Rubber industry

Butadiene or styrene or butadiene and styrene or else?

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Commentary on the paper by Sathiakumar *et al* (*Occup Environ Med*, December 2005)*

In the December 2005 issue of this journal, Sathiakumar and colleagues[1] report on the extended follow up of the University of Alabama cohort in the styrene–butadiene–rubber industry. The update confirms the increased risk of haemato-lymphopoietic malignancies in work areas with high exposure to butadiene and styrene. This study is both potentially informative and at the centre of controversies regarding the evidence for the human carcinogenicity of butadiene and styrene.

In 1999, an IARC Working Group concluded that butadiene is ''probably carcinogenic to humans'' (Group 2A) on the basis of ''limited evidence'' of carcinogenicity in humans and ''sufficient evidence'' in experimental animals.[2] A case-control study nested in the University of Alabama cohort[3] showed a consistent excess of leukaemia and a statistically significant dose–response relationship with cumulative exposure to 1,3-butadiene, which remained after adjustment for exposure to styrene. Studies among workers in butadiene production reported an excess of lymphohaematopoietic cancers.

In 2002 a separate IARC Working Group concluded that styrene is ''possibly carcinogenic to humans'' (Group 2B) on the basis of ''limited evidence'' in epidemiological studies of cancer in humans as well as in experimental animals.[4] Studies of glass fibre reinforced plastics workers were considered to be the most informative with regard to the carcinogenicity of styrene, but findings from the styrene–butadiene–rubber industry also contributed to the evidence: an excess of leukaemia mortality increased with cumulative exposure to styrene in analyses that only considered this exposure; however, in analyses that adjusted for exposure to 1,3-butadiene, the exposure–response relationship became non-monotonic.

Thus, there was agreement in different IARC Working Groups regarding an increased risk for haemato-lymphopoietic malignancies in work areas with high exposures to butadiene and styrene. However, the Working Groups struggled with the interpretation and consistency of these findings across studies. Challenges included: (1) the high correlation between butadiene and styrene exposures, which made it difficult to disentangle the effects of the two; and (2) the aetiologically most sensible categorisation of the haemato-lymphopoietic malignancies into leukaemias and lymphomas, given that this information is derived from death certificates coded according to the International Classification of Diseases in effect at the time of death.

Both IARC evaluations have been criticised[5 6] and other committees came to different conclusions regarding the carcinogenicity of butadiene and styrene. In 1998, the German MAK commission[7] categorised butadiene as a ''substance that causes cancer in man'' (category 1). In the 9th edition, in 2000, the NTP Report on Carcinogens raised the classification of butadiene to ''known to be human carcinogen'',[8] and in 2002 the US EPA characterised butadiene as ''carcinogenic to humans''.[9] In 2002, the NTP Report on Carcinogens first listed styrene oxide, the reactive metabolite of styrene, ''as reasonably anticipated to be a human carcinogen'', while styrene is not classified. Styrene oxide is listed in IARC's Group 2A. The German MAK characterised styrene as ''carcinogen with no significant contribution to human cancer risk'', provided that the MAK and BAT values are observed (category 5).

There was also agreement that occupational exposure to these agents needs to be drastically reduced. The American Conference of Governmental Industrial Hygienists (ACGIH) (which is not a governmental agency) classified butadiene as ''suspected human carcinogen'' (A2), and styrene was considered as ''not classifiable as a human carcinogen'' (A4).[10] Nevertheless, over the last decades, the ACGIH recommended a substantial reduction of time weighted average threshold limit values (TLV-TWA), from 5000 to 2 ppm and from 400 to 20 ppm, for butadiene and styrene respectively. There was a large reduction for butadiene, from 1000 to 10 ppm, that accompanied the A2 designation in 1986.

With the extended follow up, the overall number of haemato-lymphopoietic malignancies increased from 115 to 162, with increased risks primarily observed for leukaemia among hourly paid workers (SMR 123, 95% CI 94 to 157). Risks were concentrated among workers with 10 or more years of employment and 20–29 years after hire (SMR 258, 95% CI 156 to 403), and in workers employed in polymerisation (SMR 204, 95% CI 121 to 322), coagulation (SMR 231, 95% CI 111 to 425), maintenance labour (SMR 203, 95% CI 114 to 335), and laboratories (SMR 326, 95% CI 178 to 546).[1] Thus, the study will allow for enhanced exposure specific analyses. Yet, the cancer hazard identification for butadiene and styrene has been controversial, and one may safely assume that these controversies will last. So far, this study only adds to the concern.

What's next? Due to the inherent problems of this study there is also a need to advance updates of other epidemiological studies potentially informative with regard to the carcinogenicity of butadiene or styrene. Further, molecular epidemiological studies are ongoing[11] and mechanistic studies may also contribute to the overall evidence. Some countries, by setting more stringent occupational limit values for butadiene and styrene, have taken steps towards primary prevention of butadiene and styrene related occupational cancers. Finally, one should not forget that butadiene is also an important environmental pollutant[8 12] with much larger populations being exposed for more than 40 hours a week, including potentially more susceptible populations such as young children.

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*Sathiakumar N, Graff J, Macaluso M, *et al*. An updated study of mortality among North American synthetic rubber industry workers. *Occup Environ Med* 2005;**62**:822–9.

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