Comments on the Review of Epidemiology Data in the NTP 12th Report on Carcinogens Draft Styrene Profile

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1 Introduction

The *NTP 12th Report on Carcinogens Draft Styrene Profile* (NTP, 2009) states: "There is limited evidence of the carcinogenicity of styrene in humans based on studies of workers exposed to styrene showing (1) increased mortality or incidence of lymphohematopoietic cancer and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers." The first claim is untrue because:

- The preponderance of analyses showed null associations between styrene and cancer risk;
- Elevated risks were not found consistently in workers with higher exposures;
- Increased risks were not consistently noted within or across studies;
- The types of lymphohematopoietic cancers suggested to be associated with styrene vary across studies;
- The two main studies relied upon by NTP (Kogevinas *et al.*, 1994 and Delzell *et al.*, 2006) do not provide sufficient evidence of an association and neither study concluded styrene caused cancer;
- Although the Kogevinas *et al*. (1994) study includes many short term workers (more than in the SBR industry), the number of long-term workers (≥ 10 years) is comparable with the number in the Delzell *et al*. (2006) study, so the null results from Kogenivas *et al*. should not be dismissed;
- Confounders limit the interpretation of studies of styrene-butadiene rubber workers;
- The appropriate exposure metric was not consistently relied upon by NTP; and
- Risks of other cancer types were not consistently observed.

These points and their bearing on the carcinogenicity classification of styrene are discussed in more detail below.

2 The draft profile emphasizes positive findings over null findings for the same endpoints

According to the *2008 National Toxicology Program (NTP) Report on Carcinogens: Draft Background Document for Styrene (Draft Document),* the major epidemiology studies of styrene focus on 10 cohorts from 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) (Table 1) (NTP, 2008). The draft profile focuses on certain results from only three of these cohorts: "an incidence study of male Danish [RPC] workers (Kolstad *et al.,* 1995; 1994) and a European multinational mortality study of male and female [RPC] workers (which included a subset of the Danish workers) (Kogevinas *et al.,* 1994)," and "the large multi-plant cohort mortality study of male and female styrene-butadiene workers in the United States and Canada by Delzell and colleagues (Delzell *et al.,* 2006; Graff *et al.,* 2005)." The draft profile emphasizes the positive results of these studies, but only mentions some of the null findings. More importantly, the draft profile does not discuss the null findings in the other cohorts described above. This leaves the reader with the incorrect impression that, overall, the data suggest an association between styrene exposure and cancer risk. As discussed in greater detail below, and shown in Tables 2 to 8, the preponderance of evidence does not support an association between styrene and any cancer type analyzed, including lymphohematopoietic cancers and, according to NTP's criteria, styrene should be considered "not classifiable" with regard to its potential human carcinogenicity.

3 Elevated risks were not found in workers with higher styrene exposures

The draft styrene profile states: "Elevated risks of cancer were found among workers with higher exposure to styrene after an appropriate latency period." This statement is not in accord with the evidence. If styrene were associated with cancer, then one would expect an exposure-response relationship within studies and also among industries with differing characteristic levels of exposure. Because workers in the RPC industry have higher exposures than do those in the SBR and PS industries, stronger associations should be observed among RPC workers. This is not the case for lymphohematopoietic cancers (Tables 2 to 6). In addition, within studies, there were very few instances of an increase in cancer risk with an increase in exposure.

As stated in the draft profile, for all lymphohematopoietic cancers combined, in the European cohort, 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) or duration of exposure. Average exposure was calculated as the cumulative exposure divided by total exposure time, yet no explanation is provided as to why statistical significance differed between these correlated measures of exposure. In addition, in the European cohort whose time since first exposure was < 10

years, the risk was non-significant but < 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). There were also no trends of increased lymphohematopoietic cancer risk with job/exposure category, employment duration, exposure duration, cumulative exposure, or time since first hire in the US cohort (Wong *et al.*, 1994).

Associations between styrene and cancer risk were examined by job/exposure category, employment duration, exposure duration, cumulative exposure, employment start date, time since first hire, time since first exposure, and average exposure. No *consistent* trends of increased risk with increased exposure were noted for individual lymphohematopoietic cancers (*e.g.*, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, and leukemia) either in the European and US RPC cohorts or the North American SBR cohort (Kolstad *et al.*, 1994; 1995; Kogevinas *et al.*, 1993; 1994; Sathiakumar *et al.*, 2005; Graff *et al.*, 2005; Delzell *et al*., 2006). Although emphasis has been placed by NTP on associations between leukemia and peak styrene exposures in the Delzell *et al*. (2006) study, this effect was singled out among their findings of no-effect based on many other measures of exposure in this study. There is no biological explanation as to why associations weren't seen with other types of exposure metrics in this cohort, suggesting this finding is likely due to chance.

4 Increased lymphohematopoietic cancer risks were not consistently reported within cohorts

In most styrene epidemiology studies, risk estimates for the same cancer endpoint were calculated a number of ways: they were calculated using several alternative exposure metrics, and within each metric, at several exposure levels (Table 1). To properly interpret the results of a study, one must determine whether the risk estimates from *all* analyses for a cancer endpoint are consistent and, if not, determine what factors were likely to contribute to the inconsistency.

The draft profile states: "Without *a priori* knowledge, it is difficult to know which exposure metric is most appropriate for evaluating causality, so a positive relationship observed with any exposure metric is a concern." It is certainly true that any positive association should be explored. Yet, if this effect is not noted consistently within a study, then it is unlikely to be indicative of a causal relationship. Moreover, when many alternative ways of analyzing the same data are presented in parallel without *a*

priori reasoning for which is most appropriate, there is the increased possibility that chance alone will produce a few apparently significant results. To conclude after the fact that those particular analyses showing significance are the informative ones, and that other analyses not showing significance must somehow have been the "wrong" analyses, is an exercise in *post-hoc* justification. Such results can only be used to generate hypotheses about appropriate metrics, but they cannot serve as evidence for the correctness of those metrics.

The draft profile cites two cohorts (among 12 that were addressed in the NTP draft background document) for which some effects were reported. Regarding the European RPC cohort, it states:

> Positive (significant or approaching significant) exposure-response relationships were found for average exposure and time since first hire for all lymphohematopoietic cancers (P_{trend} = 0.019 and P_{trend} = 0.012, respectively) and malignant lymphoma (P_{trend} = 0.052 and P_{trend} = 0.072, respectively) in the multinational cohort (Kogevinas *et al.* 1994). No relationship with cumulative exposure was observed; however, analyses of cumulative exposure are limited by the control for duration of exposure, which is correlated with cumulative exposure and thus may represent overcontrol.

It is not evident why this would represent overcontrol. While it is possible that the association with time since first exposure, but not cumulative exposure, could be interpreted as meaning a threshold must be reached and a period of time must elapse for styrene to exert its carcinogenic effects, it is just as likely that the statistically significant results observed using these two exposure metrics are due to chance. Indeed, the latter possibility maybe more likely for several reasons. In individuals whose time since first exposure was < 10 years, risk was non-significant but < 1 (SMR = 0.6, 95% CI = 0.32-1.03), and the observed trend may have been 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). Also, there were no dose-response patterns in external analyses stratified by time since first exposure (< 10, 10-19, ≥ 20 years, and total), length of exposure (< 2, ≥ 2 years, total), or with each combination of these factors – the only significant finding of increased risk was for all lymphohematopoietic cancers combined and leukemia in individuals exposed for < 2 years with 10-19 years since first exposure.

With regard to the North American SBR cohort, the draft profile refers to results from three publications (Delzell *et al.*, 2006; Graff *et al.*, 2005; Sathiakumar *et al.*, 2005). As discussed in more detail in Section 9, although some statistically significant associations were reported (particularly with

peak styrene exposures), these were more likely attributable to confounders than to styrene (Boffetta *et al.*, 2008).

Overall, while some statistically significant findings were reported in some studies, no risk estimates were consistent within a study. They differed both within ordinal exposure measures (*e.g.*, an association is observed at a middle category but not a higher one) and among categories (*e.g.*, an association with cumulative, but not average, exposure). Thus, increased lymphohematopoietic cancer risks were not consistently reported within cohorts.

5 Increased cancer risks were not consistently reported across cohorts

The draft profile states: "In some studies, the [cancer] risks increased with increasing measures of exposure, such as average exposure, cumulative exposure, or number of years since first exposure." What the draft profile does not state is that in the *majority* of studies, cancer risk did *not* increase with increasing measures of exposure. Based on the NTP Draft Document (NTP, 2008), there are 12 major styrene cohorts (Table 1). The draft profile emphasizes some of the positive results (though few of the predominantly null results) from two of these cohorts (the European RPC cohort and the North American SBR cohort, discussed above), but does not discuss the largely null results in each of the other 10 cohorts (Tables 2 to 8). Most of these other cohorts were large with long periods of follow-up. Had the profile described these studies, it would be evident to the reader that styrene is not associated with increased cancer risks in the majority of studies.

6 The types of lymphohematopoietic cancers suggested to be associated with styrene exposure varied across studies

The draft profile states that "the types of lymphohematopoietic cancers observed in excess varied somewhat across different cohort studies, and excess risks were not always found in smaller cohorts." 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 (Schottenfeld and Fraumeni, 2006). In that vein, examining risks of all lymphohematopoietic cancers combined is inappropriate. One should systematically examine each cancer type one-by-one and determine whether

there is consistent evidence for an association with styrene across studies for that specific cancer type. If one study reports a significant finding for one cancer type (A) but not another (B), and another reports a significant finding for cancer type B, but not A, this should not be considered consistent evidence of an association.

The draft profile suggests that styrene exposure increased risks of all lymphohematopoietic cancers and malignant lymphoma in the European RPC cohort; leukemia in the Danish RPC cohort; and non-Hodgkin's lymphoma, non-Hodgkin's lymphocytic leukemia, and leukemia (overall and specific types) in the North American SBR cohort. As discussed above (and in detail in Goodman, 2008), no *consistent* trends of increased risk were noted for individual lymphohematopoietic cancers in any cohort, either when examined by job category (Tables 2a, 3a, 4a, 5a, and 6a) or by exposure measures (*i.e.*, employment duration, exposure duration, average exposure, cumulative exposure, employment start date, time since first hire, time since first exposure – see Tables 2b, 3b, 4b, 5b, and 6b). But even if one were to accept the premise of the draft profile that certain cancers were increased in some studies, it is clear the types of cancer differed among those cohorts. Because risks of the same type of lymphohematopoietic cancer were not consistently observed among studies, evidence does not suggest styrene is a causal factor.

7 The Kogevinas *et al.* (1994) and Delzell *et al.* (2006) studies do not provide sufficient evidence for an association between styrene and lymphohematopoietic cancers

The draft profile suggests that the evidence that styrene exposure increases risks for lymphohematopoietic cancer comes primarily from the study of reinforced plastic workers by Kogevinas *et al.* (1994) and that of styrene-butadiene rubber workers by Delzell *et al.* (2006). Based on both study limitations and results, these studies do not actually support this association.

The draft profile actually discusses some (but not all) of the limitations of these studies:

> Workers in the reinforced plastics industry were exposed to the highest levels of styrene, and they had few other potentially carcinogenic exposures. However, the majority of the workers had short periods of employment. In the styrene-butadiene rubber industry, workers were exposed to lower levels of styrene than in the reinforced plastics industry, but a large number of workers studied had adequate follow-up to permit detailed analyses of lymphohematopoietic cancers. The principal limitation of the latter studies is potential

confounding due to other exposures, principally butadiene, which is a known human carcinogen associated with leukemia risk (Grosse *et al.,* 2007, as cited in NTP 2004).

The preponderance of short-term workers in the RPC industry is discussed below in Section 8. Confounding from other chemical exposures in the North American SBR cohort likely has a very large impact on the interpretation of results, and is discussed in Section 9.

It should be remembered that Kogevinas *et al*. (1994) assembled previously examined cohorts from a number of earlier European studies. A major limitation of the Kogevinas *et al*. (1994) study that is not discussed in the draft profile is that one-third of the study subjects are the "highly-exposed" workers from a Danish cohort (described by Kolstad *et al*., 1994; 1995). Kolstad *et al*. (1994) made no attempt to determine the percentage of workers in the Danish cohort that was actually exposed to styrene. Among Danish workers, Kolstad *et al*. (1994; 1995) defined their low- and high-exposure groups by the percentage of employees in a company involved in some aspect of reinforced plastic manufacture, based on the recollection of two suppliers. These groups do not represent individuals with low and high exposures, but rather with low and high probabilities of being exposed. That is, the "low"-exposure group consists of companies in which fewer than 50% of the employees are involved in reinforced plastic manufacture, and the "high"-exposure group consists of companies in which 50% or more of the employees are involved in reinforced plastic manufacture. Kolstad *et al.* made no attempt to determine any particular individual's exposure, so a person in either exposure group could have had high, low, or no exposure to styrene at all. In fact, Kolstad *et al.* estimated that only ~43% of all employees were involved in the production of reinforced plastics based on the assumption that 25% of employees in the "low-exposure" category and 75% of employees in the "high-exposure" category worked in production. No attempt was made to determine whether any of the 112 reinforced plastic workers with lymphohematopoietic cancers were actually exposed to styrene. Also, although Kogevinas *et al*. (1994) followed the "high"-exposure group workers from the Kolstad *et al*. (1994) study for one additional year, they report fewer lymphohematopoietic cancers than did Kolstad *et al*. (24 *vs*. 31).

Even ignoring these limitations, results within these cohorts are not consistent for any particular cancer type or for all lymphohematopoietic cancers combined (see Sections 3 to 6 and Tables 2 to 6). Thus, the epidemiological studies most relied on by NTP to support an association between styrene and exposure and cancer do not actually support such an association. This lack of association is supported by null results in other studies not described in the draft profile, but described in the background document (NTP, 2008).

8 Short-term workers do not make studies of reinforced plastic workers less useful than studies of styrene-butadiene workers

The draft profile suggests that because the majority of workers had short periods of employment in studies of the reinforced plastic industry, these studies are less useful than studies of styrene-butadiene rubber workers for determining cancer risks. It is true that short-term workers are less informative than long-term workers because people who engage in short-term employment may have lifestyle factors – which will stay with them throughout life – that affect cancer risk. If effects are noted in short term workers, they should be interpreted with that possibility in mind.

With regard to the European RPC cohort, however, two things should be noted. First, this study followed over 40,000 workers. Even though the majority of them were employed for a short period of time, this still left thousands of individuals with longer-term employment under study. In fact, of the 539,479 person-years of follow-up in the Kogevinas *et al*. (1994) study, 214,965 person-years accounted for exposures 10 years and beyond. This is similar to the 54% of workers who worked ≥ 10 years in the Delzell *et al*. (1994) study. In addition, the average follow-up period in the Kogevinas *et al*. (1994) study was 13 years, which is quite similar to that of subjects in the Delzell *et al*. (2006) study, who worked for a median of 11 years. Also, these individuals had higher exposures than workers in any other industry, so a lack of effects in these workers is strong evidence for a lack of association. Finally, as discussed in Section 9, styrene exposures in the SBR industry occur with exposures to other chemicals that are known carcinogens, making it difficult to tease out effects of styrene alone. This means that results from the RPC industry should be weighted even more heavily in a weight-of-evidence analysis.

9 Confounders limit the usefulness of styrene-butadiene rubber worker studies

The draft profile suggests that the association between styrene and lymphohematopoietic cancers cannot be fully explained by exposure to butadiene or DMDTC. Specifically, it states:

> These analyses suggested an exposure-response relationship between NHL or NHL-CLL and exposure to styrene that was not explained by exposure to butadiene. Relative risks of NHL or NHL-CLL (combined) increased with increasing levels of cumulative exposures to styrene and were not attenuated after controlling for exposure to butadiene.

> However, the relative risks were only statistically significant for the highest exposure level of styrene in the styrene only model. Exposure to butadiene was not associated with NHL-CLL or NHL risk in this study (Delzell *et al.* 2006, Graff *et al.* 2005). The strongest evidence for an association between styrene exposure and leukemia comes from analyses of cancers among workers exposed to styrene peaks. Relative risks increased with exposure to increasing numbers of styrene peaks in all three chemical models and statistically significant risk estimates were observed at the two highest exposure levels after controlling for butadiene exposure. Analysis by cumulative exposure showed increased relative risks of leukemia with increasing cumulative styrene exposure, but the response was attenuated with control for butadiene exposure, and no association remained after additional control for DMDTC. (The relevance of including DMDTC in these models is not clear, since there is no current evidence that DMDTC is carcinogenic in animals or humans.)

This description overstates the potential association. As noted by Boffetta *et al*. (2008): "The excess leukemia mortality in the SBR industry is in line with what would be expected from exposure to the established carcinogen, 1,3-butadiene (IARC, in press), with no evidence for an amplified effect from the co-exposure to styrene." In fact, Boffetta *et al*. (2008) re-analyzed the data from the Delzell *et al*. (2006) study. They stated:

> The Spearman rank correlation coefficient between cumulative exposure to 1,3-butadiene and styrene was 0.79, that between styrene and DMDTC was 0.63…. Internal analyses were conducted on leukemia risk (including an additional 10 cases with leukemia mentioned on the death certificate), according to cumulative exposure to 1,3-butadiene, styrene, and DMDTC…. A dose-risk relation was present when styrene alone was included in the regression model, which was reduced when either 1,3-butadiene or DMDTC were added to the model. Given the correlation between the exposures to the three agents and the unavoidable exposure misclassification, statistical adjustment might not allow adequate control for confounding. However, an analysis of styrene exposure stratified by 1,3-butadiene or DMDTC exposure did not indicate a consistent pattern of risks for styrene exposure in any category of exposure to the other agents. Analyses including a 10-year lag yielded similarly inconclusive results, and analyses of leukemia subtypes did not reveal subtype-specific associations with styrene exposure. The analysis of styrene exposure and NHL risk revealed a non-significant trend across increasing cumulative styrene exposure categories.

The study by Delzell *et al*. (2006) and other studies of this North American SBR cohort should not be used to classify the potential human carcinogenicity of styrene because co-exposures to butadiene and DMDTC cannot be ruled out.

10 The use of average exposure as a metric is not necessarily more appropriate than the use of cumulative exposure

Kogevinas *et al.* (1994) found statistically significant associations with average exposure and time since first hire for all lymphohematopoietic cancers and near-significant associations with malignant lymphoma in internal analyses (RR calculations). They did not find such an association with external analyses (SMR calculations) or internal analyses using cumulative exposure as the exposure metric. The draft profile stated:

> No relationship with cumulative exposure was observed; however, analyses of cumulative exposure are limited by the control for duration of exposure, which is correlated with cumulative exposure and thus may represent overcontrol. Moreover, measures of intensity of exposure (such as average exposure) may be more informative for evaluating risks in populations with a high-percentage of short-term workers than cumulative exposure.

The draft profile offers no explanation as to why controlling for the duration of exposure "represents overcontrol." Kogevinas *et al*. (1994) stated that the average exposure was calculated by dividing the cumulative exposure by total exposure time, which means these values are necessarily correlated with one another. Thus, the reason for a significant association with one and a non-significant association with the other should be explored. For example, as discussed in Section 3, in Europeans whose time since first exposure was < 10 years, the risk was < 1, so the observed trend may have been more a product of unusually low risks in the lowest latency group rather than elevated risks in the higher latency groups. In addition, exposure was assessed using many other metrics in this cohort, including time since first exposure, < 2 *vs*. ≥ 2 years' exposure, and combinations of these two metrics, in external analyses. As no consistent associations with all lymphohematopoietic cancers combined or individual lymphohematopoietic cancers (*i.e.*, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, leukemia) were found using these other exposure metrics, it further brings into question the statistically significant associations using average exposure or time since first exposure in internal associations.

The most appropriate exposure metric should never be chosen based on statistically significant results. A *post hoc* decision that the average exposure is more appropriate than other metrics for which statistically significant results were not found leads one to question whether another metric would have been chosen were those results statistically significant.

11 Risks of other cancer types were not consistently observed

Regarding other types of cancers, the draft profile states:

> Some studies in the reinforced plastics industry provide suggestive evidence for increased incidences or mortality due to pancreatic and esophageal tumors; however, no excess of cancer at these sites was observed in the styrene-butadiene industry (NTP 2008). Increases in cancer at these sites were also observed in some of the individual cohort studies (Ruder *et al.* 2004, Wong *et al.* 1994, Kolstad *et al.* 1995), and there was some evidence of an exposure-response relationship with pancreatic cancer (NTP 2008). The risk of pancreatic cancer was somewhat higher among the Danish workers with longer-term employment and earlier start date in the internal analyses (Kolstad *et al.* 1995), and increased with cumulative exposure in the European multiplant cohort (P_{trend} = 0.068) (Kogevinas *et al.,* 1994; 1993).

This is highly misleading. For pancreatic cancer, Kogevinas *et al.* (1994) found a near-significant trend (p = 0.068) with cumulative exposure in the European cohort, but there was no trend based on cumulative exposure indicated by Wong *et al.* (1994) in a US cohort (Tables 7a and b). There were also no trends of increased pancreatic cancer risks with job/exposure category, employment duration, exposure duration, or time since first hire in the US cohort. Only one risk estimate for pancreatic cancer was statistically significant, and this was in the Danish "high exposure" group, which may not actually have had higher exposures because this group is defined by the percentage of employees in a company involved in some aspect of reinforced plastic manufacture (Kolstad *et al.*, 1994; 1995).

Most studies also reported no association with esophageal cancer (Tables 8a and 8b). Among 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. When stratified by job category, risks were increased in the low, but not the high, exposure Washington-state workers (SMR = 1.23; 95 % CI = 1.02-1.47, Ruder *et al.*, 2004), although it should be noted that there were only 2 observed cases in the high-exposure category. Wong *et al*. (1994) also reported a significant association in all workers, but this was not significant in workers who had been employed for one year or more.

Even if the weight of evidence suggested an association between styrene exposure and either esophageal or pancreatic cancer (which it does not), the modes of action of these cancer types differ from each other and from each of the lymphohematopoietic cancers. 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.

12 Conclusions

When considering the epidemiology evidence as a whole, there are no consistent associations between styrene exposure and any specific cancer type either within or among studies. There were some statistically significant associations noted with some styrene exposure metrics for specific cancer types in certain studies, but these were far outnumbered by null associations for each cancer type. There was no indication of an increased risk with increased exposure. Although the draft profile suggests increased risks for lymphohematopoietic cancers, each of these cancer types is unique with an independent mode of action, and there were no consistent associations with any specific lymphohematopoietic cancer within or across studies. Studies of RPC workers should carry the greatest weight in an assessment of the epidemiology data because these workers have the highest exposures, even though these workers are comprised of many short term workers. Studies of SBR workers should carry less weight because exposures are far lower and butadiene can not be completely ruled out as a confounder, even when adjusted for. When weighting these studies accordingly, the evidence for a lack of an effect becomes even stronger. Finally, risks of other types of cancer, such as pancreatic and esophageal cancer, were not consistently observed among studies. Taken together, the evidence does not support the draft profile's classification of limited evidence of carcinogenicity based on "increased mortality or incidence of lymphohematopoietic cancer" and styrene should be characterized as "not classifiable" based on NTP's criteria.

13 References

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Tables

Table 1
Styrene Cohorts

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	

Table 1
Styrene Cohorts

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
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 2a
Risks of All Lymphohematopoietic Cancer Risk in Job/Exposure Categories

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[f]	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 2b
Risks of All Lymphohematopoietic Cancer Risk Based on Several Exposure Measures

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	1 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** 15 24 11	*(Table 3)* 0.60 1.25 1.32 1 **2.90** **3.97** **0.012** 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	1 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 3a
Non-Hodgkin's Lymphoma Cancer Risk in Job/Exposure Categories

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 e*t 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 3b
Non-Hodgkin's Lymphoma Cancer Risk Based on Several Exposure Measures

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

Styrene-Butadiene Rubber Industry (SBR)[a]

	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 4b.

Table 4a
Hodgkin's Lymphoma Cancer Risk in Job/Exposure Categories

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 4b
Hodgkin's Lymphoma Cancer Risk Based on Several Exposure Measures

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 1-1.9 2-4.9 5-9.9 ≥ 10	2 1 1 0 0	1.75 1.00 0.87 -- --
Exposure Duration (Years)					< 1 [e] ≥ 1 [e] < 2 [e] ≥ 2 [e]	2 5 5 2	0.77 1.33 1.34 0.87	0.09-2.79 0.43-3.10 0.44-3.13 0.11-3.14	< 1 1-1.9 2-4.9 5-9.9 ≥ 10	2 1 1 0 0	1.72 0.99 0.85 -- --
Cumulative Exposure (ppm-yr)					< 75 [f] 100-199 200-499 ≥ 500 p_{trend}	5 5 5 3	1 2.63 2.99 1.64 0.52	0.74-9.32 0.82-10.91 0.34-7.82	< 10.0 10.0-29.9 30.0-99.9 ≥ 100.0	2 1 1 0	1.74 0.85 0.83 --
Employment Start Date	1964-1970 1971-1975 1976-1988	9 3 4	1.45 0.71 0.92	0.66-2.76 0.15-2.07 0.25-2.37							
Time Since Hire/First Exposure (Years)	< 10 ≥ 10	11 5	1.21 0.87	0.61-2.17 0.28-2.04	*1994* < 10 10-19 ≥ 20 *1994* [f] < 10 10-19 ≥ 20 p_{trend} *1993* < 10 10-19 ≥ 20		*(Table 3)* 0.82 1.53 2.44 *(Table 4)* 1 2.43 5.16 0.072 *(Table 3)* 0.79 1.43 2.38	 0.17-2.41 0.32-4.47 0.06-13.59 0.69-8.49 0.90-29.47 0.16-2.32 0.29-4.17 0.06-13.27	< 10 10-19 ≥ 20	3 1 0	1.29 0.64 --
Average Exposure (ppm) [f]					< 60 [f] 60-99 100-119 120-199 ≥ 200 ***p trend***	3 4 1 8 2	1 2.51 1.65 7.15 4.40 0.052	0.49-12.87 0.15-18.57 1.21-42.11 0.42-45.99			

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 3b.

Table 5a
Multiple Myeloma Cancer Risk in Job/Exposure Categories

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 5b
Multiple Myeloma Cancer Risk Based on Several Exposure Measures

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 6a
Leukemia Cancer Risk in Job/Exposure Categories

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 6b
Leukemia Cancer Risk Based on Several Exposure Measures

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

Styrene-Butadiene Rubber Industry (SBR)[a]

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

Environmental Exposure

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

Table 7a
Pancreatic Cancer Risk in Job/Exposure Categories

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 7b
Pancreatic Cancer Risk Based on Several Exposure Measures

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 ≥ 1	20 21	2.5 1.8	0.8-7.2 0.6-7.4					< 1 1-1.9 2-4.9 5-9.9 ≥ 10	6 3 5 0 5	2.09 1.05 1.33 -- 1.18	> 1	7	1.49	0.60-3.08
Exposure Duration (Years)									< 1 1-1.9 2-4.9 5-9.9 ≥ 10	6 3 5 0 5	2.03 1.04 1.29 -- 1.30				
Cumulative Exposure (ppm-yr)					< 75 100-199 200-499 ≥ 500 p_{trend}	9 5 6 10	1.0 1.44 1.90 2.56 0.068	 0.48-4.34 0.65-5.53 0.90-7.31	< 10.0 10.0-29.9 30.0-99.9 ≥ 100.0	5 6 3 5	1.40 1.61 0.63 1.06				
Employment Start Date	> 1970 ≤ 1970	14 27	1.1 1.1	0.4-3.5 0.4-3.4											
Time Since Hire/First Exposure (Years)	< 10 ≥ 10	15 26	1.3 1.5	0.5-3.5 0.5-4.3					< 10 10-19 ≥ 20	5 6 8	1.45 0.87 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 1992-1998 1944-1998	49 27 76	0.76 1.16 0.87	0.56-1.01 0.76-1.68 0.68-1.08

Styrene Monitored Workers[a]

	Anttila *et al.* (1998)			
	Category	**Obs**	**SIR**	**95% CI**
Time Since First Measurement (Years)	0-9 ≥ 10	0 3	0.00 3.64	0.00-3.76 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 8a
Esophageal Cancer Risk in Job/Exposure Categories

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 8b
Esophageal Cancer Risk Based on Several Exposure Measures

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.