HHS Public Access

Author manuscript

Am J Ind Med. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Am J Ind Med. 2017 November ; 60(11): 930–946. doi:10.1002/ajim.22766.

Occupational Styrene Exposure and Acquired Dyschromatopsia: A Systematic Review and Meta-Analysis

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Abstract

Background—Styrene is a chemical used in the manufacture of plastic-based products worldwide. We systematically reviewed eligible studies of occupational styrene-induced dyschromatopsia, qualitatively synthesizing their findings and estimating the exposure effect through meta-analysis.

Methods—PubMed, EMBASE, and Web of Science databases were queried for eligible studies. Using a random effects model, we compared measures of dyschromatopsia between exposed and non-exposed workers to calculate the standardized mean difference (Hedges' g). We also assessed between-study heterogeneity and publication bias.

Results—Styrene-exposed subjects demonstrated poorer color vision than did the non-exposed (Hedges' $g = 0.56$; 95% CI: 0.37, 0.76; $p < 0.0001$). A non-significant Cochran's Q test result (Q

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Work completed at The Warren Alpert Medical School of Brown University

Authors' contributions: JMB and PBG (guarantor) conceived the study. ARC searched and selected the articles, extracted data, and drafted the manuscript. All authors contributed to data analysis and interpretation. GDP conducted statistical analyses with the assistance of ARC. JMB, GDP, and PBG reviewed and revised the manuscript for its intellectual content. ARC, JMB, and PBG provided final approval of the current iteration of this work. All authors have claimed accountability for the intellectual content herein presented and are prepared to carefully examine and resolve any questions that may arise regarding the accuracy or integrity of any aspect of the work.

Institution and Ethics approval and informed consent: Ethics review/approval and informed consent were not acquired; they were not required given the nature of this work, a systematic review/meta-analysis (no studies were conducted by the authors as a part of this work).

Disclosure: The authors declare no conflicts of interest.

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= 23.2; $p = 0.171$) and an I^2 of 32.2% (0.0%, 69.9%) indicated low-to-moderate between-study heterogeneity. Funnel plot and trim-and-fill analyses suggested publication bias.

Conclusions—This review confirms the hypothesis of occupational styrene-induced dyschromatopsia, suggesting a modest effect size with mild heterogeneity between studies.

Keywords

styrene; styrene monomer; color vision; dyschromatopsia

Introduction

Styrene (synonyms: ethenylbenzene, vinylbenzene, cinnamene, phenylethylene, styrol, styrene monomer) is an organic solvent and cross-linking agent characterized by a sweet, pungent odor and colorless-to-light-yellow appearance.[1–3] A benzene derivative, this hydrocarbon is used in the production of numerous polystyrene plastics and resins.[1,4] Accordingly, styrene represents one of the most prolific industrial solvents worldwide, and it is present in plastic packaging, disposable containers, insulation materials, parts of buildings and vehicles, and even some forms of artificial flavoring.[1,2] Styrene's rise to prominence in the United States (US) manufacturing industry marks a relatively recent phenomenon, as total production more than doubled between 1977 and 2010.[4] In 2011, the Styrene Information & Research Center estimated that 90,000 American workers, employed by approximately 5,000 plants across all 50 US states, participated directly in the manufacture of styrene products.[5] The growth of the styrene industry in the U.S. has shown little evidence of slowing down in recent years. American export of styrene in 2015 was 4.6 billion pounds, the highest value currently recorded by the United States International Trade Commission.[6]

Inhalation represents the primary route of exposure to styrene, which is found at concentrations of 0.06–4.6 parts per billion (ppb) in outdoor air and 0.07–11.5 ppb in indoor air for the general population.[1,4] Other potential routes include ingestion and dermal contact, although the latter usually occurs occupationally in certain jobs that involve direct exposure to styrene.[7] Dermal absorption of styrene can contribute a significant amount to total exposure[8] and occurs even among styrene workers using respirators as personal protective equipment (PPE).[7] While the carcinogenic potential of styrene remains heavily disputed based on a lack of human evidence, there is a sizeable body of evidence surrounding its neurotoxicity in humans, with observed impairments in indices like reaction time, vibration perception, hearing, and nerve conduction velocity.[3,4]

Industrial workers—particularly those in fiberglass-reinforced plastics (FRP) production for items like car parts, boats, and bathtubs—are most likely to be exposed to potentially neurotoxic concentrations of styrene (>1,000 times higher than those encountered in the environment).[3,4] Notably, the recommended workplace limit of styrene varies widely depending on the agency or organization making the determination, is often advisory and not enforced by law, and does not define a single threshold for preventing neurotoxicity. For instance, current Occupational and Safety Health Administration (OSHA) regulatory guidelines prescribe a threshold limit value time-weighted average (TLV-TWA) of 100 ppm

over 8 hours, while the American Conference of Governmental Industrial Hygienists (ACGIH) sets a non-enforceable 8-hour TLV-TWA at a much lower 20 ppm.[3, 4] Supplemental Table SI provides an overview of airborne styrene exposure limits prescribed by various national and international agencies and organizations.

As neurotoxicant-induced impairment of color vision (dyschromatopsia) is an early marker of neurotoxicity,[9] previous research efforts have aimed to elucidate the relationship between styrene exposure and dyschromatopsia. In these studies, dyschromatopsia is most commonly measured using the Lanthony D-15 hue desaturated panel (D-15d). This test evaluates a subject's ability to arrange 15 low-saturation, colored caps in a defined chromatic sequence.[10] The D-15d was designed to detect mild dyschromatopsia in individuals who successfully complete the standard Farnsworth D-15 test,[11] which assesses more severe deficits in chromatic discrimination.[12–14] The D-15d is also useful for classifying color vision defects, based on the confusion axis on which the predominance of errors occur (blue-yellow, red-green, or both). According to Köllner's rule on acquired dyschromatopsia, blue-yellow defects suggest retinal dysfunction, while impairment of red-green discrimination (generally a more advanced development) indicates optic nerve disease.[15,16]

Acquired deficiencies in color vision are generally subtle and subclinical in nature.[14] Moreover, they are potential manifestations of various pathological conditions, including diabetes mellitus,[17,18] Parkinson's disease,[19] and chronic alcoholism.[20] By providing sensitive early markers, dyschromatopsia-related findings may be useful for initiating treatment, as well as monitoring the progression of disease and injury.[18,21]

While there are two previous meta-analyses of styrene-induced dyschromatopsia, they are over a decade old and produced conflicting results.[13,22] In addition, the potential implications of styrene-induced color vision loss with respect to instrumental activities of daily living (IADLs) are not well described. Herein, we address these limitations by conducting a joint systematic review and meta-analysis to elucidate the impact of occupational styrene exposure on color discrimination. Furthermore, we investigate the characteristics and potential implications underlying acquired dyschromatopsia in styrene workers.

Materials and Methods

Search strategy

We queried the PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com), and Web of Science (http://www.webofknowledge.com) electronic literature databases using the following search command: Styrene AND (Dyschromatopsia OR "color vision" OR "Retinal Cone Photoreceptor Cells" OR "Color Vision Defects"). No restrictions related to the date of publication or study design were implemented for this initial literature search, which was conducted on October 1, 2016.

Study selection strategy

Figure 1 demonstrates our strategy for study selection in the form of a Preferred Reporting Items and Meta-Analyses checklist (PRISMA) flow diagram. As part of a preliminary

screen, we reviewed publication titles and abstracts of identified records. Studies were excluded if they were determined to be (a) review articles, (b) animal or laboratory studies, and/or (c) unavailable in the English language. Additionally, records that clearly lacked relevance to the subject of this review were removed from further consideration. Next, in an assessment of study eligibility for systematic review, we read the full-text articles for the remaining records. We deemed studies ineligible if they (a) did not include a direct measurement of styrene exposure (either biological or airborne), (b) indicated significant co-exposure of subjects to chemicals other than styrene, without identifying styrene exposure as the primary exposure of interest, or (c) reported findings contained within another eligible study (in which case we included the more recent study with the longer follow-up). To ensure full coverage of pertinent literature, we also examined reference lists of eligible studies. Among the studies included in our systematic review, only those that compared color discrimination indices between styrene-exposed and non-exposed participants using the D-15d test were chosen for meta-analysis.

Data extraction

We extracted the following descriptive information, as applicable: study design, site of exposure (including country), characteristics of study participants, method(s) of styrene exposure measurement, method(s) of color vision assessment, type of color discrimination index, characteristics of color vision deficits, PPE use, and co-exposure to other substances. Quantitative data variables extracted for review included sample size, environmental measurements of styrene exposure, biological measurements of styrene exposure, duration of exposure (i.e., years of employment in high-exposure site), and color confusion index (CCI). All quantitative variables except sample size were recorded as mean values with associated standard deviations; when this information was unavailable, the median and range were extracted in lieu of the mean and standard deviation, respectively. All quantitative variables are herein reported with their original units.

Meta-analysis

In preparation for meta-analysis, we transformed mean CCIs and associated standard deviations into their natural logarithmic equivalents.[23] The decision to conduct a meta-analysis in the logarithmic scale was prompted by two observations. Firstly, one of the eligible studies[24] reported dyschromatopsia using geometric means and standard deviations, rather than arithmetic values. As the standardized mean difference (the effect size variable of interest) assumes normality in a given outcome, and normality is more likely to hold for the logarithm of CCI than the CCI itself, we determined that data analysis in the logarithmic scale was warranted for all studies. A preliminary calculation of effect sizes in the original non-logarithmic scale had indicated considerable variability among estimates. Thus, we reasoned that calculation of log-transformed effect sizes would also help weaken the mean-variance relationship, which none of the previous meta-analyses had done.[13,22]

Assuming heterogeneity across studies, we employed a random effects model to investigate the effect of styrene exposure on CCI. As we had fewer than ten studies, we quantified exposure effects using estimates of Hedges' g, which offer bias-corrected standardized mean differences.[25] We were unable to recover Hedges' g from one study description;[24] however,

we were able to obtain Cohen's *d*.[26] Specifically, we used the reported two-sided *p*-value (derived from a log-scale comparison by the authors) to determine a *t*-test statistic from which we could directly calculate the effect size.[27] Calculations of Hedges' *g* were performed using exact formulae, rather than small sample approximations, which have been shown to be unreliable and impractical with modern software.[28] Outcomes were pooled using the inverse variance method. Of note, random effects analyses include the between-study variance component τ^2 in calculating the overall study-level variances. Hence, they downweight larger studies in favor of smaller ones, relative to the fixed effects model.

To assess between-study heterogeneity, we calculated the DerSimonian-Laird estimator for τ^2.[29,30] We also obtained the I^2 statistic and Cochran's Q, both of which are derived from the chi-squared test statistic.[31] Due to concerns about power for conducting formal heterogeneity tests based on Cochran's Q, between-study heterogeneity was examined primarily through I^2,[31] which quantifies the proportion of total variation attributable to the between-study component τ^2.[30,32]

Effect estimates and confidence intervals for all analyzed studies were depicted on a forest plot. In addition, a funnel plot was created for assessment of publication bias. To supplement visual inspection of the funnel plot, we conducted Egger's linear regression test of funnel plot asymmetry,[33] modified to accommodate between-study heterogeneity.[34] Moreover, we employed the nonparametric trim-and-fill method. This analysis involves estimating the number of missing studies in a meta-analysis and hypothetically correcting funnel plot asymmetry, to gauge the effect that these missing studies would demonstrate upon inclusion.[35] Although the method assumes a fixed effects model, it should perform adequately under random effects models with low-to-moderate levels of between-study heterogeneity.[36]

Analyses were conducted using the "metacont" function in the R software (4.7.0) "meta" package.[37,38] For reporting of results, we followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[39] *P*-values less than 0.05 were considered statistically significant.

Results

Literature search

Our queries of the PubMed ($n = 35$), EMBASE ($n = 40$), and Web of Science ($n = 66$) databases produced 73 unique records after de-duplication (Fig. 1). Screening of titles and abstracts resulted in 51 exclusions, due to clear violation of the predetermined exclusion criteria and/or failure to address our review question. Subsequent evaluation of full-texts ($n = 22$) for eligibility resulted in seven exclusions. Absence of styrene exposure measurement accounted for four of the seven exclusions, while two other studies were excluded due to significant evidence of co-exposure to numerous solvents. Moreover, one study[40] was excluded because its primary findings were incorporated into a larger, cohort study by the same research group.[41] In aggregate, 15 studies[24,41–54] were selected for qualitative synthesis (Table I). Among the 15 included studies, eight[24,43,45–47,49,51,54] were eligible for meta-analysis based on the criteria described above in the Methods section (Figure 2).

Characteristics of included studies and subjects

Table I summarizes the main characteristics of studies selected for review. We identified eight cross-sectional studies, six cohort studies, and one case report. In order to investigate the reversibility of styrene-induced dyschromatopsia following a reduction in exposure (e.g., after a vacation), four studies conducted a follow-up assessment on a subset of subjects,[41,45–47] while two others employed a multi-phase study design that aimed to incorporate the entire study sample.[53,54] Follow-up periods were 1 to 12 months apart, whereas Castillo *et al.*[41] compared measurements obtained nine years apart.

Across the 15 studies, samples ranged from 18 to 352 subjects (total of 1949 subjects). Nine of the 15 samples were reported to be exclusively male. Eight studies took place in Europe, four in Asia, and three in North America. Only one study was conducted in the United States.[52] We noted considerable overlap among the investigators overseeing the selected studies; eight independent research groups could be discerned from the author lists.

All studies characterized subjects as "exposed" strictly according to the nature of their occupation (i.e., involving direct exposure to styrene). In all but two studies,[53,54] exposed subjects were explicitly linked to reinforced plastics manufacture, most commonly as painters and laminators. Exclusion criteria varied across studies but typically entailed excess alcohol consumption, tobacco smoking, and congenital dyschromatopsia, as defined by the authors. Diabetes, hypertension, cerebrovascular disease, and poor (corrected) visual acuity were also commonly cited as exclusion criteria. Although three studies acknowledged past or present co-exposure to other substances (most studies did not address this consideration), the authors suggested that the levels of exposure were sufficiently low to be considered negligible (Table II). In the nine studies that reported statistically significant confounding variables, age was always among the reported covariates. Other covariates (such as alcohol consumption and tobacco smoking) were less commonly reported.

Four studies specified a minimum duration of employment (ranging from six months to five years) in their inclusion criteria. Workers tended to exhibit long tenures of employment, and the lowest mean or median duration of exposure in any study was 4.5 years. Among the eight studies that divulged details about the workers' use of personal protective equipment (PPE), four reported little to no use of cartridge masks (Table II). Authors of more recent studies tended to report increased PPE use and/or recent systemic improvements in training and ventilation; these were general reflections of temporal changes in worker safety, seldom supported by longitudinal analysis.

Nine studies recruited referent subjects without occupational exposure to styrene or other industrial solvents. Lack of occupational styrene exposure was assumed on the basis of one's job title. Non-exposed subjects were often matched to their exposed counterparts for sex and age, and less frequently for alcohol consumption, tobacco smoking, socioeconomic status, and ethnicity. Only two studies reported that all non-exposed subjects worked at the same plant(s) that employed the styrene workers.[24,54] These two studies were also the only studies that described a quantitative assessment of styrene exposure for the non-exposed group. One study selected all referents from a different factory,[47] three studies selected referents from the same or other factories,[43,49,51] and three others did not clearly specify the non-exposed

workers' site(s) of employment.[44–46] Efforts to blind investigators to participant exposure status were noted in five studies.[24,41,46,49,53]

Exposure and outcome measurements

The methods of styrene exposure measurement were variable, but studies usually incorporated some combination of environmental and biological measurements (Table I). Studies typically measured absorbed styrene exposure through urinary analysis of the primary styrene metabolites, mandelic acid (MA) and phenylglyoxylic acid (PGA), which exhibit half-lives of 25 and 11 hours, respectively.[4,55,56] Given the rapid urinary clearance of styrene (~13 hours) and its metabolites, urinary measurements are presumed to reflect acute exposure.[57] Not all reported urinary concentrations were corrected for creatinine concentration or specific gravity.[43,49,51]

Area sampling (capturing representative air samples) and passive personal sampling (using a dosimeter) represented the predominant strategies for quantifying current or acute environmental exposure. No studies reported monitoring for dermal exposure. Five studies—coincidentally also the most recent studies—included an assessment of cumulative exposure.[41,49,50,52,53] Among this group of studies, two studies without historical records of exposure or biomonitoring data estimated cumulative styrene exposure based on current measures of exposure.[50,52]

Acquired dyschromatopsia represented the primary visual outcome in all selected studies. Most studies conducted monocular testing of color vision. Five studies additionally examined changes in visual contrast sensitivity (VCS) as a secondary outcome, using the Vistech grating charts. With only one exception,[44] wherein the more intensive and time-consuming Farnsworth-Munsell 100 hue test (FM-100) was administered,[11] color vision deficits were evaluated via the D-15d panel. Since acquired color vision defects are generally subclinical, the D-15d is regarded as the test of choice for human toxicology studies.[9,14]

Quantitative evaluation of the subject's performance is commonly performed according to Bowman[58] and involves calculation of the Total Color Distance Score (TCDS), or the sum of perceptual distances. Improper arrangements on the D-15d increase the TCDS, such that the minimum TCDS score of 56.4 indicates a perfect performance. A subject's TCDS is subsequently divided by the minimum TCDS to give the Color Confusion Index (CCI), the primary measure of solvent-induced color vision loss. Accordingly, a CCI of 1.0 indicates perfect performance on this task, and increases in this index correspond to increased impairment of color vision.

Fourteen out of the 15 studies provided evidence in support of styrene-induced dyschromatopsia, and 13 (excluding the case report by Gobba *et al.*[48]) reported statistically significant findings. Supporting evidence usually involved comparison between mean color vision indices (typically CCI), demonstrating that exposed participant groups exhibited significantly higher values than did non-exposed comparison groups. Several studies reported a dose-dependent relationship between (acute) styrene exposure and color vision impairment.[43,45,47,49,51,54] Three studies extrapolated threshold exposure levels from their

data,[49,51,54] and all concluded that airborne styrene concentrations below 20 ppm were sufficient to induce dyschromatopsia. Furthermore, two studies investigated the significance of past peak exposure in the context of acquired dyschromatopsia,[49,50] and they reported discrepant findings. The study conducted by Gong *et al.*[49] provided evidence of dyschromatopsia due to high peak exposure to styrene, but it did not support an association with long-term exposure. In contrast, Iregren *et al.*[50] did not find a significant correlation between acquired dyschromatopsia and peak exposure, but a significant correlation of acquired dyschromatopsia with long-term (cumulative) exposure was observed. Among the 15 studies, only Seeber *et al.*[53] did not observe an association between acute or chronic styrene exposure and acquired dyschromatopsia.

Thirteen studies reported measurements or extrapolations of airborne styrene exposure; 11 of these 13 studies identified mean or median values of 25 ppm or lower; the remaining had mean concentrations of 48.3 ppm[42] and 49.90 ppm.[49] Among studies examining urinary biomarkers of styrene exposure that also accounted for urine dilution with urinary creatinine concentrations, whole-study mean concentrations for urinary MA varied between 84.0 and 360 mg/g creatinine, and average urinary PGA varied between 57.4 and 110 mg/g creatinine. As is evident from the case report by Gobba *et al.*,[48] individual concentrations could fall significantly outside of these ranges, however. In both studies that measured biological styrene exposure in non-exposed participants,[24,54] styrene metabolite levels were confirmed to be significantly lower than those of exposed subjects, displayed in Table II. For the control group, Chia *et al.*[24] reported a mean MA value of 3.3 mg/g creatinine (range: 1.6–9.6 mg/g creatinine) and a mean PGA value of 0.7 mg/g creatinine (range: 0.3–1.9 mg/g creatinine). Meanwhile, Triebig *et al.*[54] reported median MA+PGA (combined) concentrations of 15 mg/g creatinine (range: 5–36 mg/g creatinine) and 24 mg/g creatinine (range: 4–47 mg/g creatinine) in the first and second phases of their study, respectively.

Eleven studies elaborated on the characteristics of the observed color vision deficits; impairment in chromatic discrimination manifested mostly by blue-yellow deficiency. Five studies described the deficits as subclinical (the rest of the studies did not address their clinical significance). One study made exclusions based on red-green deficiency,[53] under the premise that the majority of deficits observed along this axis are congenital, and therefore obfuscate the detection of acquired dyschromatopsia.

We observed mixed findings with respect to the reversibility of styrene-induced dyschromatopsia. The majority of studies with a one-month follow-up after an exposure-free month did not show significant recovery of color vision.[45–47] Similarly, Seeber *et al.*[53] did not find any evidence of reversibility following a 6- to 8-week vacation. In contrast, Triebig *et al.*[54] suggested that both one-month and ten-month reductions in exposure significantly diminished the difference in CCI between non-exposed subjects and exposed subjects. Castillo *et al.*[41] reported evidence of reversibility up to a certain point in time. The investigators noted a significant improvement in color vision two years after the systemic implementation (in 1990) of formal respirator training and improvements in the ventilation system. While urinary MA levels indicated significantly reduced exposure over the following seven years (1992–1999), there was no concomitant recovery in color vision.

Synthesis of results

In total, we analyzed data from 352 styrene workers and 355 subjects without occupational styrene exposure (Figure 2). Pooled analysis using a random effects model led to an overall standardized mean difference (SMD) of 0.56 (95% confidence interval [CI]: 0.37, 0.76; $p < 0.0001$), which is interpreted as a medium-size effect.[26] A fixed effects model yielded a SMD of 0.53 (95% CI: 0.37, 0.68; $p < 0.0001$).

The 95% CIs of the mean differences from individual studies overlapped, suggesting between-study consistency. This was supported by formal examination of between- and within-study variation. The between-study variance component, τ^2, was estimated at 0.0242. A test of between-study heterogeneity using Cochran's Q ($Q = 23.2$; $df = 10$; $p = 0.171$) was not significant, even at a less stringent significance cut-off of 0.10, as described by Dickersin and Berlin.[59] Consistent with this, the observed magnitude of I^2 (32.2%) denoted low-to-moderate heterogeneity.[31] Similarly, we observed that the corresponding 95% CI [0.0%, 69.9%] included both the low-level (25%) and moderate-level (50%) cut points described by Higgins and colleagues; it did not contain the high-level (75%) cut point.

Risk of publication bias

Upon initial visual inspection of the funnel plot, we did not observe any glaring indications of asymmetry (Fig. 3). We found that all points fell under the dashed lines passing through the plot. Moreover, the higher precision studies converged around the mean, consistent with a symmetric funnel. However, closer examination suggested potential under-representation of smaller, imprecise studies in the lower left side of the plot. To investigate further the possibility of publication bias, we conducted a trim-and-fill analysis, which demonstrated that just three missing studies on the left side would have resulted in rejection of the fixed effects model and a SMD of 0.43 (95% CI: 0.20, 0.65; $p = 0.0002$). We made these adjustments, or fillins, by manipulating three studies on the opposite extreme of the plot.[24,45,54] Furthermore, we observed that Egger's linear regression test of funnel plot asymmetry was borderline significant ($t = 2.39$; $df = 6$; $p = 0.054$). Notably, our meta-analysis contained fewer than the minimum number of studies (10) that is ideal for Egger's test. A formal test of publication bias based on the funnel plot was also considered unreliable given the small number of studies (<10). Overall, funnel plot assessment and associated statistical methods— while limited by a relative dearth of studies—suggest mild publication bias against smaller studies with negative results.

Discussion

Summary of evidence

We systematically reviewed 15 studies that examined occupational styrene-induced dyschromatopsia. For a subset of these studies (n = 8), we performed a meta-analysis that compared acquired impairments in color vision as described by CCI (the endpoint of interest) between individuals with direct, and generally prolonged, occupational exposure to styrene and individuals with no history of exposure. Our quantitative synthesis incorporated eight studies, making it to date the largest meta-analysis investigating styrene-induced dyschromatopsia.

The evidence to date supports the hypothesis that chronic, occupational exposure to styrene at levels well below 100 ppm—the 8-hour TWA permissible exposure limit defined by OSHA (Table SI)—can induce measurable deficits in color vision. All but one study provided positive findings with regard to this hypothesis. Evidence came in various forms, including a higher/worse color vision index in exposed subjects, a positive correlation between color vision index and some indicator of exposure, an improvement in color discrimination with decreased styrene exposure, and a greater occurrence of abnormally high color vision indices among exposed groups.

There was some evidence to suggest a dose-response relationship, which the earlier meta-analysis by Benignus *et al.*[22] illustrated using individual-subject data. However, there was no clear consensus regarding the threshold exposure concentration that causes acquired dyschromatopsia. Deficits in color discrimination predominantly occurred along the blue-yellow axis, an observation that has been connected to early manifestation of dyschromatopsia.[47,48,52] Findings regarding the reversibility of this exposure effect were mixed (discrepancies were attributed to differences in exclusion criteria and exposure levels between studies) and in low abundance (coming from only five studies). Similar conclusions could be made with regard to studies of past peak exposure and its impact on color discrimination. The evolution of styrene-induced dyschromatopsia remains unclear, and the pathogenic mechanism(s) that underlie this evolution similarly require(s) further investigation. Future studies could also investigate potential associations between acquired dyschromatopsia and other subtle manifestations of neurotoxicity.

Overall, we observed significant variation in study location, study design, and methods of exposure assessment between studies. We also found an overall inconsistency in work conditions and practices, which represents an important consideration for interpretation of styrene-induced dyschromatopsia. For instance, proper PPE use[60,61] and improvements in ventilation systems and other work practices[62,63] have been linked to reduced styrene body burden. Divergence in these study characteristics may explain, to some degree, the reports of pronounced between-study heterogeneity from earlier meta-analyses.[13,22] While heterogeneity can complicate effect size calculation, the consistent finding of styrene-induced dyschromatopsia despite study-level variation supports the validity of this effect. Hence, the observed between-study heterogeneity represents both a strength and a limitation in this review. In contrast, we found significant homogeneity in both the methods of outcome assessment (14 of the 15 studies herein reviewed used the D-15d to assess dyschromatopsia) and the type of work site(s) from which exposed subjects were recruited (13 studies mentioned involvement in fiberglass-reinforced plastics manufacture).

Under the random effects assumption, meta-analysis yielded an overall standardized mean difference (Hedges' g) of 0.56 (95% CI: 0.37, 0.76), suggestive of a medium-size effect (Fig. 2). Visual inspection of the forest plot did not provide any indication of significant between-studies heterogeneity. Although quantitative estimates hinted at low-to-moderate heterogeneity levels, evidence for heterogeneity was relatively weak in comparison with that reported by Paramei *et al.*[13] This discrepancy may be attributed to our inclusion of three additional studies.[24,46,49] Furthermore, the reduced variation in effect size may reflect our decision to implement a variance-stabilizing, log-scale transformation of mean CCI.

Analysis of publication bias was limited by the relatively small number of studies. With this limitation in mind, both quantitative and qualitative tests suggested that there is reason to suspect biased publication of studies and/or selective reporting of outcomes—presumably toward studies and outcomes that report strong exposure effects. Additionally, trim-and-fill analysis demonstrated that inclusion of missing studies would appreciably diminish the standardized mean difference, and that the true effect may be modestly weaker than that herein reported. A moderate effect size (SMD = 0.43; 95% CI: 0.20, 0.65; $p = 0.0002$) was nevertheless observed following trim-and-fill analysis.

Limitations

With regard to limitations of the review process, our decision to restrict eligible studies to peer-reviewed papers available in the English language may have resulted in some bias and inaccuracy in our effect size estimate. Other challenges to interpretation included small sample sizes and a paucity of relevant studies, which further hampered our assessment of heterogeneity and publication bias. It is also worth noting that this review lacked a comprehensive risk of bias analysis. Thus, the extent to which potential factors other than publication bias (e.g., selection bias, confounding, and exposure misclassification) affected our determination of the exposure effect remains unclear. Future work incorporating systematic evaluation of these sources of bias would enhance causal interpretations of this literature.

We also identified other potential methodological limitations within studies. In the absence of a formal appraisal, we consider that the lack of blinding in 10/15 studies may have contributed to overestimation of the exposure effect due to observer bias. We also noted that some studies derived cumulative exposure from a simple multiplication of exposure duration with current exposure level. These estimations rely on the assumption of constant exposure levels, which is unlikely and difficult to prove without formal assessments (either biological or environmental). In addition, several studies used mean biological measurements to estimate airborne styrene levels through a linear relationship model; however, this model may not be accurate at high levels of exposure (>150 ppm) to which a contingent of workers were likely subjected.[64] Lastly, the D-15d panel—while highly efficient and uniquely designed to identify acquired dyschromatopsia—can be accompanied by concerns of high false positive rates.[65,66] Related to this, over-detection due to certain conditions of D-15d test administration (e.g., low level of illumination during testing) may have contributed to effect size miscalculation.

Implications for instrumental activities of daily living

No study has investigated the impact of styrene-induced dyschromatopsia on a person's ability to perform IADLs. Although the reviewed studies reported certain characteristics of the workers' dyschromatopsia, the aggregate pool of information was limited and incomplete. The two principal observations regarding the color vision deficits were their subclinical nature and predominance along the blue-yellow chromatic axis. Based on this information alone, the significance of the workers' dyschromatopsia with respect to their IADLs remains uncertain.

Studies of individuals with congenital dyschromatopsia (which presents most frequently as a red-green deficit) suggest that dyschromatopsia can lead to significant impairments in one's ability to perform IADLs.[67,68] The clinical impact of acquired dyschromatopsia, in comparison, is not well studied. Consistent with this research gap, the confusion patterns of acquired dyschromatopsia tend to be more poorly defined than those that arise from congenital color blindness (commonly assessed using the Ishihara pseudoisochromatic plate test).[65,66] The clinical implications surrounding acquired color vision deficiency warrant further investigation—especially in light of previous suggestions that acquired dyschromatopsia may actually be more prevalent (5–15%) than the congenital subtype (2–8%) in certain populations.[69]

It is questionable whether the styrene-induced color vision defects herein discussed could interfere with IADLs. However, acquired dyschromatopsia is unique in its mutability (from blue-yellow to red-green or a combination of both), and its level of severity has the potential to change according to the presence and intensity of the underlying exposure.[13,15,16,53,70] In addition to potential shifts in severity, the very nature of the deficits may change. Some have suggested a model of occupational exposure wherein early manifestations of dyschromatopsia occur along the blue-yellow axis, but, upon continued exposure, evolve to include more clinically significant defects in red-green discrimination.[14,47,48,52,65,71] A similar model has been described for acquired dyschromatopsias associated with ocular disease.[15,65]

In sum, these models are not well characterized and require further examination. Nonetheless, they bring forth an intriguing possibility with regard to styrene-induced dyschromatopsia—especially given that most studies in our review identified red-green defects in a small contingent of subjects. The only cross-sectional or cohort study that did not report any cases of red-green dyschromatopsia was that conducted by Seeber *et al.*,[53] due to its unique exclusion criteria. Of potential significance, this was the only study in our review that did not support the hypothesis of styrene-induced dyschromatopsia. Taking into account Köllner's rule, we consider the possibility that—by excluding all subjects with defective red-green discrimination—the researchers may have inadvertently excluded advanced cases of acquired dyschromatopsia, with more clinically significant symptoms. Reduced visual acuity may represent one such symptom, as red-green deficiencies in acquired dyschromatopsia have been linked to moderate-to-severe deficits in visual acuity.[15,72]

There is evidence to suggest that among all visual measures, visual acuity is most strongly correlated with observed performance of IADLs.[73] The likelihood of this particular outcome in the styrene workers is unclear, however, given that visual acuity was examined only for screening purposes. In addition, as investigators typically excluded subjects with poor (corrected) visual acuity, the association between visual acuity loss and styrene-induced dyschromatopsia remains unclear. Ultimately, acquired dyschromatopsias are fundamentally complex and unpredictable in their prognosis.[15] Thus, until the emergence of carefully planned studies built around this research question, one can only speculate about the "real-world" implications of styrene-induced dyschromatopsia.

Future directions

Our review highlights the need for more focused research efforts in several areas, including:

- The dose dependence of the exposure-outcome relationship and its associated threshold level of exposure.
- The evolution of color vision loss upon increased or prolonged exposure, including associated pathogenic mechanism(s).
- The potential reversibility of styrene-induced dyschromatopsia upon reduced exposure.
- Effects of short-term styrene exposure on color discrimination in humans. Only one study to date has examined this effect;[74] in this experimental study, subjects without prior occupational styrene exposure did not exhibit significant dyschromatopsia after exposure to five 6-hour-long sessions (peak 50 ppm) inside an exposure chamber.
- The impact of styrene exposure with respect to other neurological endpoints (such as delayed reaction, hearing loss, and impaired vibration perception), which have individually received less attention in human studies than has acquired dyschromatopsia.
- Effects of dyschromatopsia and styrene-induced neurological effects more generally on IADLs.
- Potential methodological improvements for the study of D-15d results from styrene-exposed workers. These include increased use of the Vingrys and King-Smith Confusion index,[75] which provides a detailed evaluation of early color vision loss that may be more suitable and useful (relative to the CCI index) for this occupational setting.[13,46]
- The practical application of biological monitoring (using sensitive blood and urinary indices) in exposure evaluation of styrene workers, so as to address salient issues such as workload differences.
- Current work conditions and practices at high-exposure sites (e.g., fiberglass-reinforced plastics plants). Future studies should prioritize accurate and thorough assessments of exposure that rely on the usual biological and environmental measures, but could also consider assays of dermal exposure to avoid underestimation of occupational exposure.

Conclusions

Our review indicates that prolonged occupational exposure to styrene, at levels below most regulatory agency-prescribed exposure limits, can impair color discrimination. Acknowledging the small number of studies in our review, our quantitative analyses suggested a medium-size effect size with low-to-moderate heterogeneity between studies. The consistency of results across studies despite use of divergent methods and work practices further substantiates the styrene exposure effect.

Several questions remain regarding dyschromatopsia due to occupational styrene exposure; these include questions about the seemingly low dose-response threshold, the evolution of color vision loss over time, associated pathogenic mechanism(s), and the effects of acute vs. chronic exposure. In addition, the significance of styrene-induced dyschromatopsia (and other neurological impairments) as it pertains to IADLs is unclear. Future studies should place an emphasis on extensive and accurate measurement of styrene exposure, to clarify the exposure-outcome relationship and evaluate the usefulness of currently prescribed exposure limits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Grant sponsor: NIEHS; Grant number: R01 ES024381

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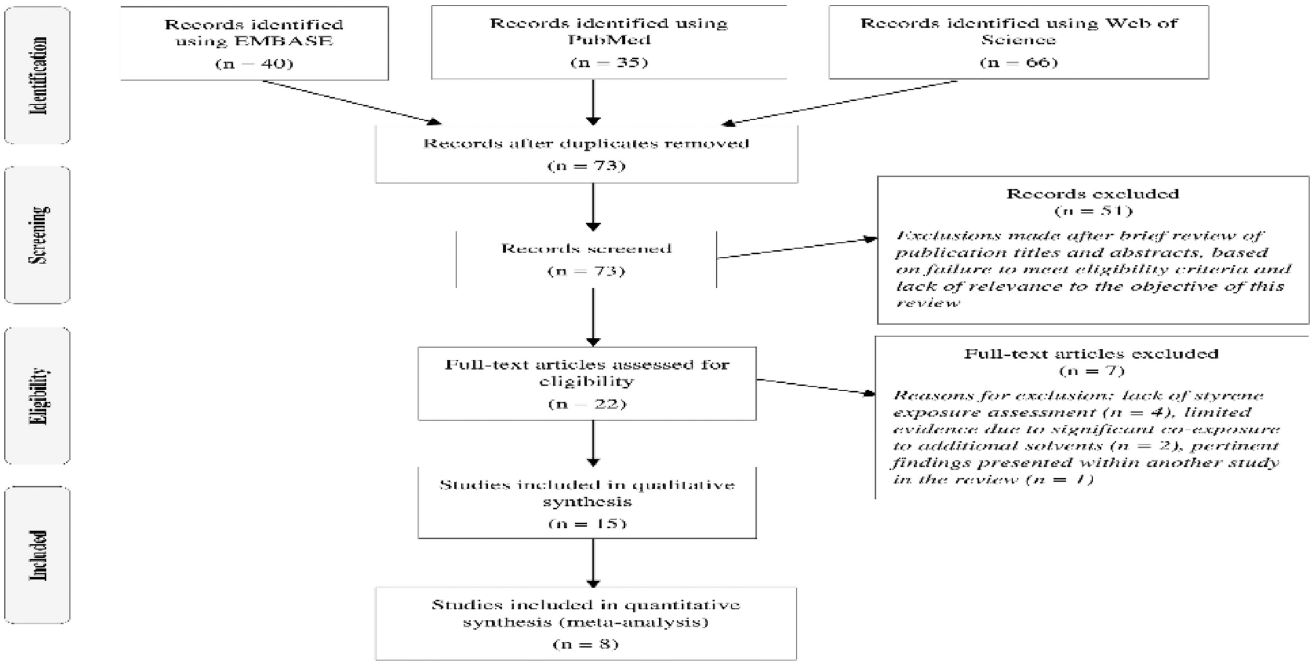

Figure 1.

Flow diagram illustrating the study selection process. Exclusions from qualitative synthesis were conducted in two consecutive steps, screening and eligibility assessment (involving title/abstract review and full-text review, respectively). Separate exclusion criteria were applied to select studies for meta-analysis.

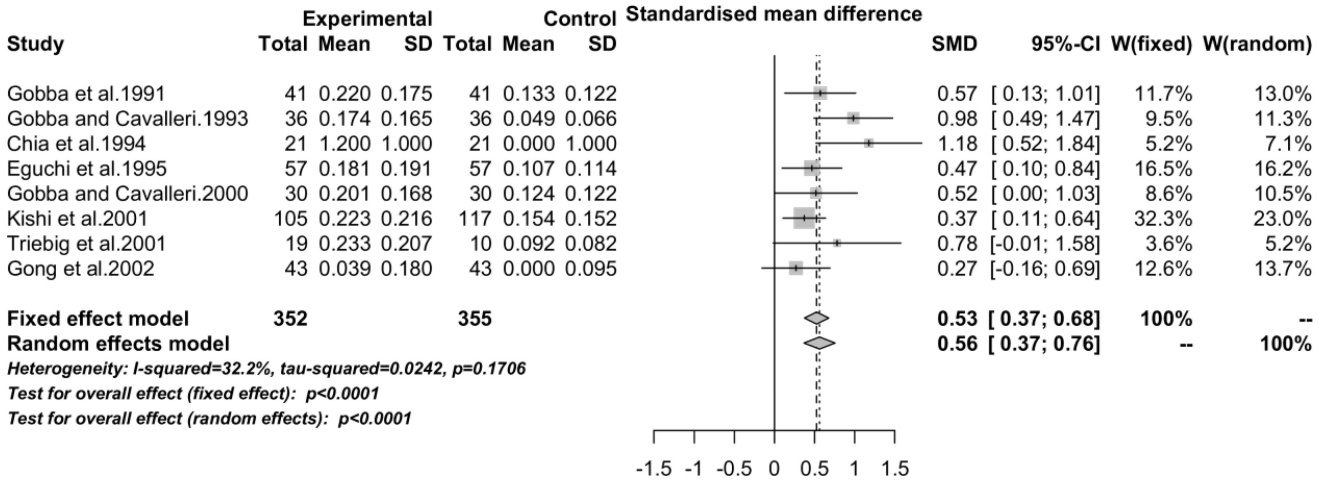

Figure 2.

Forest plot showing the standardized mean differences (with 95% CIs) in log-transformed CCI between exposed and non-exposed samples. Weights are estimated according to random effects and fixed effects models to calculate the overall effect size with its associated 95% CI. Measures of heterogeneity (I^2, τ^2, and the p-value for Cochran's Q test of heterogeneity) are included.

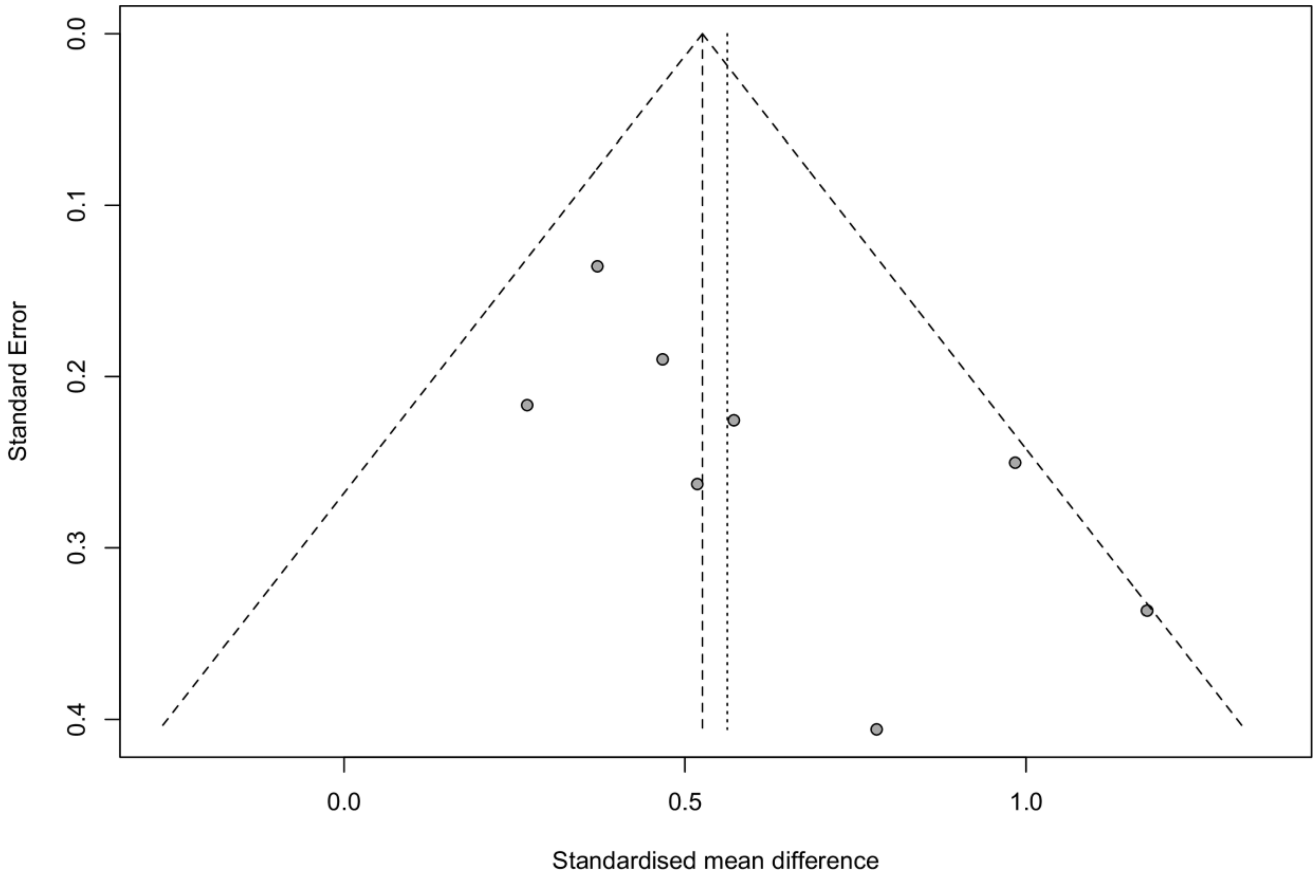

Figure 3.

Funnel plot of study-specific estimates of the standardized mean difference. The vertical dashed line passing through the apex of the funnel represents the effect size estimate derived from fixed effects analysis. The estimated effect size from random effects analysis is also herein depicted as a vertical dotted line.

Table I

Description of studies included in qualitative synthesis.

Study Name	Study Design	Site(s) of Exposure	Sample Size	Participant Characteristics	Styrene Exposure Assessment Methods[a]	Vision Assessment Methods[b]
Gobba et al. (1991)[47]	Cohort	Seven FRP plants (Italy)	n = 130 workers	73 exposed (mean age: 32.0 yrs); 57 non-exposed in rock wool industry (mean age: 37.6 yrs)	Environmental: Personal sampling Biological: End-shift urinary MA and styrene analyses	**D-15d** (CCI), visual acuity exam
Fallas et al. (1992)[44]	Cross-sectional	FRP boat plant (France)	n = 120 male workers	60 exposed (mean age: 29.5 yrs); 60 age-matched referents	Environmental: Area sampling Biological: End-shift urinary MA and PGA analyses, blood styrene	**FM-100** (error score), WHO NCTB psychometric exam
Gobba and Cavalleri (1993)[45]	Cohort	Ten FRP plants (Italy)	n = 202 workers	Group 1: 73 exposed; 57 non-exposed (mean age: 37.6 yrs) Group 2: 36 matched pairs (mean age of non-exposed: 32.0 yrs)	Environmental: Personal sampling Biological: Pre-shift/end-shift urinary MA and styrene analyses, blood styrene analysis	**D-15d** (CCI)
Chia et al (1994)[24]	Cross-sectional	FRP boat plant (Singapore)	n = 42 male workers	21 exposed (mean age: 43.7 ± 5.4 yrs); 21 referent manual workers from same plant (mean age: 50.5 ± 6.4 yrs)	Biological: End-shift urinary MA and PGA analyses	**D-15d** (TCDS), WHO NCTB
Campagna et al. (1995)[42]	Cross-sectional	Three FRP plants (Canada)	n = 81 exposed workers	79 men, 2 women Mean age: 29 ± 8 yrs	Environmental: Personal sampling Biological: End-shift urinary MA analysis	**D-15d** (CCI), Vistech grating charts for VCS, visual acuity exam, visual symptom survey
Eguchi et al (1995)[43]	Cross-sectional	Six FRP plants (Japan)	n = 133 male workers	64 exposed (mean age: 38.0 yrs); 69 non-exposed (mean age: 38.0 yrs)	Environmental: Area sampling Biological:	**D-15d** (CCI)

Study Name	Study Design	Site(s) of Exposure	Sample Size	Participant Characteristics	Styrene Exposure Assessment Methods[a]	Vision Assessment Methods[b]
					End-shift urinary MA analysis	
Gobba et al (1995)[48]	Case report	FRP plant (Italy)	n = 2 male exposed workers	38-yr-old (CC) and 49-yr-old (PL) [c] men; no notable medical problems or past histories	Biological: End-shift urinary styrene and MA analysis	**D-15d** (CCI)
Gobba and Cavalleri (2000)[46]	Cohort	FRP plants (Italy)	n = 138 workers	39 exposed workers with 1 month follow-up (with 39 age-matched referents), and 30 with 12 month follow-up (with 30 age-matched referents)	Environmental: Personal sampling	**D-15d** (CCI)
Castillo et al (2001)[41]	Cohort	FRP plant (Canada)	n = 18 male, exposed workers from Campagna et al. (1995)[42] study	Mean age: 38.3 ± 7.6 yrs Four job categories: laminator/chopper, painter, finisher, other	Environmental: Personal sampling reports collected 1987–1998 (cumulative exp.) Biological: End-shift urinary MA analysis	**D-15d** (CCS), Vistech grating charts for VCS, visual acuity exam, visual symptom survey
Kishi et al. (2001)[51]	Cross-sectional	Seven FRP plants (Japan)	n = 222 male workers	105 exposed (mean age: 37.7 ± 12.9 yrs); 117 non-exposed (mean age: 37.7 ± 11.2 yrs)	Environmental: Area sampling Biological: End-shift urinary MA analysis	**D-15d** (CCI)
Triebig et al (2001)[54]	Cohort	Boat plant (Germany)	n = 33 male workers	22 exposed laminators (median age: 38 yrs); 11 referent non-laminators (median age: 37 yrs)	Biological: End-shift urinary MA and PGA analyses	**D-15d** (CCI), Ichikawa color perception tables, ophthalmic examination
Gong et al. (2002)[49]	Cross-sectional	FRP boat plant (Japan)	n = 126 male workers	57 exposed (mean age: 29.3 ± 4.5 yrs); 69 non-exposed (mean age: 38.3 ± 11.2 yrs; students and employees of several manufacturing plants)	Environmental: Personal sampling of airborne levels Biological: End-shift urinary MA analysis, end-shift urinary analyses for styrene, MA (cumulative and acute exp.), and PGA	**D-15d** (CCI)

Study Name	Study Design	Site(s) of Exposure	Sample Size	Participant Characteristics	Styrene Exposure Assessment Methods[a]	Vision Assessment Methods[b]
Iregren et al (2005)[50]	Cross-sectional	Eleven FRP plants (Sweden)	n = 108 exposed workers	55 low LWAE subjects (mean LWAE: 39.5 mg/m^3) and 53 high LWAE (mean LWAE: 96.1 mg/m^3) Mean age: 40.4 (range: 21–51) and 45.6 (range: 34–65) yrs, respectively	Environmental: Personal sampling Biological: End-shift urinary MA analysis Other: Questionnaire and company records (cumulative exp.)	**D-15d** (Vingrys confusion index)
Seeber et al (2009)[53]	Cohort	Boat plant (Germany)	n = 242 male, exposed workers	According to urinary MA+PGA: 97 low exp. (mean age: 37.9 ± 9.0 yrs), 115 medium exp. (38.4 ± 8.9 yrs), 30 high exp. (38.5 ± 11.2 yrs)	Environmental: Personal sampling reports collected 1982–2006 (cumulative and acute exp.) Biological: End-shift urinary MA and PGA analyses (cumulative and acute exp.), blood styrene analysis	**D-15d** (CCI), Ishihara plates (pre-screening), Vistech grating charts
McCague et al. (2015)[52]	Cross-sectional	FRP windblade plant (US)	n = 352 exposed workers	75.9% males (mean age: 37.5 yrs; range: 19–65 yrs)	Environmental: Area sampling Biological: End-shift urinary MA, PGA, and PHEMA[d] analyses (cumulative and acute exp.)	**D-15d** (CCI), FACT for VCS, visual acuity exam with Rosenbaum vision screener

Abbreviations: CCI, color confusion index; CCS, color confusion score; D-15d, Lanthony D-15 hue desaturated panel; exp., exposure; FACT, functional acuity contrast test; FM-100, Farnsworth-Munsell 100 hue test; FRP, fiberglass-reinforced plastics; LWAE, lifetime weighted average exposure index; MA, mandelic acid; NCTB, Neurobehavioral Core Test Battery; PGA, phenylglyoxylic acid; PHEMA, N-acetyl-S-(1-phenyl-2-hydroxyethyl)-L-cysteine + N-acetyl-S-(2-phenyl-2-hydroxyethyl)-L-cysteine; TCDS, Total Color Difference Score; VCS, visual contrast sensitivity; WHO, World Health Organization; yrs, years.

[a] The methods described below were intended for acute exposure measurement, unless otherwise specified.

[b] The primary color discrimination test employed by the investigators is in bold, with the associated color vision index in parentheses.

[c] CC and PL represent the subjects' initials in the study by Gobba et al.,[48] herein used as identifiers.

[d] PHEMA represents the third major styrene metabolite.

Table II

Exposure characteristics of styrene workers.

Study Name	Mean Styrene & Metabolite Concentrations (Exposed)	Mean Duration of Exposure[a]	Co-Exposure to Other Substances[a]	PPE Use[a]
Gobba et al. (1991)[47]	Environmental (mg/m^3): 69.02 ± 3.6, approx. 16.2 ppm[b,c] Urinary styrene (μg/L): 49.5 ± 44.8 Urinary MA (mg/L): 342.9 ± 425.3	84 months (range: 1-324 months)	--	No mask use (Campagna et al., 1995)[d]
Fallas et al. (1992)[44]	Environmental (ppm): 24.3 (peak of 469) Urinary MA (mg/g cr.): 230 (range: 2-1460) Urinary PGA (mg/g cr.): 57.4 (range: 0.4-421.2)	6.5 yrs (median: 3.75 yrs)	Very low atmospheric concentrations of polyvinyl alcohol and isophtalic resin	Usually wore gloves but no masks
Gobba and Cavalleri (1993)[45]	*Group 2 statistics:* Environmental (mg/m^3): 68.2, approx. 16.0 ppm[b] Urinary styrene (μg /L): 41.4	--	--	--
Chia et al. (1994)[24]	Urinary MA (mg/g cr.): 84.0 (range: 1.3-504.1) Urinary PGA (mg/g cr.): 66.0 (range: 0.3-297.4)	18.8 ± 3.9 yrs	--	Usually wore gloves but no masks
Campagna et al. (1995)[42]	Environmental (mg/m^3): 205.78 ± 262.35, approx. 48.3 ppm[b] Urinary MA (mmol/mmol cr.): 0.36 ± 0.52	5 ± 4 yrs	--	68/81 participants did not use a chemical cartridge mask during exposure assessment Painters and choppers usually wore half-face respirators with charcoal cartridge, little to no PPE use in other occupations (Castillo et al., 2001)[d]
Eguchi et al. (1995)[43]	Environmental (ppm): 18.5 (range: 6.6-36.4) Urinary MA (g/L):	7.0 yrs (range: 0.2-26.8 yrs)	--	--

Study Name	Mean Styrene & Metabolite Concentrations (Exposed)	Mean Duration of Exposure[a]	Co-Exposure to Other Substances[a]	PPE Use[a]
	0.22 ± 0.48			
Gobba et al. (1995)[48]	Urinary styrene (μg/L): 1991: 78.8 (CC); 126.5 (PL)[e] 1992: 107.4 (PL) Urinary MA (mg/g cr.): 1991: 940 (CC); 960 (PL) 1992: 763 (CC); 1001 (PL)	12 and 6 yrs	Acetone (few minutes a day, during tool cleaning)	--
Gobba and Cavalleri (2000)[46]	*1-month follow-up group:* Environmental (ppm): 13[c] (range: 3.1-28)	--	--	--
Castillo et al.(2001)[41]	Urinary MA (mmol/mmol cr): Ranged from 0.036 (finishers) to 0.119 (painters), all individual values lower than 0.25 (equivalent to 25 ppm styrene, according to the authors)	13.3 ± 2.4 yrs	Several with previous history of occupational exposure to varied organic solvents	1999: additional ventilation, training, more regular use and changing of organic vapor cartridges
Kishi et al. (2001)[51]	Environmental (ppm): 21.0 (range: 6.6-36.4) Urinary MA (g/L): 0.21 ± 0.44	6.2 ± 6.2 yrs	--	--
Triebig et al. (2001)[54]	Urinary MA+PGA (mg/g cr.): Phase 1: 472 (median); range: 11-2399 Phase 2: 273 (median); range: 39-910	Median: 4.5 yrs; range: 1-21 yrs	--	--
Gong et al. (2002)[49]	Environmental (ppm): 49.90 ± 35.9 Urinary styrene (μg/L): 138.62 ± 174.08 Urinary MA (g/g cr.): 0.26 ± 0.35 Urinary PGA (g/g cr.): 0.11 ± 0.11	76.7 ± 25.1 months	Atmospheric acetone (mean 49.4 ppm, considerably lower than 500 ppm threshold limit), 2-hexanone, ortho-xylene, meta-xylene, and para-xylene —all below 0.1 ppm (deemed negligible by authors)	Effective use of chemical cartridge masks
Iregren et al. (2005)[50]	Environmental (mg/m^3): 17.5 (low LWAE group; range: 0.3-95.9) and 15.9 (high LWAE group; range: 0.3-66.1), approx. 4.11 and 3.73 ppm, respectively[b] Urinary MA (mmol/g cr.):	Low LWAE group: 12.9 yrs (range: 2-31 yrs) High LWAE: 17.8 yrs (range: 3-39 yrs)	--	--

Study Name	Mean Styrene & Metabolite Concentrations (Exposed)	Mean Duration of Exposure[a]	Co-Exposure to Other Substances[a]	PPE Use[a]
	1.0 (low LWAE; 0.1-2.7) and 0.8 (high LWAE; 0.1-2.1) Lifetime styrene (mg years/m^3): 522 (low LWAE; range: 18-1592) and 1843 (high LWAE; range: 181-4455)			
Seeber et al. (2009)[53]	Blood styrene (μg/L): 54.5 ± 69.3 (low exp.), 61.1 ± 54.4 (medium exp.), 112 ± 109 (high exp.) Urinary MA+PGA (mg/g cr.): 50.8 ± 26.8 (low exp.), 229 ± 102 (medium exp.), 977 ± 414 (high exp.)	Low exp.: 6.3 ± 4.3 yrs (range: 1-26 yrs) Medium exp.: 5.7 ± 3.5 yrs (1-23 yrs) High exp.: 6.3 ± 4.9 yrs (1-26 yrs)	--	Among 94 laminators surveyed, 53% wore helmets with full protection, 33% charcoal filter masks, 13% paper masks
McCague et al. (2015)[52]	Environmental (ppm): 7 ppm (median); range: <1 ppm-51 ppm Urinary MA+PGA (mg/g cr.): 69.5 (range: 0.7-941.0) Cumulative styrene exposure (mg/g cr.): 3945 (range: 10.7-69800)	4.8 yrs (range: <1-22.7 yrs)	None identified by the authors upon evaluation	PPE use significant but variable

Abbreviations: approx., approximately; cr., creatinine; exp., exposure; LWAE, lifetime weighted average exposure index; MA, mandelic acid; PGA, phenylglyoxylic acid; PPE, personal protective equipment; yrs, years

[a] Not all entries within the column could be filled, mainly due to incomplete reporting; '--' denotes that the authors did not address this variable in text.

[b] Conversion factor 1 ppm = 4.26 mg/m^3 (at 25 °C) was used to approximate airborne styrene levels in parts per million.[84]

[c] This value was reported as the geometric mean, not the arithmetic mean.

[d] Information about a variable was occasionally omitted in the original text but provided by later studies; names of such studies are included in parentheses.

[e] CC and PL represent the subjects' initials in the study by Gobba et al.,[48] herein used as identifiers.

Table III

Principal findings from assessments of color discrimination.

Study Name	Primary Outcomes (Comparisons Between Exposed and Unexposed Groups)	Color Vision Loss Characteristics [a]
Gobba et al (1991)[47]	- Significantly greater mean CCI in styrene-exposed workers (1.265 ± 0.223 vs. 1.151 ± 0.141), based on age-matched comparisons - No recovery of color vision following a one-month holiday (subset of 20 subjects)	Mostly B–Y, with a few B–Y/R-G
Fallas et al. (1992)[44]	- No significant difference in error scores on the Farnsworth-Munsell 100 hue test, but in the exposed group, higher proportion of subjects with errors in the B–Y and/or R–G ranges (32/60 vs. 20/60)	B-Y, R–G, or both; deficits implied to be subclinical in title of study, though no in-text mention
Gobba and Cavalleri (1993)[45]	- First group of subjects (n = 130): significant positive correlation between styrene exposure indices and color vision impairment - Second group of subjects (n = 72): mean CCI of 1.206 ± 0.2 among exposed workers, significantly higher than the 1.053 ± 0.07 value among non-exposed referents - In an analysis of 39 workers, no significant recovery of color vision after a one-month break from exposure	Mostly B–Y, a few R–G
Chia et al (1994)[24]	- Environmental styrene exposure of ~6.0 ppm, extrapolated from regression equation, with mean urinary MA value of 84 mg/g cr - Significantly higher geometric mean TCDS (poorer performance) among exposed subjects than non-exposed (164.0 ± 0.04 vs. 131.8 ± 0.04)	Mostly B–Y and R–G
Campagna et al (1995)[42]	- Significant positive correlation between airborne styrene concentration and urinary MA excretion—only when non-mask users were excluded - After adjustments for age and alcohol: positive correlation between CCI (both mean and eye-specific) and styrene concentration (both environmental and biological)—only when analysis was limited to non-mask users	25/81 (30.9%) with acquired dyschromatopsia; 22 B–Y, 1 R–G, 2 mixed, 6 without specific axis
Eguchi et al (1995)[43]	- Comparing between 57 age-matched pairs: significantly higher CCI among exposed workers than non-exposed (1.220 ± 0.235 vs 1.120 ± 0.128) - Significantly higher CCI values among exposed subjects with urinary MA concentrations > 0.42 g/L than low-exposure subjects (<0.42 g/L) - After adjustment for several variables: significant positive correlation between urinary MA concentration and CCI	Mostly B–Y, a few complex, none R–G; subclinical
Gobba et al (1995)[48]	- CC and PL[b] exhibited levels of exposure—urinary styrene and MA—similar to (<50% difference) the corresponding ACGIH limits at the time (80 μg/L and 800 mg/g cr., respectively) - Subclinical impairment in B–Y chromatic discrimination in both CC and PL (mean CCI scores in 1991 1.34 and 2.10, respectively)	B-Y; subclinical
Gobba and Cavalleri (2000)[46]	- Significantly greater color vision impairment among first group of exposed workers (39/69) relative to non-exposed (CCI 1.24 ± 0.21 vs. 1.14 ± 0.14) - No significant recovery among said workers after 1-month interruption in exposure - Second group of 30 workers, followed after 12 months: significant progression of color vision loss only among the 10/30 workers whose exposure had increased	--
Castillo et al (2001)[41]	- One year following Campagna et al. (1995)[42] study (conducted in 1990 by the same group), systemic measures implemented to reduce styrene exposure in	--

Study Name	Primary Outcomes (Comparisons Between Exposed and Unexposed Groups)	Color Vision Loss Characteristics [a]
	one of the plants; significant decrease in CCS over subsequent 2-yr span of reduced exposure - ~2-fold decrease in mean urinary MA over a nine-year period for 18 workers from this plant; no similar improvement in CCS (between 1992 and 1999)	
Kishi et al (2001)[51]	- Comparisons of 87 age-matched pairs: CCI of exposed workers significantly higher than that of non-exposed - 3 subgroups (exposed) formed according to urinary MA excretion: groups A, B, and C (<0.1 g/L, 0.1–0.2 g/L, and >0.2 g/L, respectively) - Mean CCI values higher than those of age-matched referents only for groups B and C; 0.1–0.2 g/L urinary MA concentration (~10–20 ppm styrene exposure) suggested as threshold for styrene-induced dyschromatopsia	Mostly B–Y; subclinical
Triebig et al (2001)[54]	- Measurements obtained during two phases, ten months apart (reduction of exposure in shipyard immediately after Phase 1 due to improved ventilation measures) - Significant drop in exposed group's (laminators') mean CCI following a four-week vacation, in both phases - In Phase 1, significantly higher CCI values among laminators at the end of the work week (relative to non-exposed); in Phase 2, no significant difference - 20 ppm proposed as a threshold value - 18.5 ppm mean styrene level, according to Paramei et al. [2004]	Both B–Y and R–G, often overlapping; subclinical and not consciously perceived
Gong et al (2002)[49]	- Mean concentration of 49.90 ppm, but effective environmental styrene exposure of 17 ppm extrapolated by authors - Comparison of 43 age-matched pairs: significantly higher mean CCI in exposed group - < 10 ppm concentrations deemed sufficient to impair color vision. - Higher mean CCI for subjects with peak urinary MA greater than 0.85 g/g (~50 ppm) within the past eight years than for subjects below this peak exposure level - No significant correlation between CCI and CEI (measure of long-term exposure)	--
Iregren et al (2005)[50]	- 108 subjects divided into low exposure (≤ 57 mg LWAE, n = 55) and high exposure (>57 mg LWAE, n =53) groups; LWAE calculated based on past records, as measure of average styrene exposure - Slight positive correlations between LWAE and confusion index, also total error (both indicators of color vision impairment) - Significantly higher total error (9.0 vs. 7.6) and higher confusion index (1.6 vs. 1.3) in the high exposure group. - No significant correlation between peak exposure and confusion index	--
Seeber et al (2009)[53]	- CCI not associated with either acute (current) or cumulative exposure to styrene - No significantly increase in susceptibility to acquired dyschromatopsia after 40 ppm acute styrene exposure (≥501 mg/g cr.) or after max cumulative exposure measurement (27 ppm over 15 years, extrapolated using data from 17-subject subgroup)	Red-green color vision deficiency cited as exclusion criterion (n = 21 excluded)
McCague et al (2015)[52]	- Number of B–Y color vision deficits significantly higher among the windblade workers was higher than expected among general Western population (based on previous literature)	Elevated B–Y and complex color vision abnormality in exposed workers, while normal prevalence of R–G abnormality

Study Name	Primary Outcomes (Comparisons Between Exposed and Unexposed Groups)	Color Vision Loss Characteristics [a]
	- No association between styrene exposure (either acute or cumulative) and abnormal color vision.	

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; B–Y, blue-yellow; CCI, color confusion index; CCS, color confusion score; CEI, cumulative exposure index; cr., creatinine; LWAE, lifetime weighted average exposure index; MA, mandelic acid; PGA, phenylglyoxylic acid; R–G, red-green; TCDS, Total Color Difference Score.

[a] Not all entries within the column could be filled, mainly due to incomplete reporting; '--' denotes that the authors did not address this variable in text.

[b] CC and PL represent the subjects' initials in the study by Gobba et al.,[48] herein used as identifiers.