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Review

Review of the genotoxicity of styrene in humans

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Abstract

Styrene (CAS No. 100-42-5) is an important industrial chemical for which positive results have been reported in in vitro and in vivo genotoxicity assays. Styrene-exposed workers have been studied extensively over two decades for the induction of various types of genotoxic effects. The outcomes of these studies have been conflicting, and where positive responses have been reported, it has proved difficult to demonstrate clear relationships between levels of damage reported and exposure levels. In this review, we have assessed studies addressing mutagenicity (chromosome aberrations, micronuclei and gene mutations) and other endpoints (sister chromatid exchanges, DNA breaks and DNA adducts) using criteria derived from the IPCS guidelines for the conduct of human biomonitoring studies. Based on the re-evaluated outcomes, the data are not convincing that styrene induces gene mutations. The evidence for induction of clastogenicity in occupationally exposed workers is less clear, with a predominant lack of induction of micronuclei in different studies, but conflicting responses in chromosome aberration assays. The results of numerous studies on sister chromatid exchanges do not provide evidence of a clear positive response, despite these being induced in animals exposed to styrene at high concentrations.

However, there is evidence that both DNA adducts and DNA single strand breaks are induced in styrene workers. These types of damage are considered indicative of exposure of the target cells and interaction with cellular DNA but do not necessarily result in heritable changes. There is evidence that the metabolism of styrene in humans is affected by genetic polymorphisms of metabolizing genes and that these polymorphisms affect the outcome of in vitro mutagenicity studies on styrene. Therefore, studies that have addressed the potential of this factor to affect in vivo responses were considered. To date, there are no consistent relationships between genetic polymorphisms and induction of genotoxicity by styrene in humans, but further work is warranted on larger samples. The analyses of individual studies, together with a consideration of dose–response relationships and the lack of a common profile of positive responses for the various endpoints in different studies, provide no clear evidence that styrene exposure in workers results in detectable levels of mutagenic damage. However, evidence of exposure to genotoxic metabolites is demonstrated by the formation of DNA adducts and strand breaks.

Introduction

Styrene is a widely used industrial chemical and its polymers are used in plastics, latex paints and coatings, synthetic rubbers, polyesters and styrene alkyd coatings [1]. As well as occupational exposure, humans may also be exposed to very low levels of styrene in the atmosphere due to industrial pollution, vehicle exhausts, cigarette smoke and combustion of styrene polymers. By far, the greatest degree of occupational exposure occurs in industries involved in the fabrication of objects from glass-fibre-reinforced polyester (GRP) composite plastics, such as boats, tanks, bathroom units and car parts. Exposure of humans is primarily via the inhalation route, with absorption through the skin occurring at a low rate, approximately 2% of the pulmonary uptake [2]. Many industries, which use styrene, involve co-exposure to other potential mutagens [1]. Most notable is the co-exposure to styrene oxide in the manufacture of glass-fibre-reinforced polyester products.

The induction of genotoxic damage in styrene-exposed workers has been extensively studied since the first report of an increase in chromosome aberrations (CAbs) in these workers in 1977 [3]. To date, conflicting outcomes have been reported.

Several groups have attempted to critically review the data available on human studies on styrene. The evidence, particularly in relation to cytogenetic endpoints, was reviewed by Scott and Preston [4]. They concluded there was no evidence that styrene was genotoxic in humans, primarily due to the lack of correlation of study outcome with exposure level, the difference in outcomes between the human results and animal data (where sister chromatid

exchanges (SCEs) are the major endpoint and CAbs are seldom reported to be elevated), the aberration types recorded being atypical of those seen in in vitro systems and because some studies were confounded by possible exposure to other genotoxins. These authors also reviewed the exposure data on studies, which reported positive and negative outcomes for cytogenetic endpoints and found no evidence of a dose–response relationship. Since this review there have been 3 chromosome aberration studies, 3 studies on chromosome aberrations and micronuclei, 5 micronuclei studies and 10 SCE studies published. Additionally, a series of papers from Vodicka's group have been published covering a variety of endpoints [5], [6], [7], [8], [9], [10], [11].

A recent comprehensive review of the scientific literature relating to styrene exposure, toxicity and epidemiology has been conducted [12]. The authors concluded that there is compelling evidence of a positive association between styrene exposure at occupational levels and the frequency of chromosomal aberrations based on several studies demonstrating a positive dose–response. They found the association between styrene exposure and SCEs less certain and no association between styrene exposure and the frequency of micronuclei (MN).

To circumvent the lack of power associated with the low numbers of workers in individual studies, a meta-analysis of 19 chromosome aberration studies was conducted to determine the relationship between exposure and outcome [13]. Results were based on high ($>125\,mg/m^3$) and low ($<125\,mg/m^3$) exposures and the ratio of mean chromosome aberration frequency in exposed versus controls. Studies were weighted by their sample variance. A significant increase in this ratio in the high exposure group was found, although no such effect was seen for the low exposure group or for SCEs or MN.

In the present analysis, we have critically reviewed the literature on population monitoring studies of styrene-exposed workers. Studies on styrene have been performed over many years and the methodology and understanding of the factors impacting on population studies have been improved over time. Many early studies were based on inadequate sampling sizes, statistical methods, time courses, etc. Recently, the IPCS set out their criteria for the adequate conduct of population monitoring studies for genotoxicity [14]. They considered the endpoints most commonly used for monitoring genotoxicity in human populations and provided a comprehensive and concise guidance on the planning, performing and interpretation of these studies. We have used their recommendations to evaluate the styrene studies against defined criteria for the conduct and reporting of such studies to assess the validity of individual reports, regardless of their outcome. We have also taken into consideration whether confounding factors, specific to each assay type, have

been taken into account. For example, age is highly influential in the *HPRT* assay but may also affect SCE, MN and chromosome aberration levels to some extent; smoking may affect all endpoints, although its effect is greatest for SCE assays. Studies where age and smoking status were taken into account, either by matched controls, the use of sub-groups or use of appropriate statistical techniques, were considered to be more reliable than those omitting these analyses. The assessment for each study addressing mutagenic endpoints, i.e. gene mutation and clastogenicity (CAbs and MN) is described. The outcome of the assessment of studies with indicator endpoints (SCEs, DNA strand breaks and DNA adducts) is also described and the significance of these studies addressed.

Taking consideration of differences in genetic polymorphisms in exposed workers and the impact this may have on xenobiotic metabolism and DNA repair pathways promises to improve the resolving power of human biomonitoring studies. A number of studies on genetic polymorphisms in styrene-exposed workers have been published in recent years [15]. The effect these have had on the interpretation of the mutagenic potential of styrene is also reviewed in this publication.

Section snippets

Gene mutations

The most common assay used to evaluate this endpoint is the *HPRT* assay in circulating lymphocytes. The endpoint has a very large variability (up to 100-fold in different individuals in different labs with repeat sampling from individuals showing up to 8-fold differences [14]). Thus, large sample sizes are needed to detect significant differences and this poses problems in studying relatively small groups of exposed workers. The assay is generally considered to be the least sensitive of the …

Chromosome aberrations

Chromosome aberrations are involved in carcinogenesis and increased levels in peripheral blood are associated with an increased risk of cancer [19]. The frequency of chromosome aberrations decreases with time due to repair and cell turnover. Nevertheless, some damaged cells persist in the circulation for considerable periods so this endpoint will monitor both long-term and recent exposure.

Micronuclei indicate both clastogenic and aneugenic potential, and therefore reflect mechanisms, which are …

Sister chromatid exchanges

Whilst SCEs have been widely used in population monitoring, due to the ease of performing this assay, there is uncertainty relating to their mechanism of formation and biological significance. The study of Hagmar et al. [19] did not show an association between levels of SCEs in peripheral blood and risk of cancer. SCEs reflect predominantly short-term exposures due to repair and cell turnover. However, long-lived lymphocytes may show increased levels some time after exposure if the DNA damage …

DNA strand breaks

DNA strand breaks may be taken as an indicator of initial damage, but they are not an endpoint for mutagenesis per se. The relationship between DNA damage, persistence and repair and mutagenic endpoints is complex and complicates the evaluation of the relevance of potential genotoxic exposures. It is likely that there is a level of DNA damage which does not have any biological significance due to repair but there is no understanding of what this level is for individual genotoxins. DNA strand …

DNA adducts

DNA adducts are used primarily as biomarkers of exposure rather than effect, although their levels will be related to individual metabolic processes and DNA repair as well as exposure levels. As for DNA strand breaks, the relationship between adducts, their persistence and repair and mutagenic endpoints is complex. Their occurrence may indicate the potential for mutagenesis and therefore be the first stage of the initiation of carcinogenesis. Therefore, they can be predictive of carcinogenic …

Germ cell effects

The data available on effects on germ cells of workers exposed to styrene are very limited. Workers in reinforced plastics factories in three different areas were assessed for sperm damage [69]. A significant difference in sperm DNA damage was found in the Comet assay, although no differences in standard semen analysis were seen. The values found were not correlated with the mean exposure levels (measured by urinary mandelic acid concentrations) in the three study groups. The biological …

Impact of genetic polymorphisms

In view of the inconsistent and predominately weak effects which have been reported for the genotoxicity of styrene in humans, the investigation of the influence of genetic polymorphisms holds promise in resolving whether styrene is an in vivo mutagen through the possible identification of susceptible individuals with higher levels of damage due to their differences in activation and inactivation of styrene. In humans, the main route of metabolism of styrene is to styrene-7,8-oxide by …

Effects on DNA repair

A few papers have investigated whether an individual's exposure to styrene could modify their subsequent responses to genotoxic damage, induced either by styrene or other exogenous agents. It was postulated by Vodicka et al. [5] that the lack of accumulation of genotoxic damage over time in exposed individuals could be due to the induction of adaptive DNA repair processes. Pero et al. [87] reported styrene exposure increased UDS in leukocytes obtained from styrene workers, which were treated in …

Relationship of response to exposure levels

In the face of conflicting outcomes for the human studies conducted, evidence for an effect would be strengthened if some relationship between exposure levels and outcomes could be shown. That is, *if* styrene *were* genotoxic in vivo, then it would be expected that studies with higher levels of exposure would be more likely to be positive and that different levels of response would occur in relation to different exposures within a study population.

Any attempt to correlate a biological endpoint …

Correlation between endpoints

If the positive responses were related to styrene, a common pattern of responses at the different endpoints reported in different studies would be expected. The outcomes in groups of workers where several endpoints have been studied are shown in Table 5. There is no common pattern or profile. There are several studies where discordant responses are obtained and the endpoints which are positive and negative vary in different studies. This suggests that styrene is not responsible for the isolated …

Overall assessment of human data

Conducting studies on small groups of workers, as occurs for many occupational exposures to styrene, is problematic. An extensive literature exists on the genotoxic effects of styrene in humans, but the evidence for its effects is still unclear. The present analysis considered a large number of studies published since the last evaluation to have critically reviewed the validity of individual studies on styrene [4]. However, the overall picture is not considerably clearer, and many studies were …

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