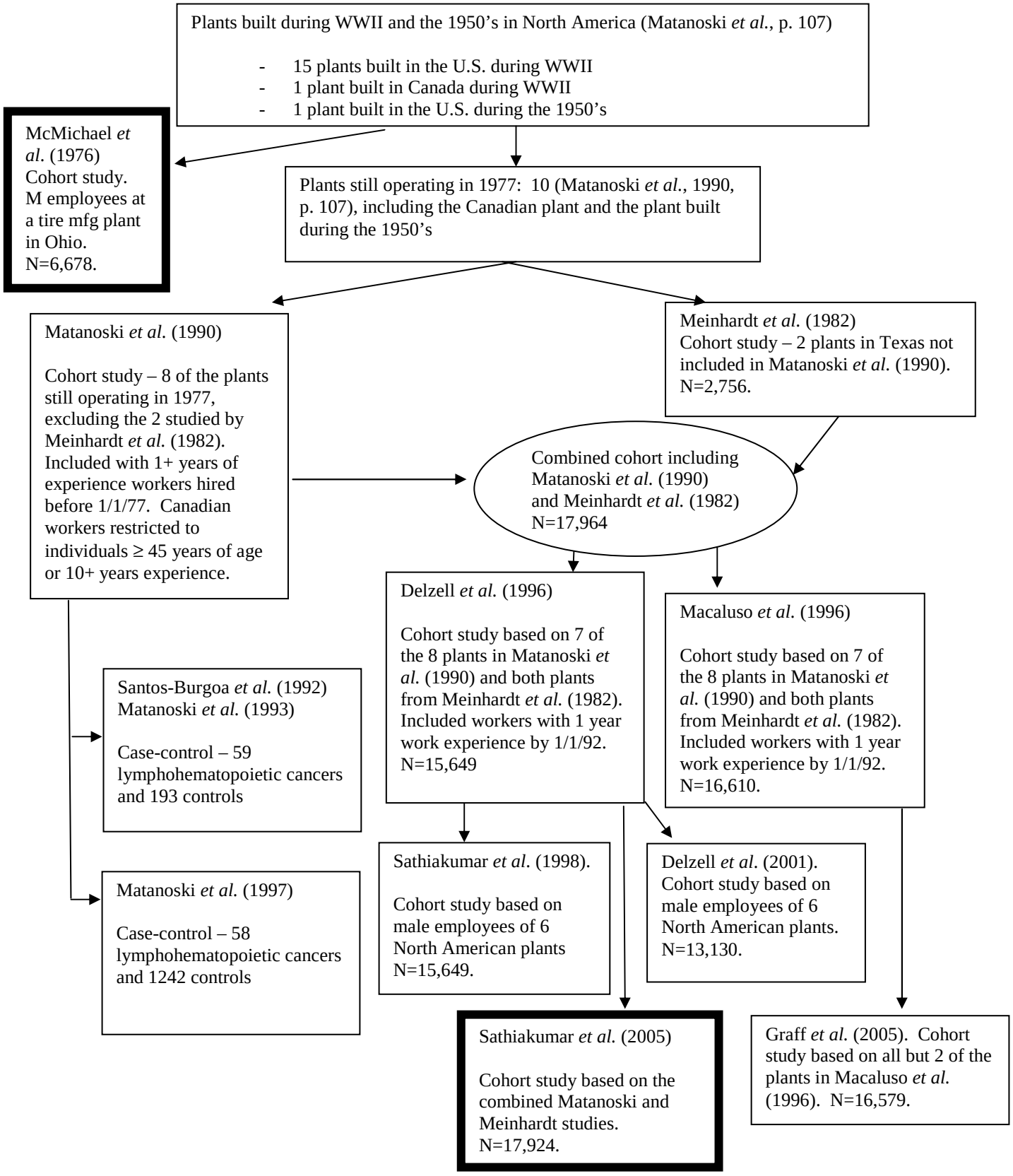

Figure 3. Major Epidemiologic Studies of the Styrene Monomer and Polymer Industry.
Studies with bold border included in NTP Draft Document Table 3-6.

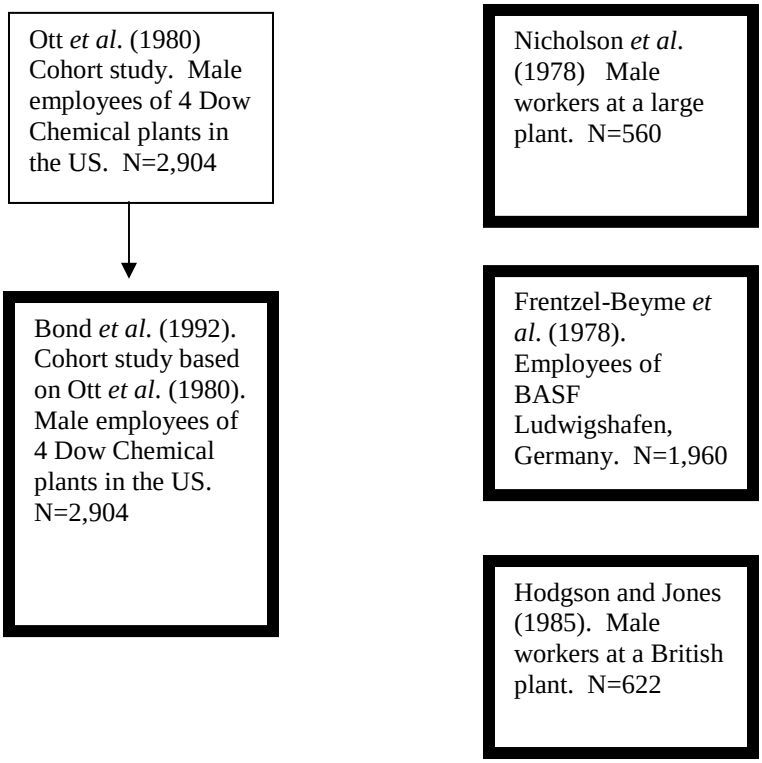

Figure 4. Major Epidemiologic Studies of Styrene: Other. ***Studies with bold border included in NTP Draft Document Table 3-6.***