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RE: FR 73-29139 Notice, (Styrene)

**Delivered by email on 7 July 2008**

Dear Dr. Lunn:

The International Institute of Synthetic Rubber Producers, Inc. (IISRP) is a trade association representing the interest of the global synthetic rubber industry. We have many members in the United States and other regions of the world which will be impacted by the NTP's listing of styrene in the 12<sup>th</sup> RoC. The IISRP has sponsored and published many of the epidemiology research reports cited in the NTP draft background document. We therefore have much experience with the SBR worker cohort as we have been tracking this group of current and former employees in this industry since the late 1970's. This important research continues today.

We have reviewed the draft background document specifically on the discussion of the SBR worker cohort and have a number of comments which the NTP should consider prior to taking additional action on styrene. The listing of styrene in the 12 RoC is not supported by the epidemiology evidence.

Thank you for allowing the opportunity to provide our comments and we are prepared to respond to any specific questions raised by our comments.

Sincerely,  
(*Sent electronically*)  
James L. McGraw

Managing Director and CEO  
IISRP



## **International Institute of Synthetic Rubber Producers Comments on listing Styrene in the 12<sup>th</sup> RoC**

- The NTP is critical of revised butadiene and styrene exposure estimates developed by Macaluso et al.(1) (e.g., page 108, comment column of table, page 135, lines 29-30). For example, the revised exposure estimates are said to have given "significantly higher estimates than documented by measurement" (page 153, lines 26-27) and are not validated (page 135-136, lines 30 and 1, respectively). However, for hazard identification purposes (presumably the goal of the NTP) precise estimation of quantitative monomer exposure levels is of less importance compared with accurate relative ranking of individuals' exposures. Macaluso et al.(1) note that, "despite extensive changes, the revised exposure estimates were equivalent to the original set of estimates in ranking individual employees according to cumulative exposure levels (Spearman's  $r=0.9$  for both BD and STY, results not shown)" (page 381 of Macaluso et al. (1)). Thus, for hazard identification purposes, the above limitations have little applicability.
- In several instances, the NTP speculates that the increased risk of leukemia observed among styrene-butadiene rubber workers may indicate a "synergistic effect of these two exposures". (e.g., Executive Summary, page vii, lines 11-12) For balance, the NTP should indicate that other plausible explanations exist, such as the increased risk being due to an independent effect of butadiene alone, an independent effect of styrene alone, or an independent effect of another agent, either alone or in combination, to which SBR workers were exposed (e.g., dimethyldithiocarbamate). More importantly, the SBR worker cohorts are insufficient to adequately test the "synergistic effect" hypothesis. To demonstrate that the observed increase in leukemia risk was due to a synergistic effect of styrene and butadiene, one would need sufficient numbers (for statistical power) of workers exposed only to butadiene, only to styrene, and then to both chemicals. There are too few workers exposed only to butadiene and only to styrene to have sufficient statistical power to adequately test this hypothesis. The NTP document should adequately reflect this point.
- The NTP correctly indicates that the high correlation between styrene and butadiene exposure in the SBR industry is problematic for interpreting results. Appropriately, on page 108, the table describing the Macaluso et al. (2) study states in the comment column that "exposures highly correlated; impossible to disentangle separate styrene or butadiene effects". A similar statement about the inability to disentangle a separate effect of styrene, butadiene and DMDTC is made on page 137 (lines 11-12). Yet, the NTP implies in the Executive Summary and elsewhere that the strongest evidence for a relation between styrene and lymphohematopoietic cancer comes from the SBR industry. Moreover, the NTP puts considerable weight on the results of Matanoski et al.(3), seemingly because measured styrene data were used (as stated earlier, precise estimation of quantitative levels is less important for hazard identification purposes). However, the Matanoski et al.(3) study is based on the same industry and essentially the same workers as studied by Macaluso et al.(2), where the impossibility of disentangle independent



chemical effects was appropriately noted by the NTP. The above conflicting interpretations and positions should be rectified.

- The McMichael et al.(4) study of a tire manufacturing cohort is cited several times (e.g., page 92-93). However, this study is of questionable relevance to evaluating potential health hazards of styrene given the myriad of solvent exposures and the impact of these exposures on the lymphohematopoietic cancer risks observed.(5, 6)
- The NTP describes a paper by Lemen et al. (7) and characterizes it as an update of mortality for the Meinhardt et al. (8) cohort (page 94, lines 9-20). Numbers of observed deaths in the follow up period are described, but Lemen et al. (7) never provided standardized mortality ratio (SMR) calculations. Without SMRs, it is both scientifically inappropriate and highly misleading to present only the observed number of additional deaths because additional deaths would be expected regardless of any chemical exposures due to aging of the cohort. As such, the Lemen et al. (7) study should be excluded, as other government agency reviews have done.(9)

## REFERENCES

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9. USEPA. Health Assessment of 1,3-Butadiene. United States Environmental Protection Agency, Washington D.C., EPA/600/P-98/001F, October 2002. 2002.