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Comments on NTP Styrene Epidemiology Review

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Prepared by

M. Jane Teta, Dr.PH, MPH
Exponent
8 Dogwood Court
Middlebury, CT 06762

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1. The NTP review is generally unbalanced in that weakly positive, often non-statistically significant and imprecise measures of association are listed, without discussing relevant non-positive and subgroup results in the context of consistency of these results with an occupational risk.

The NTP review seems to focus on elevated standardized mortality ratios (SMR) and risk ratios (RR), regardless of the magnitude and statistical significance of the risk estimate or the number of cases involved. Some examples of this approach and other noteworthy errors include:

- None of the pancreas cancer SMRs emphasized in the NTP report are statistically significant, many are based on four or fewer cases, and the same elevations are not consistently observed in exposed groups. Furthermore, potential confounding factors are not mentioned.

- Table 3.6 lists the cancer sites by study and notes only if the study was positive or negative for that site by a + or – sign. This information is inadequate for determining the importance of the study results. In addition, the table indicates a positive result for the study by Nicholson et al. (1978) for non-Hodgkin's lymphoma. There was only 1 case and 1.3 expected in this study; this is not a positive finding.

- Table 3.6 includes the studies by Kolstad et al. (1993, 1994, 1995) and Kogevinas et al. (1993, 1994). Since the Kogevinas et al. studies include the high exposure workers from the Kolstad et al. studies, the same cases are considered more than once.

- Table 3.7 presents results from the reinforced plastics industry for selected cancer sites, again including both the Kolstad et al. and Kogevinas et al. studies. In the last column, the NTP authors have calculated a pooled observed/expected value for each site that only counts the overlapping results from the Kolstad et al. and Kogevinas et al. studies once. When the actual pooled RRs are calculated, they range from 0.87 to 1.19 (for cancer of the esophagus). These are all non-positive or weakly positive associations. Only the result for lung cancer is statistically significant; this result is driven by the Wong (1990) and Wong et al. (1994) studies that found that lung cancer risk was highest in short-term workers and attributed to cigarette smoking. Furthermore, no increased risk for lung cancer was reported in styrene-butadiene rubber (SBR) worker studies.

- In their Poisson regression analysis of lymphohematopoietic cancer (LHC) (all LHC and site specific), Kogevinas et al. (1994) found an association between all LHC ($p=0.019$) and lymphoma ($p=0.052$) and average styrene (STY) exposure, but not for leukemia. There was no association with cumulative STY exposure and any of these sites. These inconsistent results do not support a causal interpretation.

- The NTP review of Frentzel-Beyme et al., 1978, mentions various cancer sites for which risks were increased in this study; none of the risk estimates were statistically significant and each was based on 1-2 deaths (p. 112-113).

The NTP review also emphasizes selected results that are in conflict with the interpretation of the authors of the studies in question. Some examples of this include:

- Wong et al., 1994 – The NTP report mentions the statistically increased risks for esophageal cancer and lung cancer found in this study (p. 76). The authors, however, concluded, "[n]o relation between exposure to styrene and these increases in mortality was found, however. In fact, most of the mortality excesses could be attributed to short-term workers. The most likely explanations for these increases in mortality were low socioeconomic class, smoking, and lifestyle factors characteristic of short-term workers."

- Ruder et al., 2004 – The NTP review states that this study found an increased risk of pancreas cancer in the high exposure group (p. 72). The authors did not mention this non-statistically significant increase based on four cases in their discussion. They did, however, state, "[w]e found no excess of leukemia or lymphoma mortality," which the NTP review does not mention.

- Bond et al., 1992 – The NTP review has a long paragraph detailing all of the separate SMRs that are elevated for all LHC and specific subgroups in this study, almost all of which are not statistically significant (p. 113-114). In contrast, the authors concluded, "[n]or was a statistically significant excess of mortality observed among the employees considered to have the highest potential exposure to styrene. This observation is consistent with findings from studies of workers in the reinforced plastics industry, which have failed to show excess lymphatic and hematopoietic cancer mortality associated with high-level exposure to styrene."

- Kogevinas et al., 1994 – The NTP review focuses on the excess of LHC seen in the Kolstad et al. studies, but does not discuss the impact of the overlap of these study cohorts with the Kogevinas et al. cohorts (the Kogevinas et al. cohort includes the portion of the Kolstad et al. cohort that was considered to have the highest chance of exposure to STY (NTP, p. vii; supported by Cohen et al. (2002), p. 85 and Kogevinas et al. (1993), p. 291). In contrast to Kolstad et al., Kogevinas et al. (1994) found that "[i]n the total study population, exposure to styrene was not associated with an excess risk of mortality from major neoplasms or, specifically, with an excess risk of mortality from neoplasms of the lymphatic and hematopoietic tissues … In conclusion, these findings leave the question open of whether an excess risk of neoplasms of the lymphatic and hematopoietic tissues occurs among workers exposed to styrene."

- Kolstad et al., 1995 – In Table 3.1 of the NTP report (p. 88), the description of effects seen in the internal study for pancreas cancer states that the results for

those with probable high exposure to STY showed an overall excess of 2.2 which was statistically significant. The excess was even higher (IRR=3.4 and significant) for those employed greater than one year. These results are taken from Table 5 in the Kolstad report, which states, however, that these are results for those workers with **high exposure probability, not probable high exposure.**

Of the three industries where occupational exposure to STY occurs (SBR production, STY monomer and polymerization, and the reinforced plastics industry), the reinforced plastics industry is considered to provide the most suitable human data for reviewing the health effects of STY. The levels of STY exposure in this industry have been substantially higher compared to exposure levels in the other two industries (STY time-weighed averages [TWA] up to 200 ppm in the reinforced plastics industry versus levels generally less than 5 ppm in the other two industries). In addition, the number of workers in the reinforced plastics industry is large, and there are limited exposures to other carcinogens. The major drawbacks to studies in this industry are the high turnover of employees, lack of work history and exposure information for many of the workers, and shorter follow-up.

Although the NTP report states, "[w]orkers in the reinforced plastics industry have the highest levels of exposure and few other potentially carcinogenic exposures, and these studies may be the most informative for evaluating causality" (p. vi), the report does not elaborate on this statement or place more emphasis on the findings from this industry in their evaluation. Cohen et al. (2002) also agree, "if STY does cause cancer, the largest effect would be expected in people who have worked over the long term as reinforced plastics industry laminators" (p. 105). Cohen et al. expanded on this comment by stating, "[w]hen excess risks are found in other industries, an absence of a corresponding increased risk in this highly exposed group would favor bias, chance, and/or confounding as the explanation."

There are three main cohort studies in the reinforced plastics industry: a multi-country cohort from the European Union (Kogevinas et al., 1993, 1994) that includes cohorts from Denmark and the United Kingdom, which were also reported separately (Coggon et al., 1987; Kolstad et al., 1993, 1994); a United States cohort from 30 reinforced plastics manufacturing plants (Wong 1990; Wong et al., 1994), and a study of two plastic boatbuilding plants in Washington state (Okun et al., 1985, and its update, Ruder et al., 2004). These cohorts together included over 60,000 employees, some who had substantial exposures to STY in the past.

The NTP review considered the studies by Kolstad et al. (1993, 1994, & 1995) separately from the study by Kogevinas et al. (1993, 1994). There was serious exposure misclassification in the approach taken by Kolstad et al. to identify every company in Denmark involved in the production of reinforced plastics. Companies were classified as ever or never producing reinforced plastics by both the companies themselves and by two dealers in reinforced plastics. The authors chose to include the 386 companies that the dealers designated as producers. Note that 14 of these companies were identified as non-producers by the companies themselves, and 44 of the companies that were self-identified

as producers were not included. Furthermore, the number of companies designated as unknown (84) was similar in number to those classified as not involving reinforced plastics (82). The authors chose to use the dealers' assessment because a threefold excess risk of leukemia and non-Hodgkin's lymphoma was found in employees of companies identified by the dealers but not the companies themselves. Kolstad et al. (1994) suggest that some of the employers may be misreporting their exposure status.

The Kogevinas et al. (1994) international study, however, includes the 12,837 workers from the Kolstadt et al. cohort who worked in plants where more than 50 per cent of the work force was involved in production of reinforced plastics, defined by Kolstadt et al. as "high probable exposure", and, as such, contains the most significant data. Other reasons to focus on the Kogevinas et al. cohort include the fact that this study included over ten thousand laminators, which is the most heavily exposed group in this industry, basic job group analyses were performed, and average study follow-up was about two years longer than for Kolstad et al. Also, the percentage of short-term workers in the Kolstad et al. cohort was 81%, which was the highest of any group included in the Kogevinas studies (e.g., only 9% were short-term workers in the Finnish cohort).

As discussed above, counting the same deaths from the Kogevinas et al. and Kolstad et al. publications twice is not appropriate. Although one of the Kolstad et al. studies (1993) examined cancer incidence, which is often considered a more comprehensive measure, cancer incidence and mortality are often similar, especially for cancer sites with low survival rates such as pancreas cancer.

Studies in the reinforced plastics industry have reported increased mortality from a number of different cancer sites, as would be expected in cohort studies that by design include multiple comparisons. Most of the observed increases were small, were not statistically significant, and did not concentrate in groups with high exposure or long potential induction time. In addition, the same results were not consistently seen across the different cohorts. It is these factors that distinguish isolated chance findings from occupational risks.

There have been five cohort studies of workers employed in the manufacture, polymerization, or processing of STY (Frentzel-Beyme, 1978; Nicholson, 1978; Ott et al., 1980; Hodgson and Jones, 1985; Bond et al., 1992). Exposures in these studies were much lower than for the reinforced plastics industry, and many of the workers could have been exposed to benzene and other chemicals. The number of workers in these cohorts (i.e., 6,046 workers in manufacturing) is also much smaller than for the reinforced plastics industry. Some elevations were reported for LHC in this industry, but the interpretation of these results is complicated by the small number of deaths for many of the outcomes of interest.

Recommendation: NTP should reconsider its approach to the interpretation of this body of evidence, including focusing on findings in the reinforced plastics industry. Findings that should be given the greatest weight are those that show a strong association with STY exposure, are statistically significant, are consistent across a

number of studies, show a dose-response effect, and are seen in the largest of the studies in the reinforced plastics industry. Merely listing weakly positive, non-significant and imprecise estimates based on small numbers should be avoided.

2. NTP asserts that increases in LHC are the "most consistent finding" across STY worker studies, despite that the positive results from the lowest exposed workers are subject to confounding and the findings related to the highest exposed workers (reinforced plastics production) are inconsistent.

It is unclear what "most consistent finding" means, since there are no consistent findings related to STY exposure. There is a consistent finding of leukemia excess among SBR workers, but this has not been attributed to STY, and specific LHCs are not increased in the most highly exposed STY workers (reinforced plastics). The NTP conclusion cannot be justified for several additional reasons: the lack of consistent dose-response patterns, the inclusion of disparate diagnostic entities (CML, AML, ALL, CLL, Hodgkin lymphoma and non-Hodgkin lymphoma) with different etiologies (Linet et al., 2006) under the rubric of LHCs and failure to consider the contrary conclusions of study authors. The following sections discuss the research on SBR and STY workers, in the context of the NTP report's discussions.

SBR Worker Studies

Delzell and her colleagues at the University of Alabama-Birmingham (UAB) examined in great detail the relative contributions of butadiene (BD) and STY to the consistent leukemia excess observed in their large cohort of SBR workers in various analyses and updates. They also analyzed relationships with BD and STY to other specific LHCs. The NTP report represents a number of selective results from Delzell et al. (2001) (p.100-101) with follow-up of SBR workers from 1943-1991, but does not take into account the following specific results and conclusion of the authors, as stated in their abstract: "[a]fter further adjusting each agent-specific set of RRs for the other two agents, a positive but imprecise relation remained for butadiene and DMDTC [dimethyldithiocarbamate] **but not for styrene.** …. Butadiene and DMDTC, **but not styrene**, were positively associated with leukemia in multivariable analyses. The independent effect of each agent was difficult to evaluate because of correlations with other agents and imprecision" (emphasis added).

Graff et al. (2005) investigated the association between exposure to BD, STY, and DMTC and mortality due to LHCs among the 16,579 SBR workers in the UAB cohort. In their abstract, the authors summarized, "after controlling for butadiene, neither styrene nor DMDTC displayed a consistent exposure-response trend with all leukemia, chronic myelogenous leukemia or chronic lymphocytic leukemia." They concluded, "this study found a positive association between butadiene and leukemia that was not explained by exposure to other agents examined." On p. 922, they stated, "*styrene was inversely associated with leukemia, without dose-response,* after adjusting RRs for butadiene ppm-years and DMDTC" (italics added). They further noted, "the positive association, without dose-response, remained for DMDTC … ." The results by Graff et al. (2005) are

reviewed on p. 101, line 29 through p. 102, line 29 of the NTP report, but these findings and summary conclusions are absent.

Non-Hodgkin's lymphoma accounted for 58 deaths in the study by Graff et al. (2005). On pg. 930, the authors indicated, "[i]n our study, NHL was associated with styrene and DMDTC, but RRs for this disease category displayed no consistent exposure-response pattern with either agent. The *rather uniformly elevated RRs among subjects exposed to styrene or DMDTC in part reflect large deficits of NHL deaths* among unexposed subjects compared to external populations. Matanoski et al. [43], in an investigation that included many of the same subjects in our study, reported a positive association between styrene and NHL. However, their findings and those from the present study are inconsistent with other research. *Notably, studies of occupational groups exposed to levels of styrene higher than those found in the synthetic rubber industry* have not reported any consistent increase in NHL deaths or cases [40, 41, 23, 45-50]" (italics added). The NTP report outlines some of the detailed results in Graff et al. (2005) regarding non-Hodgkin's lymphoma (p. 102, lines 22-29), but again these results and the authors' conclusions are absent.

A case-control study based on the earlier and heavily overlapping cohort of SBR workers studied by Matanoski et al. (1990) included 59 LHCs (Santos-Burgoa et al., 1992). The study was nested in a cohort of male workers employed between 1943 and 1982 in eight North American plants. In Table 6, Santos-Burgoa et al. (1992) present the odds ratios (OR) under the conditional logistic model for the categorical exposure variables of 'styrene' and 'butadiene' for the leukemia analysis. They found that the OR for leukemia and BD exposure (without STY in the model) was increased and statistically significant (OR = 7.61; 95% CI: 1.62 – 35.6). The OR for leukemia and STY exposure in a model that did not include BD was elevated but not significantly increased (OR = 2.92; 95% CI: 0.83 – 10.3). When both BD and STY were included in the model, however, the OR for BD remained high and significantly increased (OR = 7.39; 95% CI: 1.32 – 41.2), whereas the OR for STY decreased to 1.06 (95% CI: 0.23 – 4.95). The authors further noted that a model that included variables for STY and BD, as well as interaction terms, showed no improvement in fit over one that included BD alone. This finding contradicts the statement in the NTP review speculating about a possible synergistic effect of BD and STY (p. vii, lines 10-12). The authors of this case-control study stated on p. 850 that, "elevated odds ratio for styrene was probably due to the correlation between styrene and butadiene exposures." Further, in the discussion on p. 851, it is clearly concluded, "[o]nce a correction was made for butadiene exposure, styrene was not related to an increased risk of leukemia." In contrast to these clear conclusions of Santo-Burgoa and colleagues (1992), the NTP review included this study in the statement on p. 137, lines 9-13 that "[a]djustment for butadiene [Delzell et al. 2001, Graff et al. 2005, Santo-Burgoa et al. 1992] and DMDTC [Delzell et al. 2001, Graff et al. 2005] reduced the association between styrene exposure and leukemia, but it is not possible to disentangle a separate effect of styrene, butadiene, or DMDTC from these analyses, and these findings should be interpreted with caution." Rather than focusing on the best evidence from the SBR studies, the NTP draft focuses on the residual uncertainty.

STY Worker Studies

The evidence for an increase in LHC comes primarily from the SBR industry, as discussed above. The evidence from the reinforced plastics industry and STY manufacturing industry is not consistent for this category of deaths (see Table 1). The largest cohort of reinforced plastics workers (Kogevinas et al., 1994) included over 41,000 workers in the European Union. The authors examined mortality by job type, employment duration, time since first employment, cumulative exposure, and average exposure. While SMRs were elevated for some job groups for some of the LHCs, no consistent pattern was observed. In addition, none of the elevations were statistically significant. The same lack of a consistent pattern and of statistical significance was also seen for the other types of analyses. Furthermore, there is no suggestion of an association of STY with any of the LHCs in any of the other reinforced plastics cohorts.

Kogevinas et al. (1994) also conducted a Poisson regression analysis of all LHC and leukemia and malignant lymphomas separately. They examined risk with relation to age, time since first exposure, cumulative STY exposure, and average STY exposure. There was an increasing risk for each disease category with increasing time since first exposure; however, this was only statistically significant for all LHC combined. There was an increasing risk for all LHC (statistically significant) and for malignant lymphomas (borderline significant) associated with increasing average STY exposure, but no suggestion of an increasing risk in any of these disease categories with increasing cumulative exposure to STY (Table 2). These inconsistent results argue against a causal association with STY and any of these lymphohematopoietic outcomes.

The NTP report claims that the risk of LHC was elevated in three of the four STY manufacturing cohort studies (Nicholson et al., 1978; Hodgson and Jones, 1985; and Bond et al., 1992). Only one of the SMRs for LHCs in these studies is significantly elevated (non-Hodgkin's lymphoma in Hodgson and Jones [1985], which is based on only three cases), and most of the elevated SMRs are based on small numbers. The only elevation in the Nicholson et al. (1978) cohort was for leukemia, and it was based on only one case (there was an additional death certificate that mentioned leukemia as a contributory cause of death; however, there are no comparison statistics for this death so it cannot be counted). The NTP report mentions a review of additional death certificates that identified five more cases of LHC in the Nicholson et al. (1978) study. Again, there is no information on the underlying cohort or of any comparison statistics, so no conclusions regarding risk can be drawn.

In summary, there is no evidence of a consistent elevation in any LHC type in the cohorts of STY production workers. Finally, note again that the workers in these cohorts may have had the potential for exposure to other chemical carcinogens (including benzene, which is associated with an increased risk of leukemia), and none of the results were adjusted for these other confounding exposures.

Table 1. Results for LHCs in the reinforced plastics and STY manufacturing industries

All LHC

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced plastics	13	16	81	43-139
Kogevinas et al. (1994)-unspecified	Reinforced plastics	30	25.2	119	80-170
Kogevinas et al. (1994)-other exposed	Reinforced plastics	7	10.8	65	26-134
Wong et al. (1994)	Reinforced plastics	31	37.7	82	56-117
Ruder et al. (2004)-high exposure	Reinforced plastics	4	5.6	72	20-184
Ruder et al. (2004)-low exposure	Reinforced plastics	12	16.2	74	38-130
Bond et al. (1992)	STY manufacture	28	19.5	144	95-208
Frentzel-Beyme et al. (1978)	STY manufacture	1	NA	-	-
Hodgson and Jones (1985)	STY manufacture	4	1.6	250	68-640
Nicholson et al. (1978)	STY manufacture	2	2	98	12-361

Non-Hodgkin's Lymphoma

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced plastics	7	5	140	56-288
Kogevinas et al. (1994)-unspecified	Reinforced plastics	4	7.3	55	15-139
Kogevinas et al. (1994)-other exposed	Reinforced plastics	1	3.3	30	1-167
Wong et al. (1994)	Reinforced plastics	10	12.4	81	39-148
Ruder et al. (2004)-high exposure	Reinforced plastics	2	2.4	82	10-296
Ruder et al. (2004)-low exposure	Reinforced plastics	8	8.9	90	-
Bond et al. (1992)	STY manufacture	7	6	117	47-240
Hodgson and Jones (1985)	STY manufacture	3	0.4	750	155-2192
Nicholson et al. (1978)	STY manufacture	1	1.3	80	2-429

Hodgkin's Disease

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced plastics	3	2.3	133	27-388
Kogevinas et al. (1994)-unspecified	Reinforced plastics	3	2.8	107	22-312
Kogevinas et al. (1994)-other exposed	Reinforced plastics	1	1.3	80	2-446
Wong et al. (1994)	Reinforced plastics	4	4.5	90	25-230
Ruder et al. (2004)-high exposure	Reinforced plastics	1	0.6	166	4-924
Ruder et al. (2004)-low exposure	Reinforced plastics	0	-	-	-
Bond et al. (1992)	STY manufacture	5	2.3	222	71-518
Hodgson and Jones (1985)	STY manufacture	0	0.4	0	0-922

Multiple Myeloma

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced plastics	0	0	0	0-155
Kogevinas et al. (1994)-unspecified	Reinforced plastics	7	3.6	193	78-398
Kogevinas et al. (1994)-other exposed	Reinforced plastics	1	1.9	53	1-295
Wong et al. (1994)	Reinforced plastics	6	4.5	134	49-292
Ruder et al. (2004)-high exposure	Reinforced plastics	NA	-	-	-
Ruder et al. (2004)-low exposure	Reinforced plastics	NA	-	-	-
Bond et al. (1992)	STY manufacture	7	3.8	184	74-380
Hodgson and Jones (1985)	STY manufacture	0	0.2	0	0-1844

Leukemia

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced plastics	3	6.3	48	10-139
Kogevinas et al. (1994)-unspecified	Reinforced plastics	16	11.4	140	79-228
Kogevinas et al. (1994)-other exposed	Reinforced plastics	4	4.3	94	26-240
Wong et al. (1994)	Reinforced plastics	11	14.8	74	37-133
Ruder et al. (2004)-high exposure	Reinforced plastics	1	2.2	46	1-258
Ruder et al. (2004)-low exposure	Reinforced plastics	4	6.3	64	17-163
Bond et al. (1992)	STY manufacture	9	7.6	118	54-224
Hodgson and Jones (1985)	STY manufacture	1	0.6	167	4-929
Nicholson et al. (1978)	STY manufacture	1	0.8	127	3-696

Table 2. Modeled Risk of LHC & STY Exposure in Kogevinas et al. (1994)

	All LHC			Leukemias			Malignant Lymphomas		
Variable	Obs	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI
Avg. Exp (ppm)									
< 60	7	1		3	1		3	1	
60-99	9	1.7	0.6-4.8	4	1.6	0.3-7.8	4	2.5	0.5-12.9
100-119	10	3.1	1.1-9.1	8	4.4	1.0-20.0	1	1.7	0.2-18.6
120-199	13	3.1	1.0-9.1	3	1.4	0.2-8.5	8	7.2	1.2-42.1
200+	8	3.6	1.0-13.1	3	2.2	0.3-16.2	2	4.4	0.4-46.0
Test for linear trend		p=0.019			p=0.47			p=0.052	
Cumulative Exp (ppm)									
<75	20	1		11	1		5	1	
75-199	8	0.98	0.43-2.26	2	0.46	0.10-2.09	5	2.63	0.74-9.32
200-499	10	1.24	0.57-2.72	3	0.69	0.19-2.53	5	2.99	0.82-10.91
500+	9	0.84	0.35-2.02	5	0.86	0.26-2.83	3	1.64	0.34-7.82
Test for linear trend		p=0.65			p>0.52			p=0.52	

Recommendation: The NTP report acknowledges that, "[t]he evidence for lymphohematopoietic malignancies appears to be the strongest in the styrene-butadiene industry … Findings for lymphohematopoietic cancers from studies in the reinforced plastics industry were less consistent." The NTP report should acknowledge that the authors of studies in the SBR industry have suggested that the exposure most strongly associated with the excess risk of leukemia was BD, not STY. Since findings from the reinforced plastics industry also do not support an association with STY (especially if the Danish cohort is only counted once), the NTP report should conclude that the current data do not support this association.

3. The NTP report overemphasizes pancreas cancer in their overall conclusions, despite clear non-positive results in SBR workers and inconsistent findings in other STY worker studies, as described below.

SBR Worker Studies

There is clearly no increased risk of pancreas cancer in SBR workers. In the most recent update of SBR workers (1944 – 1998), Sathiakumar et al. (2005) reported no increased mortality due to pancreas cancer (SMR = 87; 95% CI 68 – 108; 76 observed deaths). Probably due to this deficit, pancreas cancer was not mentioned in the text of the article, nor analyzed further. These results were consistent with the results reported earlier by Matanoski et al. (1990), who found no increased overall mortality due to pancreas cancer (SMR = 0.83; 95% CI 0.54 – 1.20; 27 observed deaths) among workers in the SBR manufacturing industry (1943 – 1983). Matanoski and colleagues (1990) further analyzed all site-specific SMRs based on major work divisions, assigning employees to a work area based on the job longest held. The SMR for pancreas cancer among production workers was 0.69 (95% CI: 0.22 – 1.62; 5 observed deaths). The SMR for pancreas cancer among maintenance workers was 0.80 (95% CI: 0.36–1.51; 9 observed deaths). The SMR for pancreas cancer among workers in the 'other' category was 1.26 (95% CI: 0.61 – 2.32; 10 observed deaths). The NTP review ignores these non-positive results for pancreas cancer from the studies of SBR workers, yet relies on the positive leukemia findings from this cohort and attempts to attribute them to STY.

STY Worker Studies

The NTP review states that the risk of pancreas cancer was elevated in five occupational studies of STY workers (three in the reinforced plastics industry, one in the STY manufacturing industry, and one study of workers monitored using urinary biomarkers by Anttila et al., 1998). For the reinforced plastics industry, the NTP reviewers have counted both the Kolstad et al. and the Kogevinas et al. cohorts.

Table 3 summarizes the pancreas cancer results for the various studies, including those cited in the NTP report. There are a number of elevated SMRs, but none is statistically significant, and many are based on small numbers with extremely wide confidence limits. None of these studies looked at any possible confounding factors for pancreas cancer, such as cigarette smoking.

(Note: In section 3.3.1, the NTP report mentions that mortality from pancreas cancer was increased in the Frentzel-Beyme cohort, but later states in section 3.8.2 that it was decreased.)

Table 3. Results for Pancreas Cancer and STY Workers

Study	Industry	Obs	Exp	SMR	95% CI
Kogevinas et al. (1994)-laminators	Reinforced Plastics	12	8.1	148	76-258
Kogevinas et al. (1994)-unspecified	Reinforced Plastics	17	14.5	117	68-188
Kogevinas et al. (1994)-other exposed	Reinforced Plastics	2	6.7	30	4-110
Wong et al. (1994)-	Reinforced Plastics	19	16.8	113	68-177
Ruder (2004)-high exposure	Reinforced Plastics	4	2.2	181	49-464
Ruder (2004)-low exposure	Reinforced Plastics	10	7.9	126	61-233
Bond et al. (1992)	STY manufacture	5	10.3	49	16-113
Frentzel-Beyme et al. (1978)	STY manufacture	2	0.7	285	32-1031

Hodgson and Jones (1985)	STY manufacture	NA	-	-	-
Nicholson et al. (1978)	STY manufacture	NA	-	-	-
Anttila et al. (1998)*	Biomarker study	3	0.8	364	75-1060

*Cancer incidence study

Kogevinas et al. (1994) also examined the risk of pancreas cancer with duration of employment and with cumulative exposure to STY and found a relationship with each. None of the other studies, however, showed similar results. Wong et al. (1994) found no increasing risk for pancreas cancer with increasing cumulative exposure to STY and that the increase in pancreas cancer was highest in workers employed less than one year (Table 4). Ruder et al. (2004) reported that, in workers employed more than one year, the SMR for pancreas cancer was higher in low exposure workers than in high exposure workers. These results further emphasize the inconsistency in pancreas cancer results. The totality of the evidence from the reinforced plastics and other STY cohort studies does not support a causal relationship between STY and pancreas cancer.

Recommendation: The NTP report should note that the elevations seen for pancreas cancer are not observed consistently across all studies of STY workers and that they are more likely to be seen in short-term workers; thus, these findings are unlikely to be due to STY exposure and more likely to be due to confounding or associated with lifestyle factors such as smoking and alcohol consumption.

Table 4. Risk of Pancreas Cancer & Cumulative STY Exposure

Cumulative Exposure (ppm-years)			
Kogevinas et al., 1994	**Obs**	**RR**	**95% CI**
<75 ppm–years	9	1.0	-
100-199 ppm-years	5	1.44	0.48-4.34
200-499 ppm-years	6	1.90	0.65-5.53
500+ ppm-years	10	2.56	0.90-7.31
Test for trend		p=0.068	
Wong et al., 1994	Obs	**SMR**	**95% CI**
<10.0 ppm –years	5	140.1	Not reported
10.0-29.9 ppm –years	6	160.7	Not reported
30.0-99.9 ppm –years	3	62.8	Not reported
100+ ppm –years	5	106.3	Not reported

4. In their discussion of specific studies and in the overall conclusions, the NTP draft pays inadequate attention to confounding factors, especially for those findings related to leukemia and to cancers of the lung and pancreas.

One possible reason for the inconsistent results with regard to various cancer sites across industries and cohorts is confounding. The NTP report gives very little attention to potential confounding factors that may have contributed to the elevated SMRs seen in some of the studies. Possible confounding factors in these studies include both occupational factors like other chemical exposures (e.g., benzene and asbestos) and non-occupational factors such as smoking and socioeconomic status (SES).

- **Leukemia** – Elevated risks for leukemia were not consistently observed for the studies mentioned in the NTP review. Depending on the facility (e.g., a chemical plant using and producing multiple chemicals), workers may have been exposed to numerous other chemicals, which were usually not adjusted for in the statistical analyses of these cohorts. In the STY manufacturing, polymerization, and processing industry, for example, results may have been confounded by possible exposure to benzene, a known leukomogen. In addition, the strongest RRs for leukemia were seen in the STY-butadiene industry where exposures to BD and DMDC were higher and more strongly associated with leukemia risk and where benzene exposures were too low to be considered as a possible confounder.

- **Pancreas Cancer** – Smoking has been associated consistently with an increased risk of pancreas cancer and some studies have reported an association between alcohol consumption and pancreas cancer, although the NTP did not mention these associations in their report. Many of the workers in the reinforced plastics industry were short-term workers, and short-term workers or workers who change jobs often are more likely to have lower SES and, therefore, higher rates of smoking and alcohol consumption. Thus, higher smoking rates and/or increased alcohol consumption among short-term workers could explain the elevated SMRs observed for this cause of death, and not STY (or any other chemical) exposure. No information was provided in any of the studies to allow adjustment for smoking or alcohol

consumption. As noted in the next paragraph, confounding by smoking was responsible for an increased risk of lung cancer in one STY cohort.

- **Lung Cancer** – In their site-specific summary (section 3.8.4), the NTP report notes that lung cancer was significantly increased in Wong et al. (1994) and non-significantly increased in Kolstad et al. (1995) and Ruder (2004). Wong et al. (1994), however, note that, "workers with less than one year of employment had the highest risk of lung cancer." They found no increased risk in the group with 10+ years of employment or in the highest cumulative exposure group. In addition, in an earlier nested case-control study of lung cancer in the same cohort, Wong (1990) found that excess lung cancer mortality was associated with cigarette smoking.

- **Studies of short-term workers** – A large portion of the workers in the reinforced plastics industry worked for less than six months in the industry, and many of the risk ratios were highest in these workers (e.g., Wong et al. [1994] note that "most of the increases in mortality occurred among short-term workers"). A number of researchers have noted that including short-term workers can impact results independently of the exposure of interest. Checkoway et al. (1989) state that "a minimum length of employment criterion may be imposed in defining the study cohort … a cost increment (often substantial) will result from the inclusion of all workers when short-term, transient workers, who are difficult to trace, comprise a large proportion of the workforce … short-term workers may have atypical life-styles that make them noncomparable to longer-term workers" (p. 110). Nicholson et al. (1987) states, "the personal factors affecting health associated with such transient populations may adversely bias a study. In many industries, if not most, approximately half the individuals that are hired quit or are terminated within a year. Inclusion of such individuals in a study can give rise to spurious increases in overall SMR's [sic]."

Recommendation: The NTP report should discuss the possible role of confounding factors in elevated risks and evaluate whether confounding is a more likely explanation than STY, particularly in short-term workers.

5. Several studies are included in the NTP review that add no meaningful information, given the existence of enormously more informative studies.

A number of the additional studies included in the NTP review do not add significant information to that already provided by the occupational cohort studies discussed above. These include:

- Loughlin et al. (1999) examined lymphatic and hematopoietic cancer in a population that attended high school near two SBR facilities. This population would have had much lower exposures to STY than employees in the facilities, and no information was available about other exposures experienced by this population. No excess LHC was found.

- Three case-control studies of various LHCs examined risk associated with past possible exposure to STY and other chemicals. Flodin et al. (1986) carried out a case-control study of acute myeloid leukemia. There was an elevated risk associated with STY, but it was based on only 3 cases out of 59, and it was not adjusted for other exposures. Guenel et al. (2002) conducted a case-control study of leukemia in French utility workers. The OR for STY was 1.1 and not statistically significant. Seidler et al. (2007) carried out a population-based case-control study of malignant lymphoma. No association with STY was seen.

- Two studies of breast cancer found an increased risk associated with exposure to STY. One was a case-control study that reported a weak, statistically significant risk with no trends by exposure probability or level (Cantor et al., 1995). The other was an ecological study looking at the risk of breast cancer and toxic releases in Texas (Coyle et al., 2005); a statistically significant association with STY releases was seen. A review of the Coyle et al. study by Burns et al. (2006) noted that these results are likely to be an example of an ecological fallacy. Ambient STY exposures in the Houston, TX area average 0.018 ppb. Industrial exposures are about 3 million times greater, but no excess risk of breast cancer has been found in these populations.

- Several population-based case-control studies in Canada examined the risk of several sites of cancer with numerous occupational exposures. Dumas et al. (2000) and Gerin et al. (1998) both found associations between rectal cancer and STY exposure. Gerin et al. (1998) also found excess risk associated with STY for prostate cancer, non-Hodgkin's lymphoma, and Hodgkin's lymphoma. Parent et al. (2000) found an association between SBR production exposure and renal cell cancer.

- Scélo et al. (2004) conducted a clinic-based study of lung cancer in several European countries. No association with STY exposure was seen.

These studies provide no meaningful, additional information to the occupational studies discussed above. The results are inconsistent across the studies, they are not consistent with the occupational cohort studies, and the potential for exposure to STY varies by study. Even if exposure to STY existed, the levels would be expected to be substantially lower than those for the occupational cohorts with known STY exposure.

Recommendation: For completeness, the NTP report should acknowledge the existence of other studies that mention STY as a possible risk factor, but exclude them from the overall evaluation for the above-cited reasons.

6. There are a few relevant studies missing from the NTP draft report.

The NTP report indicates that the Macaluso work was not validated. Indeed, a validation study of the BD exposure estimates used in the UAB analyses was undertaken at one of the manufacturing complexes included in the UAB study of synthetic rubber industry workers (Sathiakumar et al., 2007). The validation study was undertaken in the manufacturing complex located in Ontario, Canada, because data from a systematic,

quarterly industrial hygiene monitoring program instituted in 1977 were available for this site.

The authors concluded that BD estimates for typical SBR jobs, which comprised most operations at all but one of the plants in the mortality study, were useful for ranking workers by cumulative exposure. In general, the authors noted that estimates were about ten percent lower than measurements, indicating that possible reasons for these differences included inaccurate assumptions used in generating butadiene estimates, non-representative or unstable measurements and errors in linking measurement information to the job-exposure matrix. They also pointed out that exposure misclassification may have been more severe for subjects from the validation study center than for subjects from other plants in the mortality study, since this center was more complex than the other plants. STY estimates were not validated as part of this study.

Cheng and colleagues (Cheng et al., 2007) studied the same population and follow-up period as Graff et al. (2005) using Cox proportional hazard analyses to examine further the exposure-response relationships between several indices of exposure to BD and leukemia, lymphoid neoplasms and myeloid neoplasms. They indicated the following on p. 17: "[e]pidemiologic research has not provided consistent evidence that this agent causes leukemia in humans [4]. In our study, styrene (treated as a continuous variable) was moderately to strongly correlated with BD ppm-years … and BD average intensity … and weakly correlated with BD peaks ... Controlling for STY, in addition to other covariates, increased the strength of the association between leukemia and butadiene ppm-years and had little impact on results for other butadiene variables."

A nested case-control study of pancreas cancer (28 cases, 140 controls) was conducted within a plastics manufacturing facility that included workers producing polystyrene from 1937 to 1976 (Selenskas et al., 1995). In addition to STY, the major chemicals in this department were vinyl benzene, toluene, methyl ethyl ketone, triethylchloride and triethylchorine. Workers assigned for more than 16 years to the vinyl resins department had a significantly increased RR of 7.15 (95%CI: 1.28-40.1) for pancreas cancer. Other departments examined, including polystyrene production, showed no relationship with pancreas cancer.

References

Anttila A, Pukkala E, Riala R, Sallmen M, Hemminki K. Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. In *Arch Occup Environ Health* 71(3):187-193, 1998.

Bond GG, Bodner K, Olsen GW, and Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products-an update. *Scand J Work Environ Health* 18:145-154, 1992.

Cantor KP, Steward PA, Brinton LA, Dosemeci M. Occupational exposures and female breat-cancer mortality in the United States. *J Occup Environ Med* 37(3):336-348, 1995.

Checkoway H, Pearce N, Crawford-Brown D. Research Methods in Occupational Epidemiology. Oxford University Press, New York, 1989.

Cheng H, Sathiakumar N, Graff J, Matthews R, Delzell E. 1,3-Butadiene and leukemia among synthetic rubber industry workers: Exposure-response relationships. *Chemico-Biological Interactions* 166:15-24, 2007.

Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, and Acheson ED. Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J. Work Environ Health* 13: 94-99, 1987.

Cohen JT, Carlson G, Charnley G, Coggon D, Delzell E, Graham JD, Greim H, Krewski D, Medinsky M, Monson R, Paustenbach D, Petersen B, Rappaport S, Rhomberg L, Ryan PB, Thompson K. *J Toxicol Environ Health* 5(1-2):1-263, 2002.

Coyle YM, Hynan LS, Euhus DM, Minhajuddin AT. An ecological study of the association of environmental chemicals on breast cancer incidence in Texas. *Breast Cancer Treat* 92(2):107-14, 2005.

Delzell E, Macaluso M, Sathiakumar N, Matthews R. Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. *Chem Biol Interact* 135-136:515-534, 2001.

Dumas S, Parent M, Siemiatycki J, and Brisson J. Rectal cancer and occupational risk factors: A hypothesis-generating, exposure-based case-control study. *Int J Cancer* 87:874-879, 2000.

Flodin U, Fredriksson M, Persson B, Hardell L, Azelson O. Background radiation, electrical work, and some other exposures associated with acute myeloid leukemia in a case-referent study. *Arch Environ Health* 41(2):77-84, 1986.

Frentzel-Beyme R, Thiess AM, Wieland R. Survey of mortality among employees engaged in the manufacture of styrene and polystyrene at the BASF Ludwigshafen works. *Scand J Work Environ Health* 4(Suppl 2):231-239.

Gerin M, Siemiatychi J, Desy M, and Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case control study in Montreal. *Am J Ind Med* 34:144-156, 1998.

Graff JJ, Sathiakumar N Macaluso M. Maldonado G, Matthews R, Delzell E. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J Occup Environ Med* 47(9):916-932, 2005.

Guenel P, Imbernon E, Chevalier A, Crinquand-Calastreng A, Goldberg M. Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. *Am J Ind Med* 42(2):87-97, 2002.

Hodgson JT, Jones RD. Mortality of styrene production, polymerization and processing workers at a site in northwest England. *Scand J Work Environ Health* 11:347-352, 1985.

Kogevinas M, Ferro G, Saracci R, Andersen A, Biocca M, Coggon D, Gennaro V, Hutchings S, Kolstad H, Lundberg I, Lynge E, and Partanen T. Cancer mortality in an international cohort of workers exposed to styrene. In Butadiene and styrene: Assessment of the health hazards, IARC Scientific Publications no. 127, eds Sorsa M, Peltonen K, Vainio H, and Hemminki K, pp. 289-300. Lyon: International Agency for Cancer Research, 1993.

Kogevinas M, Ferro G, Andersen A, Bellander T, Biocca M, Coggon D, Gennaro V, Hutchings S, Kolstad H, Lundberg I, Lynge E, Partanen T, and Saracci R. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Environ Helath* 20:251-261, 1994.

Kolstad HA, Lynge E, and Olsen J. Cancer indicence in the Danish reinforced plastics industry. In Butadiene and styrene: Assessment of the health hazards, IARC Scientific Publications no. 127, eds Sorsa M, Peltonen K, Vainio H, and Hemminki K, pp. 301-308. Lyon: International Agency for Cancer Research, 1993.

Kolstad HA, Lynge E, Olsen J, and Breum N. Incidence of lymphohematopoietic malignancies among styrene-exposed workers fo the reinforced plastics industry. *Scand J Work Environ Health* 20:272-278, 1994.

Kolstad HA, Juel K, Olsen J, and Lynge E. Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry. *Occup Environ Med* 52:320-327, 1995.

Linet MS, Devesa SS, Morgan J. The Leukemias. In Cancer Epidemiology and Prevention, Third Edition, eds. Schottenfeld D and Fraumeni JF, pp. 841-871. New York: Oxford University Press, 2006.

Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Halth Perspect* 86:107-117, 1990.

Nicholson WJ, Selikoff IJ, and Seidman H. Mortality experience of styrene-polystyrene polymerization workers. Initial findings. *Scan J Work Environ Health* 4(suppl. 2):247-252, 1978.

Nicholson, William J. Comments on the Healthy Worker Effect. In Report to the Workers Compensation Board on the Healthy Worker Effect, 1987.

Okun AH, Beaumonth JJ, Meinherdt TJ, and Crandall MS. Mortality patterns among styrene-exposed boatbuilders. *Am J Ind Med* 8:193-205, 1985.

Ott MG, Kolesar RC, Scharnweber HC, Schneider EJ, Venable JR. A mortality survey of employees engaged in the development or manufacture of styrene-based products. *J Occup Med* 22(7):445-460, 1980.

Parent M, Hua Y, and Siemiatyki J. Occupational risk factors for renal cell carcinoma in Montreal. *Am J Ind Med* 38:609-618, 2000.

Ruder AM, Ward EM, Dong M, Okun AH, Davis-King K. Mortality patterns among workers exposed to styrene in the reinforced plastic boatbuilding industry: an update. *Am J Ind Med* 45(2):165-175, 2004.

Santos-Burgoa C, Matanoski GM, Zeger S, and Schwartz L. Lymphohematopoietic cancer in styrene-butadiene polymerization workers. *Am J Epidemiol* 136:843-854, 1992.

Sathiakumar N, Delzell E, Hovinga M, Macaluso M, Julian JA, Larson R, Cole P, and Muir DC. Mortality from cancer and other cause of death among synthetic workers. *Occup Environ Med* 55:230-235, 1998.

Scélo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J. Fabiánová E, Cassidy A, Slamova A, Foretova L, Janout V, Fevotte J, Fletcher T, Mannetje A, Brennan P, Boffetta P. Occupational exposure to vinyl chloride, artylonitrile and styrene and lung cancer risk (Europe). *Cancer Causes Control* 15(5):445-452, 2004.

Seidler A, Mohner M, Berger J, Mester B, Deeg E, Elsner G, Nieters A, Becker N. Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. *J Occup Med Toxicol* 2:2, 2007.

Selenskas S, Teta MJ, Vitale MS. Pancraetic cancer among workers processing synthetic resins. *Am J Ind Med* 28:385-398, 1995.

Wong O. A cohort mortality and a case-control study of workers potentially exposed to styrene in the reinforced plastics and the composites industry. *Br J Ind Med* 47:753-962, 1990.

Wong O, Trent LS, and Whroton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 51:386-396, 1994.