

COMMENTARY

Styrene exposure and risk of cancer

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Styrene is widely used in the manufacture of synthetic rubber, resins, polyesters and plastics. Styrene and the primary metabolite styrene-7,8-oxide are genotoxic and carcinogenic. Long-term chemical carcinogenesis bioassays showed that styrene caused lung cancers in several strains of mice and mammary cancers in rats and styrene-7,8-oxide caused tumours of the forestomach in rats and mice and of the liver in mice. Subsequent epidemiologic studies found styrene workers had increased mortality or incidences of lymphohematopoietic cancers (leukaemia or lymphoma or all), with suggestive evidence for pancreatic and esophageal tumours. No adequate human studies are available for styrene-7,8-oxide although this is the primary and active epoxide metabolite of styrene. Both are genotoxic and form DNA adducts in humans.

Commentary

Styrene (vinyl benzene) is an economically important industrial chemical used in the synthesis and manufacture of polystyrene and hundreds of different copolymers, as well as numerous other industrial resins. Roughly 99% of the industrial resins produced from styrene can be grouped into six major categories: polystyrene (50%), styrene-butadiene rubber (15%), unsaturated polyester resins (glass reinforced) (12%), styrene-butadiene latexes (11%), acrylonitrile-butadiene-styrene (10%) and styrene-acrylonitrile (1%) (1). The 2006 US production of styrene was 11.4 million pounds (1), produced principally by catalytic dehydrogenation of ethylbenzene.

Among others before, Teixeira *et al.* (2) recently reported cytogenetic and DNA damage in workers exposed to styrene and concluded their findings were supported by previous study results demonstrating genotoxicity associated with occupational exposure to styrene (e.g. 3). Government Agency reviews also concluded that styrene and its major metabolite styrene-7,8-oxide (SO) are both mutagenic and clastogenic as well as carcinogenic (1,4). The authors (2) quote correctly that the 'International Agency for Research on Cancer (IARC) classified styrene as possibly carcinogenic to humans (Group 2B) and SO as probably carcinogenic to humans (Group 2A)'. IARC's (5) evaluation of the available human studies nearly 10 years ago stated 'There is limited evidence in humans for the carcinogenicity of styrene',

which indicates evidence of a credible but not a clear demonstration of a causal association with lymphatic/hematopoietic neoplasms in humans. Teixeira *et al.* (2), however, dismissed IARC's Working Group evaluation in 2002 (5) by iterating from the 2009 Boffetta *et al.* (6) styrene review paper 'that no consistent increased risk of any cancer among workers exposed to styrene was found. Indeed, Boffetta *et al.* (6) concluded that the available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer' (2).

The Boffetta *et al.* (6) review on behalf of Styrene Information and Research Center, a styrene industry organisation, was presented by co-author P. Cole to the National Toxicology Program's (NTP) Board of Scientific Counsellors open-to-the-public Peer Review of styrene (7). The NTP independent Board was not swayed or particularly impressed with the analysis and conclusions of the Boffetta *et al.* review (6,7). Moreover, in 2009 (1), the US Department of Health and Human Service's NTP declared 'Styrene is reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, and supporting mechanistic data.'

NTP further affirms, regarding human studies (1), that: 'The limited evidence for the carcinogenicity of styrene in humans is based on studies of workers exposed to styrene that showed (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers. Elevated risks of lymphohematopoietic cancer were found among workers with higher exposure to styrene after an appropriate elapsed time since first exposure. In some studies, the risks increased with increasing measures of exposure, such as average exposure, cumulative exposure, or number of years since first exposure. However, the types of lymphohematopoietic cancer observed in excess varied across different cohort studies, and excess risks were not found in all cohorts. There is also some evidence for increased risks of esophageal and pancreatic cancer among styrene-exposed workers. Causality is not established, as the possibility that the results were due to chance or to confounding by exposure to other carcinogenic chemicals cannot be completely ruled out. However, a causal relationship between styrene exposure and cancer in humans is credible and is supported by the finding of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers.'

The NTP conclusion that styrene is 'reasonably anticipated to be a human carcinogen' based on induced cancers, genotoxicity and mechanism is further bolstered by the 2010 case-control study in six European countries by Cocco *et al.* (8) who reported significantly elevated risks for B-cell non-Hodgkin's lymphoma [odds ratio (OR) = 1.6; 95% confidence interval (CI) = 1.1–2.3] and for follicular lymphoma (OR = 2.6; 95% CI = 1.3–5.2) in relation to styrene exposure. Exposure-related trend analyses also demonstrated increased risks ($P < 0.05$) for lymphomas in relation to increases in styrene exposures. Budroni *et al.* (9)

in 2010 likewise demonstrated significantly elevated risks in petrochemical workers exposed to styrene when data for all categories of non-Hodgkin's lymphoma are combined (Standardized Incidence Ratio = 1.87, 95% CI = 1.01–2.99, based on 15 cases) (10). These two papers add to the accumulated evidence linking styrene exposure to human cancers. IARC in 2002, nearly 10 years ago, concluded that the evidence was already considerable but not fully sufficient for causality (5).

For possible other human cancer sites related to styrene exposures, NTP asserts 'Studies in the reinforced-plastics industry provided evidence that suggests a possible association between styrene exposure and cancer of the esophagus or pancreas.' (1). Additionally, increases in cancer 'at these sites were also observed in some of the individual cohort studies, and there was some evidence of an exposure–response relationship with pancreatic cancer' (1).

Additional evidence for styrene and human cancers is supported by carcinogenesis bioassays as sufficient evidence for the carcinogenicity of styrene in experimental animals based on the induction of tumours in multiple studies in mice exposed to styrene by two routes of exposure. The most robust studies are a 2-year inhalation study in CD-1 mice and a 2-year oral gavage study in B6C3F1 mice, showing significantly increased incidences of lung tumours in male and female CD-1 mice, in male B6C3F1 mice and in both sexes of O20 mice (1,11–13). Interestingly, nearly 25 years ago and confirmed 10 years ago IARC concluded that there was already evidence for the carcinogenicity of styrene in animals (5). These collective carcinogenicity findings clearly support, predated and predicted styrene carcinogenicity in humans (14–21), as nearly one-third of known human carcinogens were first identified in long-term bioassays (22–25).

Hence, based on both animal and human cancer studies and genotoxic findings including clastogenicity and DNA damage in workers as well as on other supportive and biologically plausible mechanistic results, styrene and styrene-7,8-oxide should be considered as presenting carcinogenic risks to humans, particularly for lymphatic/hematopoietic cancers. Moreover, in the interests of public and occupational health, we suggest that authors be more cautious in their casual acceptance of industry papers and reviews of epidemiological study results related to occupational exposure to styrene (or other chemicals). Ultimately, more emphasis needs to be directed towards primary prevention as the most reliable channel for reducing or eliminating cancer burdens, especially among workers exposed to known carcinogens and mutagens (16,26,27).

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