

## Original Contribution

# Acquired Color Vision Defects and Hexane Exposure: A Study of San Francisco Bay Area Automotive Mechanics

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Occupational exposure to solvents, including *n*-hexane, has been associated with acquired color vision defects. Blue-yellow defects are most common and may be due to neurotoxicity or retinal damage. Acetone may potentiate the neurotoxicity of *n*-hexane. We present results on nonhexane solvent and hexane exposure and color vision from a cross-sectional study of 835 automotive repair workers in the San Francisco Bay Area, California (2007–2013). Cumulative exposure was estimated from self-reported work history, and color vision was assessed using the Lanthony desaturated D-15 panel test. Log-binomial regression was used to estimate prevalence ratios for color vision defects. Acquired color vision defects were present in 29% of participants, of which 70% were blue-yellow. Elevated prevalence ratios were found for nonhexane solvent exposure, with a maximum of 1.31 (95% confidence interval (CI): 0.86, 2.00) for blue-yellow. Among participants aged  $\leq 50$  years, the prevalence ratio for blue-yellow defects was 2.17 (95% CI: 1.03, 4.56) in the highest quartile of nonhexane solvent exposure and 1.62 (95% CI: 0.97, 2.72) in the highest category of exposure to hexane with acetone coexposure. Cumulative exposures to hexane and nonhexane solvents in the highest exposure categories were associated with elevated prevalence ratios for color vision defects in younger participants.

color perception; color vision; color vision defects; *n*-hexane; occupational exposure; solvents

Abbreviations: BASS, Bay Area Solvent Study; CI, confidence interval; VOC, volatile organic compounds.

Solvent-based cleaning products are used in the automobile repair industry to remove oil and grease from auto parts. Aerosol spray cans are the most commonly used type of application. Over 12,000 metric tons of automotive cleaning aerosol solvent products were sold in the state of California in 1997 (1). During 1989–2002, some products were formulated with 25%–90% commercial hexane, and some contained both hexane and acetone (1). By 2002, hexane had been phased out of all commercial products (2). Other solvents commonly included were toluene, methyl ethyl ketone, and xylenes. The *n*-hexane isomer is not quantified in individual commercial products, although commercial hexane typically contains 20%–80% *n*-hexane (1).

Exposure to *n*-hexane has been shown to cause neurotoxicity in occupational settings, with case reports of neuropathy appearing in the medical literature as early as 1964 (3). Toxicity

is believed to occur via the metabolite 2,5-hexanedione, which binds with proteins to form cross-links between neurofilaments in both the central and peripheral nervous systems (4–7). Animal studies indicate that the neurotoxic action of *n*-hexane may be potentiated by coexposure to acetone, possibly by slowing the elimination of 2,5-hexanedione from the body (8–10). A study of workers exposed to both hexane and acetone showed increased urinary 2,5-hexanedione levels in comparison with exposure to hexane alone (11). Several studies have found associations between exposure to hexane and acquired color vision defects, although cumulative exposure was not well characterized (6, 12, 13).

Color vision defects may be congenital or acquired, and are commonly classified as red-green, blue-yellow, or nonspecific. Hereditary color vision defects are caused by missing or anomalous photoreceptors, whereas acquired color vision

defects are caused by damage to the retina or optic nerve (14). Hereditary red-green color blindness occurs in approximately 10% of males and 0.5% of females; hereditary blue-yellow color blindness is rare, occurring in 0.0001% of the population (14). Acquired color vision defects, especially blue-yellow color confusion, are associated with increasing age, eye diseases such as cataract and glaucoma, alcoholism, and exposure to solvents (14, 15).

The Bay Area Solvent Study (BASS) was initiated in 2007 to investigate possible associations between occupational exposure to *n*-hexane and a variety of health outcomes, including acquired color vision defects, among automotive mechanics employed in the San Francisco Bay Area of California. The sentinel event was a 1998 case report of an automotive repair worker diagnosed with peripheral neuropathy at an occupational health clinic in San Francisco. He reported using 1–9 cans of an aerosol solvent product containing hexane per day (16). A small follow-up study of the exposure and health status of 6 auto repair workers in a nearby repair shop revealed that 5 had symptoms of peripheral neuropathy and 3 had detectable urinary levels of 2,5-hexanedione (16). Two of these workers had sensory or nerve conduction abnormalities, and color vision defects, primarily blue-yellow color confusion, were present in all subjects (16). While color vision defects are not clinically significant outcomes, they may be an early marker of *n*-hexane neurotoxicity (17, 18).

The objective of this analysis was to investigate possible associations between past exposure to nonhexane solvents and to hexane with or without coexposure to acetone and persistent risk of acquired color vision defects, particularly blue-yellow defects, among active and retired San Francisco Bay Area auto mechanics.

## METHODS

### Study population

BASS was a cross-sectional study of 835 participants in the San Francisco Bay Area who had worked as an automotive technician (mechanic) at any point during the period in which hexane was present in aerosol automotive cleaning products. Eligible workers were identified from the records of a union representing mechanics employed at auto dealerships. Many workers had been employed at more than 1 automotive repair shop, for a total of 1,946 shops. All male workers or retirees who were employed at any time during 1989–2002 (the time period in which hexane was included in solvent cleaners) who were younger than age 60 years and still lived in the Bay Area were eligible. Since few women were employed in the industry at the time of hexane use, females were not included. The restriction to current Bay Area residents was necessary due to in-person data collection.

Following telephone contact to recruit and confirm eligibility, appointments were made for participants to visit a clinic staffed by trained study personnel. For some participants a mobile clinic was used. All clinic visits occurred between 2008 and 2011. At the clinic, participants responded to a questionnaire that obtained demographic, health, and work history information and participated in clinical assessments, including color vision testing. The work history component identified the frequency and duration of

any tasks performed that involved the use of solvents and the specific products and solvents used. A booklet containing pictures of various products that had been available over the last 2 decades was used as a memory aid.

After identifying 4,186 potentially eligible workers from union records on the basis of job title, age, and sex, we were able to contact 2,848 (68.0%) by telephone or postal mail. Of these, 1,765 were eligible, based on residence, age, job duties, and active work during 1989–2002. A total of 835 eligible workers participated in the study (47.6% participation rate). The most common reasons for refusal were lack of interest (38.0%) and being too busy (19.9%). Among BASS participants, 18 (2.2%) had missing hexane exposure data and were excluded from the current analysis. Of the remaining 817 participants, 53 (6.5%) with congenital color vision defects and 10 (1.2%) who were unable to complete the full color vision assessment were excluded, resulting in a total of 754 participants. The 81 participants who were excluded were similar to those included in all respects, except that they were less likely to be working as a mechanic at the time of the study. For the analysis of blue-yellow color vision defects, participants with acquired nonspecific or red-green defects were excluded. This left a final total of 689 for the analysis of blue-yellow color vision defects.

### Exposure assessment

Total exposure to volatile organic compounds (VOC) was calculated by combining task-based VOC concentrations with participants' reports of cleaning tasks they had performed, the daily durations of those tasks, and the types and brands of solvents used, as well as quantities used over their work history. Task-based VOC concentrations were obtained from data collected in San Francisco Bay Area automotive repair shops by Wilson et al. (1). Based on these data, each combination of task and application method (aerosol can, pump spray, solvent tank, etc.) was assigned a concentration of VOC in the breathing zone, which was multiplied by the reported time spent performing that task per day. The 8-hour (shift) time-weighted average was calculated in  $\text{mg}/\text{m}^3$  by multiplying the task-based VOC concentration by the minutes per shift spent on a given task, and summing across all tasks performed during the shift. Far-field exposure for shift time not spent on a cleaning task and inhalation equivalent exposure due to dermal contact were added to the task-based exposures.

Exposure to hexane was calculated by applying the percentage of hexane in a product, obtained from Material Safety Data Sheets (19) for each product, to the total VOC exposure. Only aerosol products contained hexane, and these products evaporated completely; therefore, the fraction of hexane in the product was the same as that in the breathing zone. Acetone exposure was not quantified but was defined as being present or absent in any hexane formulation. Hexane was subtracted from total cumulative solvent exposure to obtain a quantitative estimate of nonhexane solvent exposure.

### Color vision

Color vision was assessed with the Lanthony desaturated D-15 panel test (20, 21). The test is performed by arranging

**Table 1.** Vision Characteristics of 817 Participants With Complete Data on Exposure to Hexane and 388 Participants Aged 50 Years or Less at the Time of Study Participation, Bay Area Solvent Study, 2007–2013

Vision Characteristic	All Participants			Participants Aged ≤50 Years		
	No.	%	Median (IQR)	No.	%	Median (IQR)
Eye disease <sup>a</sup>						
Cataract	35	4.3		6	1.5	
Glaucoma	8	1.0		2	0.5	
Retinal disease	8	1.0		3	0.8	
Exclusions from color vision assay						
Congenital color vision defect	53	6.5		25	6.4	
Did not complete test <sup>b</sup>	10	1.2		4	1.0	
Lanthony color vision defect <sup>c</sup>						
Normal	534	70.8		278	77.4	
Blue-yellow	155	20.6		60	16.7	
Nonspecific	63	8.4		20	5.6	
Red-green	2	0.3		1	0.3	
Total (any defect)	220	29.2		81	22.6	
Lanthony color confusion score <sup>c</sup>						
Trial 1			11.5 (0–25.4)			8.7 (0–24.7)
Trial 2			8.4 (0–23.6)			6.0 (0–17.9)
Mean score			10.4 (3.4–24.6)			8.0 (0–19.4)
Score difference (trial 1 – trial 2)			0 (–6.0 to 9.4)			0 (–4.4–8.7)

Abbreviation: IQR, interquartile range.

<sup>a</sup> Participant report of physician-diagnosed eye disease.

<sup>b</sup> Unable to perform test or test conditions were inappropriate.

<sup>c</sup> Among 754 participants in total and 359 participants aged ≤50 years who completed the Lanthony desaturated D-15 panel test (20).

15 randomly ordered colored caps by color, starting from a fixed reference cap. Incorrect ordering of the caps indicates imperfect color vision. Quantitative scoring systems are used to assess the severity of color confusion, as well as to identify blue-yellow, red-green, or nonspecific color vision defects, based on the participant's arrangement of the caps.

All tests were administered binocularly, with participants wearing their habitual corrective lenses; all participants had sufficient visual acuity and contrast sensitivity to perform the tests. Participants were then screened for congenital color vision defects using Ishihara plates, and those without congenital color vision defects were administered 1 trial of the Adams desaturated D-15 panel test (similar to the Lanthony test but more saturated and therefore easier to complete) as a demonstration and then 2 trials of the Lanthony test. Lanthony test results were scored by an optometrist blinded to participants' exposure status using the method described by Adams and Haegerstrom-Portnoy (22) to calculate continuous color confusion score, a measure of severity (a higher score indicates worse color vision).

Reproducibility between Lanthony trials was measured by the difference between scores on the first and second trials. Participants with a mean color confusion score greater than 20 from the 2 Lanthony trials were classified as having a color vision defect. For participants with a color confusion score greater than 20 on the second trial, the Vingrys and

King-Smith method was used to classify the type of color defect as red-green, blue-yellow, or nonspecific (23). Any color vision defect and blue-yellow defects were considered separately in statistical analyses.

### Statistical methods

Cumulative exposures to nonhexane solvents, hexane, and hexane in the presence of acetone were calculated in mg/m<sup>3</sup>-year for each participant over his work history up to the date of study participation. For participants no longer working as auto mechanics, cumulative exposure was assumed to have remained constant after their last automotive repair exposure. Blue-yellow color vision defects and any color vision defects were treated as binary outcomes. Age was strongly associated with both color confusion and cumulative exposure and was therefore included in all models to adjust for confounding. Analyses were performed using all participants and then repeated in participants aged 50 years or younger; because blue-yellow color vision deteriorates due to aging beginning at approximately age 50 years, stratification was performed to reduce bias resulting from inclusion of color vision defects caused by age alone (15, 24). Based on an a-priori analysis plan informed by literature on acquired color vision defects, we considered adjustment for confounding by race, cigarette smoking, alcohol consumption, and history

**Table 2.** Demographic Characteristics of 754 Total Participants and 359 Participants Aged ≤50 Years Who Completed the Lanthony Desaturated D-15 Panel Test, Bay Area Solvent Study, 2007–2013

Characteristic	All Participants			Participants Aged ≤50 Years		
	No.	%	Median (IQR)	No.	%	Median (IQR)
Working as auto mechanic at time of assay						
Yes	350	46.4		178	49.6	
No	404	53.6		181	50.4	
Race/ethnicity						
Non-Hispanic white	476	63.1		215	59.9	
Hispanic white	114	15.1		67	18.7	
Asian	70	9.3		34	9.5	
Black	22	2.9		7	1.9	
Other or multiracial	72	9.5		36	10.0	
Smoking status <sup>a</sup>						
Current smoker	222	29.6		92	25.6	
Former smoker	115	15.3		1	15.6	
Never smoker	414	55.1		211	58.8	
Alcohol consumption (typical week), drinks/week <sup>b</sup>						
0	176	23.4		88	24.5	
≤7	341	45.3		166	46.2	
>7	235	31.3		105	29.3	
Education						
High school or less	254	33.7		122	34.0	
Some college	326	43.2		152	42.3	
College degree or more	174	23.1		85	23.7	
Year of birth			1960 (1955–1965)			1965 (1962–1969)
Year of hire			1982 (1977–1988)			1987 (1983–1991)
Age at interview, years			51 (46–56)			45 (41–48)
Duration of active work, years			26 (19–31)			21 (15–26)
Cumulative solvent exposure, mg/m <sup>3</sup> -year						
Nonhexane solvents			1,380.9 (675.7–2,511.1)			1,042.0 (558.2–1,916.3)
Hexane <sup>c</sup>			33.7 (10.6–95.3)			39.6 (11.3–113.8)
Hexane plus acetone <sup>d</sup>			17.7 (5.7–41.4)			16.2 (4.7–44.8)

Abbreviation: IQR, interquartile range.

<sup>a</sup> A total of 751 participants responded to the question on smoking status.

<sup>b</sup> A total of 752 participants responded to the question on alcohol consumption.

<sup>c</sup> Among 400 total participants and 209 participants aged ≤50 years exposed to hexane.

<sup>d</sup> Among 315 total participants and 160 participants aged ≤50 years exposed to hexane in the presence of acetone.

of concussion or head injury; covariates were retained in the model if they resulted in a >10% change in the solvent effect estimate. Eye diseases and diabetes, as intermediate variables rather than confounders, were not included in models.

Prevalence ratios for the risk of color vision defects according to exposure to nonhexane solvents, hexane, and hexane in the presence of acetone were estimated using log-binomial regression (25). Total solvent exposure was divided into quartiles based on the 689 participants in the blue-yellow analysis, with the first quartile used as the reference group; and hexane with and without acetone coexposure was divided at the exposed

participants' median value, with participants unexposed to hexane designated the reference group. Participants exposed to hexane but not to hexane in the presence of acetone were excluded from analyses of hexane exposure with acetone (85 participants (11.3%)). Effect estimates with a 95% confidence interval excluding 1 were considered statistically significant.

Statistical analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). The study protocol was approved by the Committee for Protection of Human Subjects at the University of California, Berkeley. Written

informed consent was obtained from all participants before participation.

## RESULTS

### Study population

Color vision and demographic characteristics of the BASS participants are presented in Tables 1 and 2. Physician-diagnosed eye disease was reported by 6.2% of participants, the most common condition being cataract. Of the 754 participants completing the Lanthony test, 359 (47.6%) were  $\leq 50$  years of age. The prevalence of any acquired color vision defects among younger participants was 22.6%, and 16.7% had blue-yellow defects.

Most participants (53.6%) were no longer working as a mechanic at the time of the study (Table 2). The majority of participants were non-Hispanic whites, drank alcohol in moderation, had never smoked cigarettes, and had at least some college education. All participants were exposed to solvents, and 53.1% were exposed to hexane. Fewer participants were exposed to hexane in the presence of acetone, and among them, cumulative hexane exposures were lower.

On average, Lanthony scores were lower on the second trial (Table 1), indicating improvement. However, although 46.2% of participants improved, 32.0% got worse, suggesting no con-

sistent learning effect. The median difference between trials was 0, with a narrower interquartile range among younger participants (interquartile range,  $-4.4$  to  $8.7$ ) as compared with an interquartile range of  $-6.0$  to  $9.4$  among all participants, indicating better reproducibility among younger participants.

### Blue-yellow color vision defects

Continuous age in years was the only covariate that contributed to the exposure-response model. We observed elevated prevalence ratios for blue-yellow defects for all quartiles of nonhexane solvent exposure, although all 95% confidence intervals included 1. When the analysis was restricted to participants aged 50 years or younger, a monotonic increase in prevalence ratios from 1.75 (95% confidence interval (CI): 0.89, 3.46) in the second quartile to 2.17 (95% CI: 1.03, 4.56) in the fourth quartile was observed (Table 3). There was no association with exposure to hexane at any level. For hexane in the presence of acetone, however, an elevated prevalence ratio of 1.15 (95% CI: 0.84, 1.57) in the most highly exposed group was seen among all participants, which increased to 1.62 (95% CI: 0.97, 2.72) when results were restricted to younger participants. A statistically significant protective association was seen in the first exposure quartile for hexane in the presence of acetone. Among all participants, age was associated with statistically significantly

**Table 3.** Categorical Exposure-Response Relationships Between Blue-Yellow Color Vision Defects and Cumulative Exposure to Nonhexane Solvents, Hexane, and Hexane in the Presence of Acetone (Log-Binomial Regression) Among Participants Completing the Lanthony Desaturated D-15 Panel Test, Bay Area Solvent Study, 2007–2013

Model and Exposure Category	All Participants			Participants Aged $\leq 50$ Years		
	No. of Cases	PR	95% CI	No. of Cases	PR	95% CI
Nonhexane solvents						
Exposure, $\text{mg}/\text{m}^3\text{-year}^a$						
0–670.9	155	1.00	Referent	60	1.00	Referent
>670.9–1,364.3	29	1.25	0.81, 1.92	12	1.75	0.89, 3.46
>1,364.3–2,470.7	39	1.16	0.75, 1.78	18	1.98	0.98, 4.02
>2,470.7	40	1.31	0.86, 2.00	17	2.17	1.03, 4.56
Age, years	47	1.04	1.02, 1.07	13	1.02	0.96, 1.08
Hexane						
Exposure, $\text{mg}/\text{m}^3\text{-year}^a$						
Unexposed to hexane	155	1.00	Referent	60	1.00	Referent
>0–33.7	81	0.73	0.51, 1.04	25	0.77	0.41, 1.42
>33.7	33	0.94	0.68, 1.29	13	1.26	0.76, 2.11
Age, years	41	1.05	1.02, 1.07	22	1.04	0.99, 1.10
Hexane + acetone						
Exposure, $\text{mg}/\text{m}^3\text{-year}^b$						
Unexposed to hexane	145	1.00	Referent	56	1.00	Referent
>0–17.1	81	0.65	0.43, 0.99	25	0.84	0.45, 1.57
>17.1	23	1.15	0.84, 1.57	11	1.62	0.97, 2.72
Age, years	41	1.04	1.02, 1.07	20	1.04	0.99, 1.10

Abbreviations: CI, confidence interval; PR, prevalence ratio.

<sup>a</sup> There were 689 total participants and 338 participants aged  $\leq 50$  years.

<sup>b</sup> There were 607 total participants and 291 participants aged  $\leq 50$  years.

**Table 4.** Categorical Exposure-Response Relationships Between Any Color Vision Defect and Cumulative Exposure to Nonhexane Solvents, Hexane, and Hexane in the Presence of Acetone (Log-Binomial Regression) Among Participants Completing the Lanthony Desaturated D-15 Panel Test, Bay Area Solvent Study, 2007–2013

Model and Exposure Category	All Participants			Participants Aged ≤50 Years		
	No. of Cases	PR	95% CI	No. of Cases	PR	95% CI
Nonhexane solvents						
Exposure, mg/m <sup>3</sup> -year <sup>a</sup>						
0–670.9	236	1.00	Referent	88	1.00	Referent
>670.9–1,364.3	45	1.19	0.85, 1.65	19	1.42	0.83, 2.43
>1,364.3–2,470.7	57	1.18	0.85, 1.64	24	1.73	1.02, 2.94
>2,470.7	62	1.28	0.93, 1.76	27	1.72	0.97, 3.08
Age, years	72	1.04	1.02, 1.06	18	1.04	0.99, 1.09
Hexane						
Exposure, mg/m <sup>3</sup> -year <sup>a</sup>						
Unexposed to hexane	236	1.00	Referent	88	1.00	Referent
>0–33.7	125	0.81	0.62, 1.05	35	1.01	0.64, 1.58
>33.7	56	0.82	0.63, 1.07	24	1.14	0.75, 1.74
Age, years	55	1.04	1.02, 1.06	29	1.06	1.01, 1.10
Hexane + acetone						
Exposure, mg/m <sup>3</sup> -year <sup>b</sup>						
Unexposed to hexane	219	1.00	Referent	79	1.00	Referent
>0–17.1	125	0.77	0.58, 1.04	35	1.05	0.66, 1.67
>17.1	41	0.94	0.73, 1.22	21	1.33	0.86, 2.06
Age, years	53	1.04	1.02, 1.06	23	1.06	1.02, 1.11

Abbreviations: CI, confidence interval; PR, prevalence ratio.

<sup>a</sup> There were 754 total participants and 359 participants aged ≤50 years.

<sup>b</sup> There were 669 total participants and 310 participants aged ≤50 years.

increased prevalence ratios, but in participants aged ≤50 years, all prevalence ratios for age were null.

### Any color vision defect

As with the models for blue-yellow defects, continuous age was the only covariate included in the exposure-response models. Among all participants, a nonsignificantly elevated prevalence ratio was observed for any color vision defect at all levels of nonhexane solvent exposure, with the highest risk in the fourth quartile (prevalence ratio = 1.28, 95% CI: 0.93, 1.76) (Table 4). In participants aged 50 years or younger, exposure to nonhexane solvents was associated with any color vision defect, with prevalence ratios of 1.73 (95% CI: 1.02, 2.94) in the third quartile and 1.72 (95% CI: 0.97, 3.08) in the fourth quartile. For all exposures to hexane, with or without acetone coexposure, the effect estimates pointed in a protective direction, with all 95% confidence intervals including the null. In younger participants, exposure to hexane with or without acetone was associated with an elevated prevalence ratio for any color vision defect, although the 95% confidence interval included 1.

### DISCUSSION

To our knowledge, these analyses represent the first epidemiologic study of hexane exposure and acquired color vision de-

fects with quantitative exposure assessment, and one of the few published studies on this exposure-response relationship in humans. Our findings provide evidence of an association between nonhexane solvent exposure and blue-yellow color vision defects, as well as all color vision defects, in male automotive workers aged ≤50 years. While no associations with hexane exposure were statistically significant, elevated prevalence ratios in the more highly exposed younger participants are suggestive of an association. A 2003 literature review by Gobba and Cavalleri (26) found evidence of associations between color vision defects and exposure to styrene, perchloroethylene, and toluene, with less evidence for hexane and mixtures of solvents. While acquired blue-yellow defects are generally associated with damage to the retina (27), there is also evidence that the mechanism of solvent-induced color vision defects could be neurological (28, 29). Color vision defects associated with occupational solvent exposures are most commonly of the blue-yellow type, with blue-yellow mixed with red-green occurring more rarely and with higher exposures (26).

A key reason for carrying out this study was to explore the potential of using acquired color vision defects as a sensitive early marker of *n*-hexane neurotoxicity (17, 18). Color vision defects and maculopathy were noted in 2 of 28 subjects in an investigation of a polyneuropathy outbreak among hexane-exposed Taiwanese printing press workers, with the defects persisting after 4 years of follow-up (30). A study of 15 subjects

exposed to hexane concentrations in air that were typically below 1,765 mg/m<sup>3</sup>, with peaks as high as 10,500 mg/m<sup>3</sup>, found that 12 had a color vision defect (13). A 2002 study of 26 workers exposed to hexane and 50 controls showed worse overall color discrimination among the exposed, with blue-yellow and red-green defects present (13). In our study, the presence of acetone in some solvent products provided an opportunity to examine its potentially synergistic effect on hexane toxicity (30). While no statistically significant associations were seen in younger participants for blue-yellow defects and hexane exposure, prevalence ratios in the more highly exposed participants were elevated, with stronger associations for hexane with acetone coexposure despite lower hexane concentrations.

Elevated prevalence ratios for blue-yellow defects, as well as for any defect, were seen in the 2 highest exposure quartiles of nonhexane solvent exposure; exposure concentrations for nonhexane solvents were at least an order of magnitude above those for hexane. Evidence in the current literature for an association between color vision defects and exposure to mixed solvents is inconclusive but generally reflects a positive association (26, 31, 32). The solvents used by our participants were mixed products containing toluene, xylenes, and other solvents, in addition to hexane and acetone. Combining data from available publications, Gobba and Cavalleri found a statistically significant correlation between cumulative toluene exposure and color confusion (26). Xylene is another component of automotive cleaning solvents for which there is evidence of an association with color vision defects: A 2013 study by Lee et al. (33) found an association between the xylene metabolite methylhippuric acid and blue-yellow defects and color confusion in shipyard workers.

There are 2 factors that might have attenuated the observed associations. First, there were 5–13 years between cessation of hexane exposure and color vision assessment. No previous studies of hexane exposure and color vision have reported the long-term persistence of color vision defects following exposure cessation, and little has been published on the reversibility of color vision defects associated with other solvents (26). There is evidence, however, that hexane-induced neuropathy is reversible, suggesting that acquired color vision defects might also be reversible following cessation of exposure (8, 30). Second, the concentrations of hexane exposure were low relative to the existing regulatory limits—the California Occupational Safety and Health Administration's current permissible exposure limit is 176 mg/m<sup>3</sup> as an 8-hour time-weighted average. If a worker were exposed at the permissible exposure limit for the full 13 years that hexane was in use, he would accrue 2,340 mg/m<sup>3</sup>-years of cumulative exposure; in comparison, the 99th percentile of hexane exposure in BASS is 470 mg/m<sup>3</sup>-years. Hexane exposures in the presence of acetone were even lower (99th percentile, 185 mg/m<sup>3</sup>-years); a 1997 California regulation capped the VOC content of automotive solvents at 50%, and manufacturers used acetone as a replacement for hexane and other VOCs (2).

Because of the cross-sectional study design, it was not possible to determine whether solvent exposure truly predated the development of a color vision defect; however, analyses restricted to subjects aged ≤50 years are less likely to include color vision defects due to age. Furthermore, the participation

rate of 48% raises the possibility of selection bias. However, the most commonly stated reason for refusal to participate—lack of interest—does not provide evidence that persons who refused differed from participants systematically with respect to exposure, as would occur if the reason were poor health due to a potential effect of hexane toxicity. Some exposure misclassification is likely, since the study relied on self-reported exposure assessment for the types of solvent products used and the frequency and duration of tasks performed, sometimes many years in the past.

The associations seen in this analysis suggest a relationship between nonhexane solvent exposure and blue-yellow color vision defects among workers aged 50 years or younger. For both blue-yellow color vision defects and any color vision defect, although the confidence intervals largely overlapped, prevalence ratios were greater for hexane exposure in the presence of acetone than for hexane alone. This suggests that coexposure to acetone may potentiate the toxic effects of hexane. The consistently elevated prevalence ratios for the highest exposures to hexane among younger workers occurred at levels far below regulatory limits for hexane, suggesting that these limits may not be sufficiently protective of worker health.

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