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December 16, 2008

Samuel Wilson, M.D., Acting Director
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RE: Request for NTP to Fully Consider New Styrene Epidemiology Review Prior to Finalizing Styrene Draft Substance Profile

Dear Dr. Wilson:

On December 15, both the National Toxicology Program (NTP) and the Styrene Information and Research Center[1] (SIRC) received the styrene epidemiology report from Drs. Boffetta (IARC), Adami (Harvard), Cole (University of Alabama), Trichopoulos (Harvard), and Mandel (University of Toronto) [Boffetta et. al.][2]. I am enclosing a copy of their report and request that it be made a part of the *Report on Carcinogen's (RoC)* styrene docket. This group of world-renown epidemiologists from prestigious institutions worked completely independently of our organization. We had no prior knowledge of their conclusions.

In previous correspondence we have asked that NTP delay the next step in the *RoC* process for styrene (the preparation of the draft substance profile on styrene scheduled for December 24, 2008)

[1] The Styrene Information and Research Center's (SIRC's) mission is to evaluate existing data on potential health effects of styrene, and develop additional data where it is needed. SIRC has gained recognition as a reliable source of information on styrene and helping ensure that regulatory decisions are based on sound science. For more information, visit http://www.styrene.org

[2] Epidemiological Studies of Styrene and Cancer: A review of the Literature, December 9, 2008, Boffetta, P. (International Agency for Research on Cancer, Lyon, France; Vanderbilt University, Nashville, Tennessee), Adami, HO (Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts), Cole, P.(School of Public Health, University of Alabama, Birmingham, Alabama) Trichopoulos, D., Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts), and Mandel, J.S.(Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario.

until NTP has had a chance to review this report by Boffetta et.al. *in detail*, and consider its implications for the NTP conclusions regarding styrene. With this report in hand, we now know that Boffetta et.al. have reached conclusions that are diametrically opposed to those reached by the *RoC* Expert Panel on styrene, whose un-peer-reviewed re-analysis of a published study we have repeatedly criticized and brought to your attention in correspondence.

Boffetta et.al.'s full review of the styrene epidemiological data can be summarized and contrasted with that of the NTP Expert Panel as follows:

Delzell et al (2006) – The NTP Expert Panel reported the strongest evidence comes from Delzell et. al (2006) in styrene-butadiene rubber (SBR) workers, concluding there was an exposure-response relationship for NHL and NHL plus chronic lymphocytic leukemia (CLL) that was not attenuated by control for butadiene and only mildly attenuated by control for dimethyldithiocarbamate. However, Delzell et. al., which was an update of an earlier cohort study conducted by the NTP Panel's Epidemiology Subgroup Chairperson, Dr. Genevieve Matanoski, rejected this conclusion. In effect, the NTP Panel's new conclusion served to validate Dr. Matanoski's earlier findings. *In contrast, Boffetta et. al. concluded that "...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."*

Kogevinas et al (1994a) – Without explaining their criteria, the NTP Panel essentially threw out the studies in reinforced plastics (RPC) workers because they were too small (5000, 15,000, or 40,000 workers) or had too few workers with long-term exposures (but not significantly shorter than the SBR workers). The NTP Panel did, however, cite the RPC study Kogevinas et. Al. (1994a), as providing supportive evidence, concluding increases in RR for all lymphomas with time since first exposure and estimated average exposure in the multi-plant cohort studied by Kogevinas. *In contrast, Boffetta et.al. found: "An association between average level of styrene exposure and NHL risk was **suggested** in the multicenter European study but **no trend** with duration of exposure to styrene (the SMR of NHL for 5 or more years of employment was 1.01 [95% CI 0.27-2.57]) (Kogevinas et al., 1994b) or with cumulative exposure was evident (Figure 2)."*

Overall Conclusion – The NTP Expert Panel concluded that there was "limited" evidence of carcinogenicity in humans, based specifically on Delzell et. al. (2006) and Kogevinas et. al. (1994a). The NTP Panel essentially "upgraded" the findings of these studies by arriving at conclusions about the data that were not reported by the authors themselves. These two new conclusions were then used to meet the threshold requirements for a finding of "limited" evidence. *In contrast, Boffetta et.al. concluded that "The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of cancer."*

The styrene industry has now submitted to NTP four independent evaluations of the styrene epidemiologic data – Boffetta et. al., Teta, Goodman and Rhomberg, and Delzell. All have agreed that

there is no evidence of a causal association of styrene with any type of cancer in humans.

The Boffetta report plainly shows that there is a legitimate scientific dispute that needs to be resolved in a considered, scientifically sound, and open manner. To do otherwise would raise serious questions about the integrity of the *RoC* scientific process and its dedication to fairness and to the scientific process.

Clearly the findings of these eminent epidemiologists require a re-evaluation of the NTP background document and Expert Panel recommendations. Any serious re-evaluation is incompatible with rushing ahead to incorporate the recommendations of the Expert Panel into the NTP draft substance profile, now scheduled for publication no later than December 24, 2008. We submit that the NTP needs to take the time to consider the conclusions of the Boffetta et.al. report *carefully* and address the inconsistency with the Expert Panel's recommendations, and what this means in terms of classification of styrene under the criteria of the *RoC*. We request again that you delay the development of the draft profile on styrene, remove styrene from the agenda of the February 24, 2009 Board of Scientific Counselors, and take the time needed to address these matters thoroughly in January, rather than rushing to meet the self-imposed deadline of December 24th. We also request that NTP redraft, amend, or supplement the Background document on styrene. As the report by Boffetta et. al. demonstrates, the Expert Panel's conclusions with regard to epidemiology are so fundamental to its recommendation to classify styrene as "reasonably anticipated to be a human carcinogen" that its recommendation can no longer be relied upon in the background document.

We look forward to your prompt response in light of the schedule's impending deadline of December 24th for the publication of the draft profile.

Very truly yours,

Signature

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cc: Dr. Ruth Lunn, Report on Carcinogens, NTP
Dr. Linda Birnbaum, NTP Incoming Director

Attachment: Epidemiological Studies of Styrene and Cancer: A review of the Literature, December 9, 2008, Boffetta, P. et al.

Epidemiologic studies of styrene and cancer:

A review of the literature

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December 9, 2008

Summary

Styrene, an important chemical agent used primarily in the manufacture of polymers and copolymers, has been suspected to cause cancer in humans on the basis of results from experimental studies on animals. We reviewed systematically studies of workers exposed to styrene in the manufacture and polymerization of the chemical, in the reinforced plastics industry and in styrene-butadiene rubber production. We also reviewed studies of workers monitored for styrene exposure as well as studies of environmental exposure to styrene, community-based case-control studies of lymphoma and leukemia, and studies of DNA adducts. Studies of workers in the reinforced plastics industry were considered more informative because of the higher worker exposure levels and less confounding by other possible carcinogens.

We found no consistent increased risk of any form of cancer among workers exposed to styrene. A large study of reinforced plastic workers reported an association between average estimated styrene exposure and risk of non-Hodgkin lymphoma (NHL, $p=0.05$), but no trend with increasing duration of exposure. Other studies of styrene exposure and NHL found no increased risk. In two US studies of reinforced plastic workers esophageal cancer mortality was increased, but these findings were generated in a background of multiple comparisons. Results for other cancers were unremarkable. The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer. Further updates of the most informative studies, however, are warranted.

Introduction

Styrene (ethenylbenzene) is a monomer that is incorporated into major polymers and copolymers. The major uses are in plastics, paints, coatings, synthetic rubbers, and polyesters. Styrene is, however, also used in packaging (e.g., styrene-containing foams), construction (e.g., plastic pipes, insulation for electrical uses, fittings, tanks), automotive industry (e.g., tires, reinforced plastics), and household goods (e.g., molded furniture, carpet backing) (IARC, 2002). In addition, styrene is used as co-reactant and solvent in reinforced plastic fabrications, including boats, tanks, pipes and automobile body parts (Mannsville Chemical Products Corp., 1987). Styrene is also produced naturally by plants, bacteria and fungi and is present in combustion products such as cigarette smoke and automobile exhaust. The main routes of occupational exposure are inhalation and dermal. This conversion to polystyrene resins is the most important use of styrene and the production of copolymers (acrylonitrile-butadiene-styrene [ABS], styrene-acrylonitrile [SAN] and styrene-butadiene rubber [SBR]) is the second most important use of styrene derivatives.

Based on a literature review, non-occupational exposure to styrene was estimated to be 18.2–55.2 μg/person/day, or 6.7–20.2 mg/person/year, mainly from inhalation and food intake via release of styrene from packaging material (Tang et al., 2000). Tobacco smoking is another important source of styrene exposure, with styrene exposure from 20 cigarettes/day being equivalent to that from all other non-occupational sources combined.

In rats, styrene was not carcinogenic in either gavage or inhalation studies. In mice, gavage and intraperitoneal studies also were negative, whereas inhalation studies provided evidence of an increased incidence of pulmonary adenoma. The relevance of this finding to humans is uncertain, because of the particularly high level of oxidation of styrene to styrene 7,8-oxide in the Clara cells of mice (IARC, 2002). In 2002 IARC concluded that there is limited evidence for the carcinogenicity of styrene in experimental

animals (IARC, 2002). In contrast, evidence relating to the carcinogenicity in experimental animals of the main metabolite of styrene (its 7,8-oxide derivative) - excreted in the urine as mandelic and phenylglyoxylic acids – was classified as "sufficient" (IARC, 1994). IARC Monographs are agent-specific. There is apparent inconsistency in the results for the metabolite, 7,8-oxide and the parent compound, styrene because animal experiments using styrene 7,8-oxide were positive, but experiments using styrene were not. In humans, nevertheless, occupational exposure to styrene leads to formation of DNA adducts, particularly *O*6- and *N*7-deoxyguanosine adducts (Henderson and Speit, 2005) and the same adducts are detected in exposed rodents. High-level occupational exposure to styrene produces a decrease in color discrimination, hearing loss and other nervous system symptoms (IARC, 2002). No reproductive or teratogenic effects have been reported (Brown et al., 2000).

Concern about a possible carcinogenic effect of styrene in humans arises from (i) the increased incidence of lung adenoma in exposed mice, (ii) the carcinogenicity of styrene 7,8-oxide in experimental animals, (iii) the presence of DNA adducts in exposed humans, and (iv) the carcinogenic effect in humans of compounds similar to styrene, such as benzene. Recent reviews of styrene toxicity and carcinogenicity include the IARC Monograph evaluation (IARC, 2002), the risk analysis performed by Cohen and colleagues (2002), and the Report of Carcinogen Background Document of the National Toxicology Program (NTP, 2008).

Literature search

We identified studies of styrene and cancer through a literature search via PubMed using the terms ((styrene and (cancer or neoplasms) and (epidemiology or mortality or incidence)), without restriction of language or date of publication, as well as the references in the recent IARC Monograph (IARC, 2002) and NTP Background Document (NTP, 2008). In a second PubMed search, we used the terms ((lymphoma or Hodgkin or Hodgkin's or leukemia or NHL) and (case-control) and (industry or occupation or occupational)) to identify community-based case-control studies of

lymphoma or leukemia, for which results relevant to occupational exposure to styrene could have been presented in the main text or tables but not reported in the abstract. We reviewed the abstracts of the papers to select the subset of studies which have potentially included an assessment of occupational exposure to styrene, and we reviewed the detailed results of this subset of studies. Finally, we conducted a PubMed search of studies on the presence of DNA adducts following styrene exposure using the terms (styrene and adducts): this search was supplemented by the references of the IARC and NTP reviews (IARC, 2002; NTP, 2008).

Epidemiologic studies of cancer

Mortality/morbidity studies retained for the review included (i) cohort studies of workers employed in styrene manufacturing and polymerization, styrene-based reinforced plastics manufacturing, and styrene-butadiene rubber manufacturing, (ii) cohort studies of workers who underwent biomonitoring for styrene exposure in different industries, (iii) case-control studies of lymphohematopoietic (LHP) neoplasms which presented results on occupational styrene exposure, and (iv) studies of environmental styrene exposure. The latter group of studies was included for completeness but was not considered informative with respect to styrene carcinogenicity because of the very low exposure levels encountered in the general environment. Case-reports (e.g., Nicholson et al., 1978) were not reviewed in detail. Studies on DNA adducts were reviewed separately.

The occupational cohort studies are summarized in Table 1. Results on risk of LHP neoplasms overall, and specifically of NHL and leukemia, are summarized in Table 2. Results on risk of selected solid cancers which have been suggested to be associated with styrene exposure (cancers of the esophagus, rectum, pancreas and breast) are summarized in Table 3.

Styrene production and polymerization

In recent decades exposure levels in the production and polymerization of styrene typically have been measured in the range of <1-10 ppm, with peak exposure levels up to 50 ppm (IARC, 2002). In the past, higher exposure levels have likely occurred, in particular in batch polymerization. For example exposure during container filling for batch polymerization in 1942 in a US plant ranged from 5 to 88 ppm (Ott *et al*., 1980). Other potential exposures in this industry, which could exercise confounding influences in analyses of cancer risk following styrene exposure, include benzene, acrylonitrile, 1,3-butadiene, ethylbenzene, dyes and pigments.

In a German study of 1960 workers employed between 1931 and 1976, and followed between 1956 and 1976, total mortality (74 observed and 96.5 expected deaths) and cancer mortality (12 observed and 20.4 expected) were below expectation (Frentzel-Beyme *et al.,* 1978). One death from LHP neoplasms and two from pancreatic cancer were observed (expected deaths, 0.09 and 0.7, respectively, based on 1972-75 regional mortality rates).

A study in a UK plant included 622 workers employed for at least one year between 1945 and 1974, and followed until 1978 (Hodgson and Jones, 1985). A total of 34 deaths were observed (43.1 expected), of which three were from lymphoma (0.56 expected, p=0.02). An analysis of cancer incidence identified four cases of LHP neoplasms (1.6 expected, p=0.08). This study also reported three cases of laryngeal cancer (0.5 expected, p=0.04). There was no apparent association between length of service in the styrene exposed jobs and the incidence of LHP neoplasms. All four cases worked less than seven yeas and for two of the cases, the time between first exposure and death was four and eight years, which are relatively short intervals. Two of the four cases were reticulum cell sarcomas, one was chronic lymphocytic leukemia (entities currently part of NHL) and one was Hodgkin's lymphoma.

A cohort study included 2904 workers employed for at least one year in four US plants between 1937 and 1971, who were followed up between 1940 and 1986 (Ott *et al*., 1980;

Bond *et al*., 1992). Workers were potentially exposed to a number of agents including styrene monomer, benzene, acrylonitrile, 1,3-butadiene, ethylbenzene, dyes and pigments, polymer dusts and extrusion fumes. Among the styrene based cohort, 687 deaths occurred (standardized mortality ratio [SMR] 0.76 (95% confidence interval [CI] 0.70–0.82), of which 162 were from cancer (SMR 0.81; 95% CI, 0.69–0.95). There was one death from laryngeal cancer (2.9 expected), five deaths from pancreatic cancer (10.3 expected) and 3 deaths from esophageal cancer (4.6 expected) and 28 deaths from LHP neoplasms (SMR 1.39; 95% CI, 0.92–2.08). The excess mortality was confined to workers exposed less than five years (SMR 2.35, 95% CI 1.22-4.11) while among workers with higher exposure (>5ppm) there were 4 deaths observed and 3.0 expected (SMR 1.33, 95% CI 0.36-3.41) with no significant trend with increasing duration of exposure.

In summary, studies of styrene production workers, while limited by small size, do not provide evidence for a causal association between styrene exposure and cancer.

Styrene-based reinforced-plastics manufacturing

Studies of workers employed in the manufacture of glass fibre-reinforced plastics such as boat and automobile parts, tanks, and bath units are particularly informative with respect to the potential carcinogenicity of styrene because exposure levels are typically higher than in other industries. Styrene is a major component of the polyester resin accounting for up to 40% by weight. In the open mould process, several layers of fibre glass are deposited manually or with a chopper gun and the styrene-containing resin is sprayed or brushed on. Because about 10% of the styrene may evaporate from the resin during lamination and curing, laminators are considered among the workers with the highest styrene exposures (Crandall and Hartle, 1985).

In Denmark, mean styrene exposure levels in this industry were about 200 ppm in the early 1960s, 100 ppm in the late 1960s and 20 ppm in the late 1980s (Jensen *et al*., 1990). Similar mean levels and temporal reductions in styrene levels have been reported from

other European and North American countries (IARC, 2002). Peak exposure levels above 1000 ppm have also been reported (Jensen *et al*., 1990). The high exposure levels experienced by these workers were confirmed by measurement of urinary mandelic acid and blood styrene (IARC, 2002).

Other agents present in this working environment include dust and fibers from the reinforcement materials, in particular glass fibers, as well as solvents, oxidation products including styrene 7,8-oxide, and inhibitors such as hydroquinone. None of these agents is known to cause LHP neoplasms, although this effect is suspected for some solvents (e.g., dichloromethane). One characteristic of cohort studies in the styrene-based reinforced-plastics manufacturing industry is the short duration of employment experienced by a large proportion of workers.

A US study included 15,826 workers employed 6 months or more in areas with exposure to styrene between 1948 and 1977 in one of 30 manufacturing plants and followed up to 1989 (Wong, 1990; Wong *et al*., 1994). Of these workers 23% were employed for less than one year, and 27% for more than 5 years. Individual exposure levels were estimated based on a job-exposure matrix including individual work histories and time-weighted average job-specific exposure levels. There were 1628 deaths from all causes (SMR 1.08; 95% CI, 1.03–1.13), of which 425 were from cancer (SMR 1.16; 95% CI, 1.05–1.27). The SMRs were 0.82 (95% CI 0.56-1.17; 31 deaths) for LHP neoplasms, 0.72 (95% CI 0.39-1.48, 10 deaths) for NHL and 0.74 (95% CI 0.37-1.33; 11 deaths) for leukemia. Excess mortality was observed for esophageal cancer (SMR 1.92; 95% CI, 1.05–3.22; 14 deaths); lung cancer (SMR 1.41; 95% CI, 1.20–1.64; 162 deaths); cervical cancer (SMR 2.84; 95% CI 1.36–5.21; 10 deaths), and cancer of other female genital organs (SMR 2.02; 95% CI 1.07–3.45; 13 deaths). There was, however, no upward trend in mortality with increased duration of employment for any cause of death. Indeed, most of the increases occurred among employees who worked for only six months to a year with no significant increase in mortality for the highest cumulative exposure group. Race information was not available for the cohort and therefore, all were assumed to be white for the analyses. However, the death certificates indicated that 7.6% of the decedents

were non-white. The authors speculated that some of the SMRs could have been overestimated due to the inability to adjust for race and that lifestyle factors such as smoking may have also confounded the risk estimates.

In internal Cox regression analyses including sex, age, duration of exposure and cumulative exposure, neither indicator of exposure was associated with risk of LHP neoplasms or any other cancer. In particular, there was no relation between cumulative exposure to styrene and LHP neoplasm mortality (SMR 1.05, 0.55, 0.76, 0.93 for less than 10, 10-29.9, 30-99.9 and 100 or more ppm-years).

Cohort studies of reinforced-plastics workers have been conducted in the United Kingdom (Coggon *et al*., 1987), Finland (Härkönen *et al*., 1984) and Denmark (Kolstad *et al*., 1994, 1995). Except for part of the Danish cohort, these populations were included in a multisite study that also included cohorts from Italy, Norway and Sweden (Kogevinas *et al*., 1994a, 1994b). The combined cohort comprised 40,688 workers employed in 660 plants in six countries and followed up between 1945 and 1991. Employment and follow-up periods varied among countries; the average follow-up time was 13 years. Individual exposure estimates were derived by combining job histories, environmental measurements and urine measurements. There was no minimal duration of employment; 60% of workers were employed for less than two years and 9% of workers were employed for more than 10 years. A group of 10,629 workers involved in lamination was analyzed separately, as was a group of 4044 workers not exposed to styrene.

In the whole cohort, a total of 2714 deaths were observed (SMR 0.92; 95% CI, 0.88–0.95), of which 686 were from cancer (SMR 0.87; 95% CI 0.81–0.94). The SMR was 0.93 (95% CI 0.71–1.20; 60 deaths) for LHP neoplasms, 1.04 (95% CI 0.69-1.50; 28 deaths) for leukemia and 0.77 (95% CI 0.43-1.28; 15 deaths) for NHL. Among laminators, who are generally considered as more heavily exposed, the SMRs for LHP,

leukemia and NHL were, respectively, 0.81 (95% CI 0.43-1.39; 13 deaths), 0.48 (95% CI 0.10-1.39; 3 deaths) and 1.40 (95% CI 0.56-2.88; 7 deaths). The analysis of other job types showed no evidence of an excess risk of LHP neoplasms (exposed jobs other than laminators: SMR 0.65, 95% CI 0.26-1.34; unspecified exposure jobs: SMR 1.19; 95% CI 0.80-1.70).

In internal analyses restricted to workers exposed to styrene, there was an association between LHP neoplasms, specifically NHL and average styrene exposure and time since first exposure,whereas no relationship was apparent with duration of exposure or cumulative exposure (Figures 1 and 2).

The study from Denmark, comprising 53,720 male workers employed in 552 companies selected for potential production of reinforced plastics (Kolstad *et al*., 1993, 1994, 1995), included 23,748 workers from 99 companies in which 1-49% of the workforce produced reinforced plastics ('probably low styrene exposure') and 12,837 workers from 287 companies in which 50% or more of the workforce produced reinforced plastics ('probably high styrene exposure'). This last group of workers was also part of the European study (Kogevinas *et al*., 1994a). The remaining workers were considered unexposed to styrene. Follow-up for mortality and cancer incidence was from 1970 until 1989 and pension fund data provided information on employment during 1964-89. Sixty percent of workers were employed for less than one year, and 14% for more than 5 years. In a validation study, duration of employment was underestimated for 40% of the workers, and overestimated for 13% of them. A total of 4484 deaths and 1931 incident cases of cancer were ascertained (SIR 1.02; 95% CI 0.97–1.07). Among workers employed in companies producing reinforced plastics, there were 112 cases of LHP neoplasms (SIR 1.20; 95% CI 0.98–1.44), of which 42 were leukemia cases (SIR 1.22; 95% CI 0.88–1.65), and 42 were NHL cases (SIR 1.33; 95% CI 0.96-1.80). The excess risk of leukemia was confined to workers employed for less than one year; that of NHL was restricted to the first ten years from beginning of employment.

The SIR for leukemia among workers employed between 1964 and 1970 (highest exposure to styrene) was 1.5 (95% CI 1.02–2.19; 30 cases), the corresponding SIR for NHL was 1.28 (95% CI 0.79-1.96; 21 cases) (Kolstad *et al*., 1994). In the male component of the whole cohort there was an increased incidence of lung (SIR 1.15, 95% CI 1.04-1.27) and pleural cancer (SIR 2.33; 95% CI 1.42-3.60), (Kolstad *et al*., 1993). The SIR for pancreatic cancer was 1.20 (95% CI 0.86-1.63, 41 observed deaths, 34.2 expected deaths based on national rates) (Kolstad *et al*., 1995). In an internal analysis using a Poisson regression model, the incidence rate ratio (IRR) of pancreatic cancer was 2.2 (95% CI 1.1–4.5) for workers with probable high exposure and duration of employment at least one year, compared to workers with no exposure (Kolstad *et al*. 1995).

In a later case-control study nested in the same cohort Kolstad et al. evaluated 12 cases of myeloid leukemia with clonal chromosomal aberrations, and 57 controls (Kolstad *et al*., 1996). Eleven cases and 40 controls were employed in companies with exposure to styrene (odds ratio 2.5; 95% CI 0.2-25). There was no excess risk of myeloid leukemia in relation to duration of exposure to styrene.

A study conducted in Washington State, US, included 5204 workers employed in two reinforced plastic boat-building facilities between 1959 and 1978 and followed up to 1998 (Okun *et al.,* 1985; Ruder *et al.,* 2004). A subset of 2063 workers, classified as having had high styrene exposure based on industrial hygiene surveys, included those who ever worked in the fibrous glass (TWA of 42.5 ppm in Company A) or lamination (TWA of 71.7 ppm in Company B) departments. The 3141 workers classified as low styrene exposure included those who never worked in the high exposure departments.

Based on 860 deaths, the overall SMR was 0.97 (95% CI 0.91-1.04) when national reference rates were used and 1.09 (95% CI 1.02-1.17) when rates from the state were used. Using state rates as the comparison, the SMR for all cancers was 1.17 (95%CI 1.02-1.33, 233 deaths). It was 1.26 (95% CI 0.96-1.63, 58 deaths) for the high exposure

group and 1.1 (0.98-1.32, 175 deaths) for the low exposure group. There was a total of 16 deaths from LHP neoplasms (SMR 0.74; 95% CI 0.42-1.20), four in the high exposure group (SMR 0.72; 95% CI 0.20-1.84) and 12 in the low exposure group (SMR 0.74; 95% CI 0.38-1.30). Thus, mortality from both NHL and leukemia was below expectation for the total cohort and for both the high and low exposure groups.

The SMR was significantly increased for esophageal cancer (SMR 2.30, 95% CI 1.19-4.02, 12 deaths) and prostate cancer (SMR 1.71, 95% CI 1.09-2.54, 24 deaths). The SMRs in the high exposure group were 1.85 for esophageal cancer (95% CI 0.22-6.67, 2 deaths) and 2.06 for prostate cancer (95% CI 0.43-6.04, 3 deaths). In the low exposure group, the SMRs were 2.42 for esophageal cancer (95%CI 1.16-4.44, 10 deaths) and 1.67 for prostate cancer (95%CI 1.03-2.55, 21 deaths). Because there was an excess mortality among workers with less than one year of employment, exclusion of these workers employed for less than one year lowered the SMR for esophageal cancer, prostate cancer and LHP neoplasms.

For deaths due to cancers of the urinary organs (kidney, bladder and other urinary, prostate not included), the SMR in the high exposure group was significantly increased (SMR 3.44; 95% CI 1.26-7.50, 6 deaths). An analysis by latency showed that for deaths from all cancers, esophageal cancer and prostate cancer, the SMRs were similar for those with less than 15 years and those with 15 or more years of latency.

Styrene–butadiene rubber manufacturing

The production of synthetic rubber is based on polymerization of 1,3-butadiene and styrene, in a soap solution requiring initiating agents, inhibiting agents, antioxidants, and coagulating agents. Other chemicals are typically added to this mixture, such as carbon black for tire production. Other agents used in this industry, besides 1,3-butadiene, include acrylonitrile, acrylates, toluene, benzene, formaldehyde, salts of dialkyldithiocarbamic acids, including dimethyldithiocarbamate (DMDTC), dyes and

solvents. In these facilities, concentrations of styrene are typically between 1 and 10 ppm, although slightly higher levels were occasionally reported. Macaluso and colleagues (1996) estimated exposure levels in eight North American facilities included in a large epidemiologic study. Time-weighted average styrene exposure declined from an average of 1.8 ppm during the 1940s to 0.1 ppm in the 1990s.

Several cohort studies among workers in the styrene-butadiene rubber (SBR) manufacture industry (McMichael *et al*., 1976; Meinhardt *et al.,* 1982; Matanoski *et al*. 1990,; Santos-Burgoa *et al*., 1992) were included in an updated multi-plant investigation by Delzell and colleagues (Delzell et al., 1996, 2001, 2006; Sathiakumar *et al*., 1998, 2005; Macaluso 2004; Graff *et al*., 2005). Primarily conducted to assess the carcinogenicity of 1,3-butadiene, this multi-plant study provided detailed analyses of exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate (DMDTC, used as an accelerator in the vulcanization process) (Macaluso *et al*., 1996, 2004).

The multi-plant study included 17,924 male workers employed for at least one year during 1944-1991 at seven SBR plants in the USA and one plant in Canada (Delzell et al., 2006). Analyses were limited to the 16,579 workers for whom quantitative exposures were developed. Those excluded had an employment history considered to be inadequate for exposure estimation. External analyses of major work areas and job groups were limited to the 15,612 workers employed in the SBR-related operations at the eight plants, and analyses of work area and job subgroups were limited to the 14,273 workers employed in SBR-related operations at the six plants who had detailed work histories. Eighty-four percent of the workers were exposed to styrene with median cumulative exposure of 13 ppm-years, and 57% were exposed to styrene peaks. 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.

During mortality follow-up from 1944 to 1998, 6237 deaths occurred (SMR 0.86; 95% CI 0.84-0.88), including 1608 cancer deaths (SMR 0.92; 95% CI 0.88-0.97). The SMR for NHL was 1.00 (95% CI 0.75-1.30; 53 deaths), that for leukemia 1.16 (95% CI 0.91-1.47, 71 deaths). Analyses of leukemia subtypes revealed a non-significantly increased mortality from chronic myeloid leukemia (SMR 1.67; 95% CI 0.83-2.99; 11 deaths) and chronic lymphocytic leukemia (SMR 1.51; 95% CI 0.87-2.47; 16 deaths) and a non-significantly decreased mortality from acute lymphocytic leukemia (SMR 0.42; 95% CI 0.01-2.34; one death). 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. Results for cumulative styrene exposure are reported in Figure 3. 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 (Figure 4).

Cohort studies of workers biomonitored for styrene exposure

A cohort study in Finland included 2580 workers, mainly laminators, in the reinforced-plastics industry who underwent monitoring for styrene exposure (Antilla *et al.,* 1998). The overall mean mandelic acid level was 2.3 mmol/L (range, 0–47 mmol/L). During follow-up between 1973 and 1992, a total of 48 cases of cancer were observed (SIR 0.80; 95% CI 0.59–1.06) including two cases of LHP neoplasms (SIR 0.39; 95% CI 0.05–1.40; both were Hodgkin lymphoma cases) and six cases of rectal cancer (SIR 3.11; 95% CI

1.14–6.77). Mean lifetime urinary mandelic acid level was not associated with risk either of all cancer combined or of any specific cancer.

Case–control studies of lymphoma or leukemia

Although several community based case-control studies have reported results for occupational exposure to styrene, retrospective exposure assessment is problematic, because individual environmental measurements or monitoring data are rarely available. Exposure assessment is therefore based on other methods, such as interviews or indices of exposure assigned based on occupational histories, methods that are prone to recall bias. Since case-control studies include exposure across many different industries and occupations, exposure levels tend on average to be low, although a precise quantification is problematic. Furthermore, these studies may suffer from lack of comparability of cases and controls because of differences in source populations or in the process of selection into the study.

A study from Sweden included 59 cases of acute myeloid leukemia aged 20–70 years diagnosed in various hospitals between 1977 and 1982, and 354 population controls (Flodin et al., 1986). Exposure to styrene and seven other occupational agents was estimated from self reports on mail questionnaires, a method which may result in recall bias. Styrene exposure was reported by three cases and one control (odds ratio [OR] 18.9; 95% CI 1.9–357). Although statistically significant, this result should be interpreted with caution because of the unstable results of regression models that include many covariates and few observations.

A case-control study in Canada comprised 3730 male cases with 12 different types of cancer - including non-Hodgkin lymphoma and Hodgkin lymphoma, but excluding leukemia - aged 35–70 and ascertained in 19 major hospitals (Siemiatycki, 1991; Gérin *et al.*, 1998). For each job held by study participants, duration, frequency and level of exposure to 293 occupational agents were assessed by a group of chemists and industrial

hygienists on the basis of detailed questionnaires. Cases of each cancer were compared both with 533 population controls and 533 cases of other cancers. Two per cent of study subjects - mainly firefighters, mechanics and painters - were classified as ever exposed to styrene. OR for ever exposure to styrene was 2.0 (95% CI 0.8–4.8; eight exposed cases) for non-Hodgkin lymphoma and 2.4 (95% CI 0.5–12; two exposed cases) for Hodgkin lymphoma. No dose-risk analyses were reported for these neoplasms.

A case-control study of leukemia was nested within a cohort of 170,000 French men employed in a utility company during 1978-89 (Guenel *et al.*, 2002). Leukemia cases were identified among active workers (below age 60) through the company's cancer registry and were matched to controls by birth year. Exposure to 20 agents, including styrene, was assessed by a group of experts, based on job titles and tasks. Two out of 72 cases and nine out of 285 controls were considered exposed to styrene (OR 1.1; 95% CI 0.2-5.9).

A population-based case-control study of occupational risk factors for LHP neoplasms was conducted in 11 areas of Italy from 1991to 1993 (Miligi *et al*., 2006). Cases (N=2737) were identified from hospital wards and pathology departments and controls (N=1779) were randomly selected from population registries. Response rates were 88% among cases and 81% among controls. A panel of pathologists reviewed the slides of a sample of cases. Industrial hygiene experts from each geographic area reviewed the detailed occupational questionnaires, and assessed the probability and intensity of exposure to a number of occupational agents, including styrene. A total of 1428 cases of NHL and 1530 controls were included in an analysis of NHL risk in relation to exposure to solvents (Miligi *et al*., 2006). Twenty-three cases and 28 controls were classified as ever exposed to styrene (the OR calculated based on raw data reported in the publication was 0.9 with 95% CI 0.5-1.6). The OR for medium-high exposure was 1.3 (95% CI 0.6-2.9) with no relation between duration of medium-high styrene exposure and NHL risk. Limited by small numbers, the analysis by NHL subtype yielded an OR for small lymphocytic NHL of 1.6 (95% CI 0.5- 5.1) for medium-high styrene exposure. A similar

analysis included 586 cases of leukemia and 1278 controls (Seniori Costantini *et al*., 2008). Ever exposure to styrene was assigned to three cases and 19 controls (OR 0.4; 95% CI 0.1-1.2), and medium-high exposure to two cases and 11 controls (OR 0.4; 95% CI 0.1-1.9).

A case-control study in Germany included 710 cases of lymphoma (response rate 88%) and 710 population controls (response rate 44%) (Seidler *et al*., 2007). Occupational exposure to styrene and other agents was assessed by an industrial hygienist based on detailed questionnaires. The prevalence of exposure to styrene among controls was estimated as 23.8%. Cumulative exposure to styrene was not associated with risk of lymphoma overall or risk of Hodgkin lymphoma or NHL.

In general, evidence from community-based case-control studies should be given less weight than that from industry-based studies because protection from bias is more problematic, notably selection bias (e.g., comparability of source population for cases and controls, response rate) information bias (e.g., differential report of past exposure by cases and controls), residual confounding by other occupational agents, and selective report of findings arising from multiple comparisons.

Studies of environmental exposure to styrene

Studies have been conducted on populations exposed to styrene as a general air pollutant. In industrialized urban areas, styrene exposure levels are typically less than 0.1 parts per billion, which is six or more orders of magnitude lower than levels in the workplace.

A cohort comprising 15,403 students attending a high school in Texas adjacent to a styrene–butadiene facility between 1963 and 1993 was followed up for mortality between 1963 and 1995 (Loughlin *et al.*, 1999). The overall SMR was 0.84 (95% CI 0.74–0.95; 241deaths) among men and 0.89 (95% CI 0.73–1.1; 97 deaths) among women. For all cancer, the SMR was 1.2 (95% CI, 0.83–1.7; 31 deaths) among men and 0.52 (95% CI

0.28–0.88; 13 deaths) among women. The SMR for LHP neoplasms was 1.64 (95% CI 0.85-2.87; 12 deaths) among men and 0.47 (95% CI 0.06-1.70; two deaths) among women, and the SMR for leukemia was 1.82 (95% CI 0.67–3.96; six deaths) among men and 0.45 (95% CI 0.01–2.48, one death) among women.

An ecologic study correlated 1995-2000 breast cancer incidence rates in 254 counties in Texas, USA, with 1988-2000 release data of 12 toxic agents, including styrene (Coyle *et al*., 2005). Release of styrene was reported in 61 counties. After adjusting for race, ethnicity and other agents, release of styrene was significantly associated with breast cancer incidence in women and specifically among those aged 50 or more. In contrast, no increase in breast cancer risk was detected in the occupational cohort studies (Table 3): and the plausibility of observing such as effect in an ecological study of environmental exposure is very low (Burns *et al*., 2006).

Overall, studies on environmental styrene exposure are not informative as to the carcinogenicity of this agent.

Studies of DNA adducts

Table 4 summarizes studies of DNA adducts among workers exposed to styrene. Although of small size, these studies provide evidence that styrene exposure entails formation of O6-, N2-dG, and β-N1-Ade adducts. The same adducts are produced by styrene 7,8-oxide in experimental systems. The level of O6-dG adducts was five to seven fold higher in exposed workers than in control subjects. A quantitative interpretation of the results for the other adducts is complicated by the small number of controls included in the relevant studies. When one group of workers was re-tested three years later (Vodicka 1995, 1999), the level of adducts was little changed, suggesting that in continuously exposed workers adduct formation and repair reach steady state. In one study an increased level of 8-OHdG adducts was found, suggesting that styrene could also act via oxidative damage (Marczynski *et al*., 1997).

Limitations of studies of DNA adducts in styrene exposed workers include small sample sizes, use of convenience groups of controls, lack of adjustment for potential confounders and unclear overlap between studies from the same laboratories. Despite these limitations, available evidence supports a DNA damaging effect of occupational exposure to styrene.

Discussion

Industry-based cohort studies are more informative than case-control studies or environmental studies for identifying occupational carcinogens because of higher exposure levels, better definition of exposure circumstances and less opportunity for selection and information bias. In the specific case of styrene, studies of workers in the reinforced-plastics industry are most informative because of higher exposure levels and fewer co-exposures. However, the high turnover in the workforce in this industry is a limitation in that the duration of exposure for many workers is fairly short. Results on long-term workers are more informative with respect to potential styrene carcinogenicity.

No consistent evidence of an increased risk of LHP neoplasms overall, or of lymphoma or leukemia, emerged from occupational cohort studies. An association between average level of styrene exposure and NHL risk was suggested in the multicenter European study but no trend with duration of exposure to styrene (the SMR of NHL for 5 or more years of employment was 1.01 [95% CI 0.27-2.57]) (Kogevinas *et al*., 1994b) or with cumulative exposure was evident (Figure 2). In that study, the proportion of short term workers was higher among laminators, who had the highest exposure to styrene, than among other workers (Kogevinas *et al*., 1994a). Consequently, analyses by level of exposure might be more informative than analyses by duration of exposure (or cumulative exposure). However, short-term workers are known to experience an increased mortality from many causes, likely due to lifestyle factors and exposures in other occupations (Boffetta *et al*., 1998). In this respect the excess in the risk of tobacco-related cancer observed in some of the studies of reinforced plastic workers (Kolstad *et al*., 1993; Wong *et al*., 1994) is notable, since it suggests confounding by tobacco

smoking (information on tobacco smoking is not available in most occupational studies). The increase in NHL mortality reported in the categories of increased exposure in the multicenter study of SBR workers, however, provides some support to the hypothesis of an association between styrene exposure and risk of this neoplasm.

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. Studies in styrene manufacture and polymerization are less informative because the level of styrene exposure experienced in these industries is lower. These studies, however, provide no evidence of an association with lymphoma, leukemia or other neoplasms. Furthermore, case-control studies conducted in the general population and studies based on environmental exposure provide no evidence for an increased risk of LHP neoplasms or specifically, NHL.

Given the relatively large number of studies of styrene, it is not surprising that an increased risk of a few cancers has been occasionally found in some studies. An association with esophageal cancer was evident in two US studies of reinforced plastic workers (Wong *et al*., 1994; Ruder *et al*., 2004), but not in the European studies of such workers (Kogevinas *et al*., 1994a; Kolstad *et al*., 1994), or in studies of other groups of styrene exposed workers. A meta-analysis of the results on esophageal cancer (Table 3) resulted in a summary RR (based on random-effects models) of 1.21 (95% CI 0.84-1.73) with evidence of heterogeneity (p-value for heterogeneity 0.01). The lack of available results by level of exposure or cumulative exposure limits the interpretation of the overall excess risk, which can be considered at most, as suggestive. Results for other cancers show no consistent patterns and the occasional positive findings are probably due to chance.

Several studies showed low levels of DNA adducts in lymphocytes of workers exposed to styrene. Limited by their small size and lack of control for potential confounders these studies provide evidence for a genotoxic effect of styrene in humans, probably mediated by the metabolite, styrene 7,8-oxide. Several issues should be considered in the interpretation of DNA adduct data on NHL risk. Following styrene exposure rats and mice form adducts similar to those found in humans. Although levels are higher in rats, no excess cancer incidence has been detected (IARC, 2002). Furthermore, agents known or suspected to cause NHL in humans are believed to act through immune disregulation rather than through DNA damage (Alexander *et al*., 2007).

We conclude that the suggestion of a carcinogenic effect of styrene in humans mostly comes from an association of borderline statistical significance between average level of exposure and NHL risk in a large European study of reinforced-plastics workers. However, this suggestion is not supported by results on duration of exposure in the same study, nor by results on NHL risk from other studies. The excess mortality from esophageal cancer in two studies has not been confirmed in other studies. Overall, the available data do not convincingly support an increased risk of cancer, and notably NHL and esophageal cancer, following exposure to styrene.

The evidence for human carcinogenicity of styrene is inconsistent and weak. Based on the available evidence, one cannot conclude that there is a causal association between styrene and any form of cancer. There are, however, steps that could be undertaken to better exploit the available epidemiologic data. First, the follow-up of the two largest studies of reinforced plastic workers (Wong *et al*., 1994; Kogevinas *et al*., 1994a) should be updated since 15 or more additional years of mortality experience would be available. Second, information should be obtained on NHL subtype of cases in the most informative cohorts. Third, a pooled analysis of studies of reinforced plastic workers should be considered in order to increase statistical power, to eliminate overlaps between studies and to provide results according to comparable exposure categories.

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Legends to figures

Figure 1. Relative risk of lymphoheamatopoietic neoplasms for average exposure to styrene – European multicenter study of reinforced plastic workers (Kogevinas et al., 1994a)

LHP, lymphoheamatopoietic; NHL, non-Hodgkin lymphoma; Ref, reference category

* p-value of test for linear trend

Figure 2. Relative risk of lymphoheamatopoietic neoplasms for cumulative exposure to styrene – European multicenter study of reinforced plastic workers (Kogevinas et al., 1994a)

LHP, lymphoheamatopoietic; NHL, non-Hodgkin lymphoma; Ref, reference category

* p-value of test for linear trend

Figure 3. Relative risk of leukemia for cumulative exposure to styrene – effect of adjustment for exposure to1,3-butadiene and DMDTC – North American multicenter study of styrene-butadiene rubber workers (Delzell et al., 2006)

DMDTC, dimethyldithiocarbamate; Ref, reference category

Figure 4. Relative risk of non-Hodgkin lymphoma for cumulative exposure to styrene, adjusted for exposure to 1,3-butadiene and dimethyldithiocarbamate – North American multicenter study of styrene-butadiene rubber workers (Delzell et al., 2006)

Ref, reference category

Table 1. Characteristics of cohort studies of workers exposed to styrene

Plants, country	N workers, gender	Period of employment	Period of follow-up; outcome	Overlaps, updates	Reference
Styrene production and polymerization					
One plant, Germany	1960, both	1931–76	1956-76; M		Frentzel-Beyme et al., 1978
One plant, United Kingdom	622, men	1945-74	1945-78; M		Hodgson and Jones, 1985
One plant, USA	2904, men	1937-71	1940-86; M	Updates Ott et al., 1980	Bond et al., 1992
Styrene-based reinforced plastics manufacturing					
30 plants, USA	15 826, both	1948-77	1948-89; M	Updates Wong, 1990	Wong et al., 1994
660 plants, six European countries	40 688, both	NA	1945-91*; M	Includes and updates Coggon et al., 1987; Harkonen et al., 1984 and part of Kolstad et al., 1994, 1995	Kogevinas et al., 1994a
552 plants, Denmark	53 720, men	1964-89	1970-89; I	Part of the cohort included in Kogevinas et al., 1994a	Kolstad et al. 1994, 1995
2 plants, USA	5024, both	1959–78	1959-98; M	Updates Okun et al., 1985	Ruder et al., 2004
Styrene-butadiene rubber manufacturing					
6 plants, USA and Canada	13 130, men	1944–91	1944-98; M	Includes and updates McMichael et al., 1976; Meinhardt et al., 1982; Matanoski et al., 1990; Santos-Burgoa et al., 1992; Delzell et al., 1996, 2001; Sathiakumar et al., 1998, 2005; Macaluso et al., 2004, Graff et al., 2005	Delzell et al., 2006
Workers biomonitored for styrene exposure					
Finland	2580, both	1973-83	1973-92; I		Anttila et al., 1998

I, cancer incidence; M, mortality; NA, not available

* follow-up period varies among countries

Table 2. Results of cohort studies of workers exposed to styrene – Lymphohaematopoietic neoplasms

Reference	Neoplasm	Observed	SMR	95% CI	Comments
Styrene production and polymerization					
Frentzel-Beyme et al., 1978	Lymphoma	1	16.7	0.42-92.9	SMR calculated from raw data presented in the publication;
Hodgson and Jones, 1985	NHL Leukemia	3 0	5.36 0	1.10-15.7 0-12.3	SMR calculated from raw data presented in the publication;
Bond et al., 1992	LHP NHL Leukemia	28 7 9	1.44 1.17 1.18	0.95-2.08 0.47-2.40 0.54-2.24	
Styrene-based reinforced plastics manufacturing					
Wong et al., 1994	LHP NHL Leukemia	31 4 11	0.82 0.72 0.74	0.56-1.17 0.20-1.85 0.37-1.33	
Kogevinas et al., 1994a	LHP NHL Leukemia	60 15 28	0.93 0.77 1.04	0.71-1.20 0.43-1.28 0.69-1.50	
Kolstad et al., 1994	LHP NHL Leukemia	112 42 42	1.12 1.33 1.22	0.98-1.44 0.96-1.80 0.88-1.65	Cancer incidence
Ruder et al., 2004	LHP Leukemia	16 5	0.74 0.60	0.42-1.20 0.19-1.40	
Styrene-butadiene rubber manufacturing					
Delzell et al., 2006	NHL Leukemia	53 71	1.00 1.16	0.75-1.30 0.91-1.47	
Workers biomonitored for styrene exposure					
Anttila et al.,	LHP	2	0.39	0.05-1.4	Cancer incidence

1998					Both LHP neoplasm cases were HL

LHP, lymphohaematopoietic neoplasms; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; SMR, standardized mortality ratio; CI, confidence interval

Table 3. Results of cohort studies of workers exposed to styrene – Esophageal, rectal, pancreatic and breast cancer

Reference	Neoplasm	Observed	SMR	95% CI	Comments
Styrene production and polymerization					
Frentzel-Beyme et al., 1978	Rectum Pancreas	1 2	0.99 2.78	0.03-5.52 0.34-10.0	SMR calculated from raw data presented in the publication;
Hodgson and Jones, 1985	Esophagus	1	3.33	0.08-18.6	SMR calculated from raw data presented in the publication;
Bond et al., 1992	Esophagus Rectum Pancreas	3 2 5	0.63 0.39 0.49	0.13-1.85 0.04-1.41 0.16-1.13	
Styrene-based reinforced plastics manufacturing					
Wong et al., 1994	Esophagus Pancreas Breast	14 19 14	1.92 1.13 0.62	1.05-3.22 0.68-1.77 0.34-1.05	
Kogevinas et al., 1994	Esophagus Rectum Pancreas Breast	17 21 37 13	0.82 0.62 1.00 0.52	0.47-1.31 0.38-0.95 0.71-1.38 0.28-0.89	
Kolstad et al., 1995	Esophagus Rectum Pancreas	13 47 41	0.92 0.78 1.20	0.50-1.57 0.58-1.04 0.86-1.63	Cancer incidence
Ruder et al., 2004	Esophagus Pancreas Breast	12 14 3	2.30 1.43 0.64	1.19-4.02 0.78-2.41 0.13-1.86	
Styrene-butadiene rubber manufacturing					
Delzell et al., 2006	Esophagus Pancreas	44 76	0.94 0.87	0.68-1.26 0.68-1.08	

Workers biomonitored for styrene exposure					
Anttila et al., 1998	Rectum Pancreas Breast	6 3 5	3.11 1.66 1.31	1.14-6.77 0.34-4.85 0.43-3.06	Cancer incidence

SMR, standardized mortality ratio; CI, confidence interval

Table 4. Studies of DNA adducts in workers exposed to styrene

Study	Country	Exposed group (N), controls (N)	Exposure level ($mg/m^{3)}$	Adduct	Results
Vodicka et al., 1993	NA	Laminators (10), agricultural workers (8)	300-700	O6-dG	4.7 vs. $0.3/10^8$ nucl ($p<0.05$)
Vodicka et al., 1994, 1995	Czech Republic	Laminators (9), research workers (7)	40-225	O6-dG	4.9 vs. $1.4/10^8$ nucl ($p<0.01$) 5.1 vs. $0.7/10^8$ nucl ($p<0.01$) after 2-week exposure break
Vodicka et al., 1999*	Czech Republic	Laminators (11), research workers (10)	91-122	O6-dG	5.9 ± 4.9 vs. $0.7 \pm 0.8/10^8$ nucl ($p=0.001$)
				N2-dG	1.7 ± 1.1 vs. $0/10^8$ nucl ($p<0.001$)
Vodicka et al., 2003	NA	Laminators (19), unspecified controls (7)	170.6 ± 114.5	O6-dG	8.3 ± 6.3 vs. $0.8 \pm 0.7/10^8$ nucl ($p=0.001$)
				N2-dG	2.7 ± 1.8 vs. $0.5 \pm 0.8/10^8$ nucl ($p=0.001$)
				β-N1-Ade	2.6 ± 5.3 vs. $0/10^9$ nucl
Horvath et al., 1994	USA	Styrene exposed workers (47), no	1-235	N2-dG	$15.8 \pm 10.2/10^8$ nucl correlation with exposure level

		controls			
Slyskova et al., 2007**	Slovakia	Laminators (24), clerks (18)	98.1 ± 98.9	β-N1-Ade	2.0 ± 5.0 vs. $0/10^9$ nucl ($p<0.0001$)
Marczynski et al., 1997	Germany	Boat builders (17), volunteers (67)	NA	8-OHdG	2.23 ± 0.54 vs. $1.52 \pm 0.45/10^5$ nucl ($p<0.001$)

* 3-yr follow-up of study by Vodicka et al., 1994, 1995

** possible overlap with Vodicka et al., 2003

nucl, nucleotides; NA, not available

Figure 1.

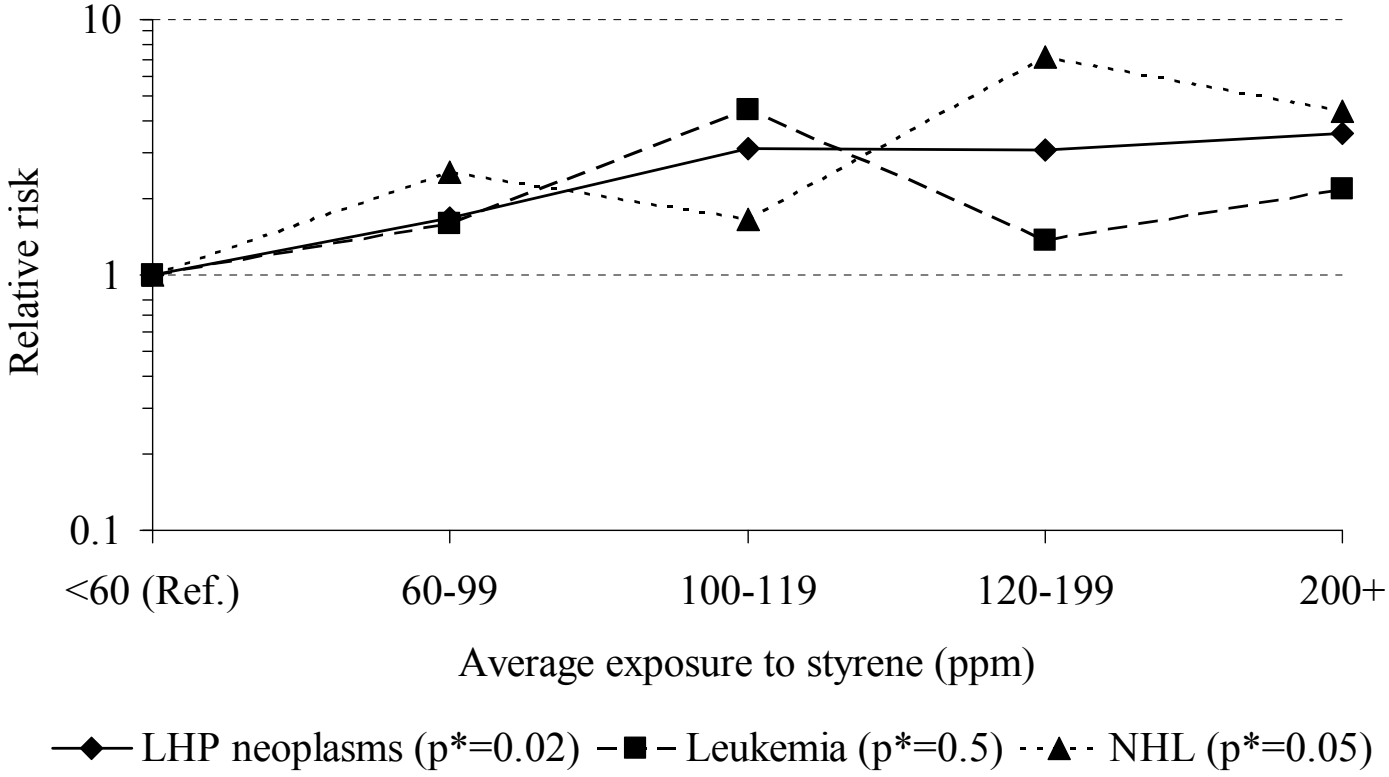

10
1
0.1
Relative risk
<60 (Ref.)
60-99
100-119
120-199
200+
Average exposure to styrene (ppm)
LHP neoplasms (p*=0.02)
Leukemia (p*=0.5)
NHL (p*=0.05)

Figure 2.

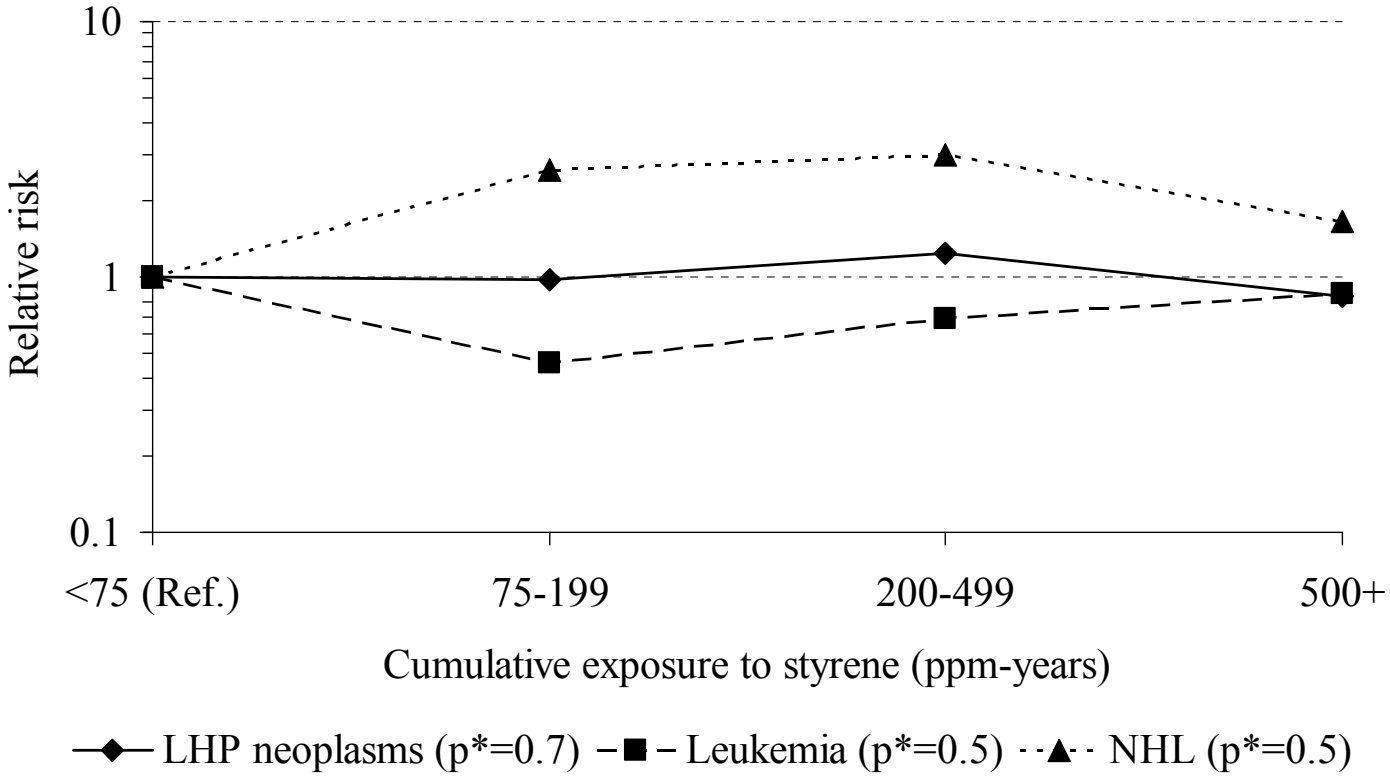

10
1
0.1
Relative risk
<75 (Ref.)
75-199
200-499
500+
Cumulative exposure to styrene (ppm-years)
LHP neoplasms (p*=0.7)
Leukemia (p*=0.5)
NHL (p*=0.5)

Figure 3.

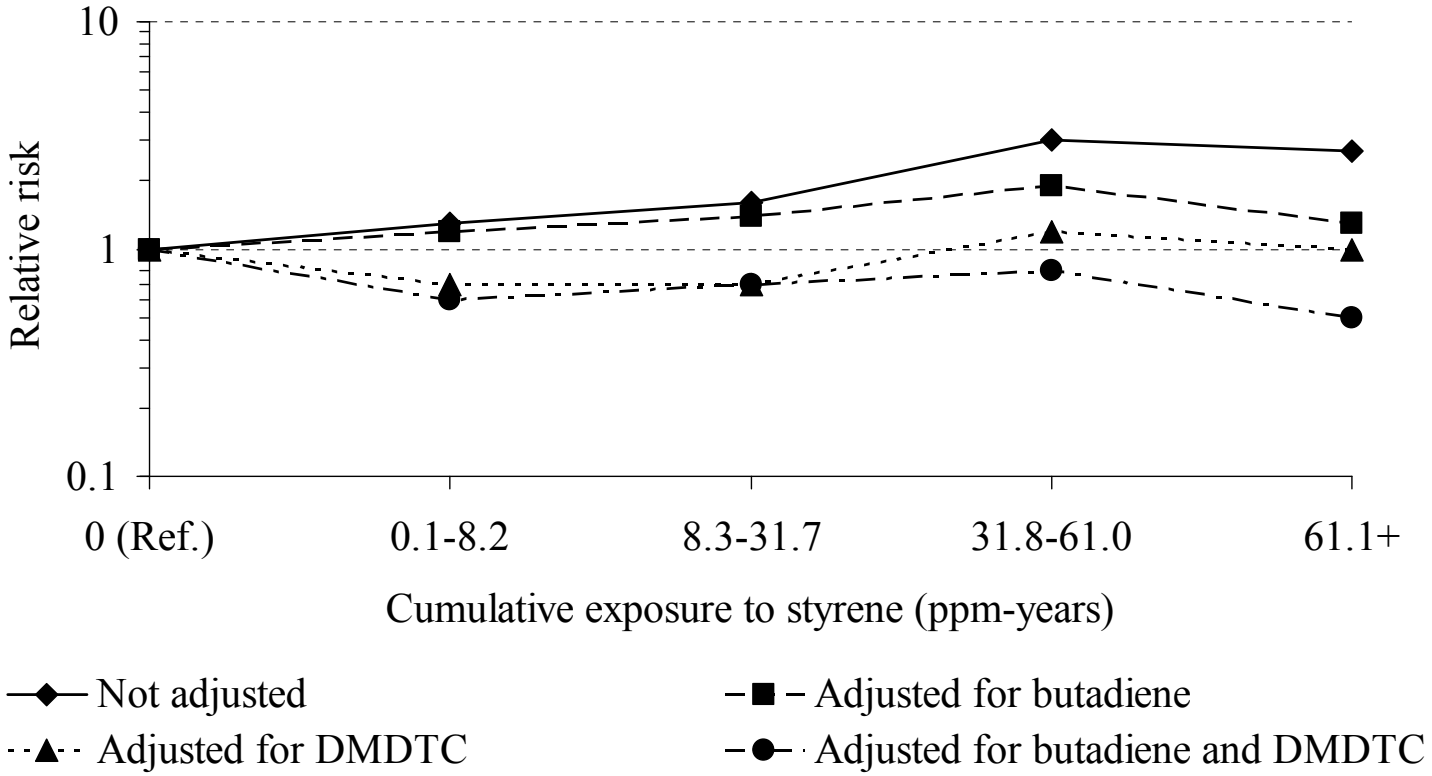
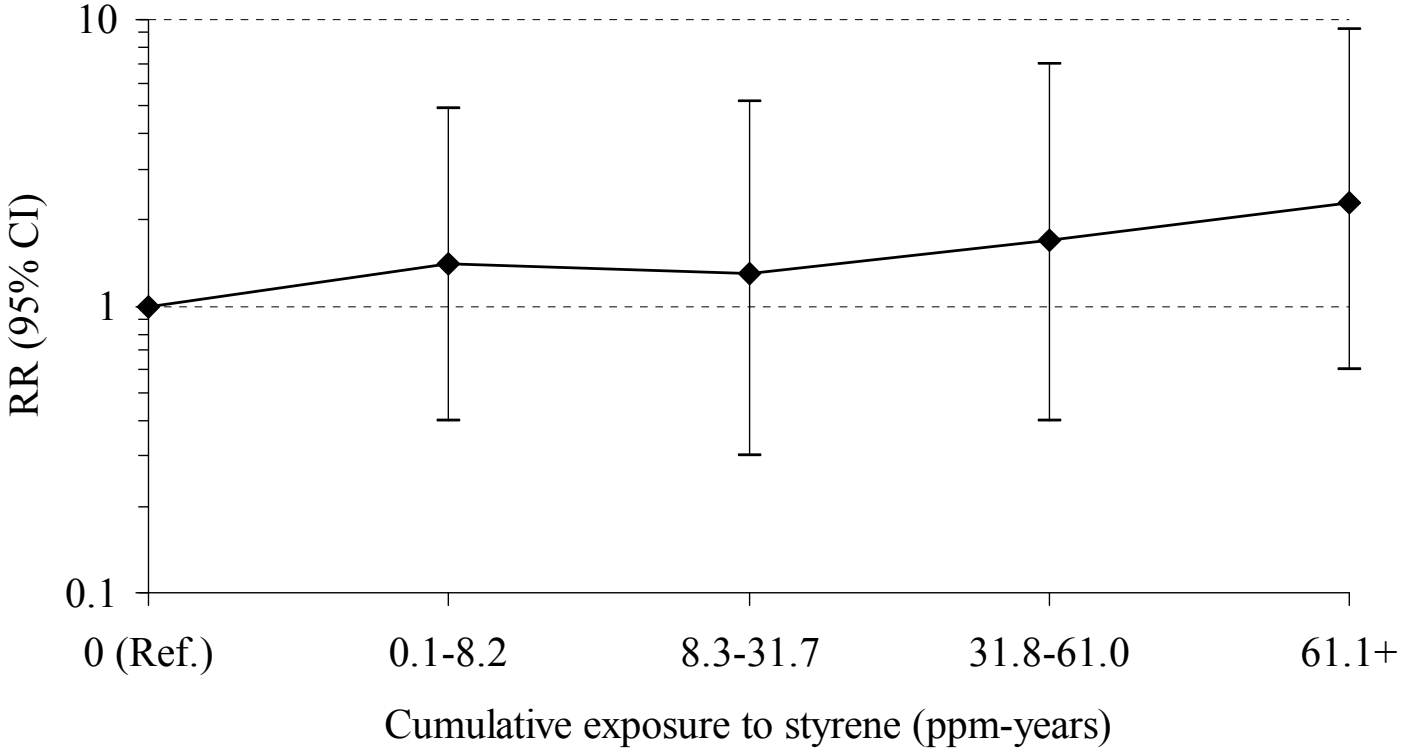

10
1
0.1
Relative risk
0 (Ref.)
0.1-8.2
8.3-31.7
31.8-61.0
61.1+
Cumulative exposure to styrene (ppm-years)
Not adjusted
Adjusted for butadiene
Adjusted for DMDTC
Adjusted for butadiene and DMDTC

Figure 4.


10
1
0.1
RR (95% CI)
0 (Ref.)
0.1-8.2
8.3-31.7
31.8-61.0
61.1+
Cumulative exposure to styrene (ppm-years)