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The neuro-ophthalmological effects related to long term occupational exposure to organic solvents in painters

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Abstract

Purpose: Organic solvents are widely used in many industries and usually the exposure occurs with mixtures of solvents. Organic solvent mixtures are known for their ability to affect tissues of high lipid content including the myelin sheath in the nervous system. The purpose of this work was to study the evidence that long term (more than 10 years) exposure to organic solvents mixture amongst painters can induce neuro-ophthalmological effects on the cell function of retinal ganglion cells and the optic tract.

Methods: Twenty workers with long-term occupational exposure to mixed organic solvents were compared to 40 subjects. They were matched for age, gender and demographic characteristics and not occupationally exposed to any known organic solvents, using the following comparators: visual evoked potential, electro-retinogram, color vision and contrast sensitivity testing. Environmental monitoring was done in the work environment with consideration to the American Conference of Governmental Industrial Hygienists Threshold Limit Values

Results: The exposed group had significantly longer latency and higher amplitude of VEP waves especially P100, higher color confusion index especially affecting the blue-yellow spectrum and lower Log contrast sensitivity. No significant difference between exposed and non-exposed groups in full-field flash ERG response, however, in the pattern ERG, the exposed group had significantly longer latency of P50 which reflects affection of the retinal ganglion cell.

Conclusion: Long-term occupational exposure to mixed organic solvents appeared to affect the optic tract functions in the form of increasing latency of VEP response, affecting the quality of color vision and decreasing contrast sensitivity. It also affects the retinal ganglion cell layer with increased latency of P50 of the pattern ERG response.

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Menoufia Faculty of Medicine committee for medical research ethics, Menoufia University, revised and officially approved the study before its beginning. All the subjects involved in study received thorough information regarding the aim of the research study.

None of the authors has any proprietary interests or conflicts of interest related to this submission

Keywords

neuroophthalmological effects; occupational; exposure; organic solvents; painters

Introduction:

A number of industries use multiple types of organic solvents (REF). These industries range from paint manufacturing to engineering. As a result, more than two million workers are regularly exposed in Egypt alone (REF). Neurological effects covering a broad range of symptoms, from chronic toxic encephalopathy to impaired color vision, have been linked with organic solvent use (Semple et al., 2000).

Organic solvents are usually volatile liquids at room temperature and tend to be strongly lipophilic. One of their marked effects on humans is their ability to cause central nervous system (CNS) depression (Grasso et al., 1984) and myelin damage with atrophy (Rosenberg et al., 2002). Notable examples of solvents that cause these negative health effects are trichloroethane, trichloroethylene, benzene, toluene, xylene and styrene (Ridgway et al., 2003). These are often linked with interference with vision, as a result of exposure.

The electrophysiological signals evoked in the brain in response to visual stimuli are called visual evoked potentials (VEPs). These VEPs can be recorded using electrodes that are laid on the scalp, which also extracts and record electroencephalographic activity in the visual cortex (Odom et al., 2009).

Full-field electro-retinogram (ERG) represents the diffuse response of different neural and non-neural retinal cells to a light stimulus. The recorded electrical activity is the result of light-induced changes in the trans-retinal movements of ions, principally sodium and potassium, in the extracellular space (Fishman, 2001).

The effects resulted from exposure to some industrial chemicals have been described in some literatures published and included data until December 2000. They described the effect of exposure to these chemicals on color perception, as well as limited descriptions of the tests applied. Numerous different tests have been used to study the acquired alterations of color vision. These changes are frequently found in the blue–yellow axis. Many of these tests were initially designed to distinguish congenital alterations in the red–green axis, and so have relatively low sensitivity when studying chemically induced discrepancies in color perception. The most appropriate test to apply in the occupational settings nowadays seems to be the Lanthony D15- desaturated panel due to its sensitivity and easiness of application (Iregren et al., 2002).

The ability of a person to determine contrast plays an important role in person's daily activity. Contrast sensitivity testing can reveal many ocular diseases. Testing the peak of contrast sensitivity function provides a useful clinical aid to standard visual acuity assessments (Richman et al., 2013).

The neurotoxicity caused by organic solvents is an exceptionally focal issue in the field of occupational health (Fiedler and Lerman, 2007). The acute neurotoxicity of organic solvents is well-known long time ago, but we need to concentrate on the impacts brought on by chronic low-level exposure to OS on the optic tract and give an account on their effects on the retinal ganglion cell layer.

This work aims to study the evidence that long term [more than 10 years] exposure to organic solvents mixture in painters can induce neuro-ophthalmological effects of on the optic tract and retinal ganglion cell function.

Subjects and methods:

Participants:

Twenty male painters with long term occupational exposure (more than 10 years) to organic solvents were recruited to represent the exposed group. The comparison group consisted of 40 healthy males (who came to the clinic for routine examination of the refractive state which is required as a pre-employment criterion by some jobs. They were matched for age, gender and demographic characteristics and, not occupationally exposed to organic solvents. All the participants were volunteers, an informed consent was obtained from each participant before all the steps of the interview process and examination procedures with adherence to the guidelines of the declaration of Helsinki.

Applicants, giving history to any hereditary or acquired retinal or neurological disorders that may interfere with the results of the supposed tests (eg. CNS strokes, DM, ischemic maculopathies) were excluded from the study.

The questionnaire included personal data (e.g. age, occupation, residence), medical history (e.g. history of chronic diseases or drugs), and ophthalmological history (e.g. eye trauma, glaucoma, hereditary or congenital disorders like congenital cataract, congenital glaucoma, retinitis pigmentosa and rod/cone dystrophies)

All the participants filled in a questionnaire consisting of: sociodemographic data, current and past medical history, family history, occupational history, questions for any abnormal neurological manifestations.

They were examined clinically in a well-qualified ophthalmological clinic by the ophthalmology consultant and tested for color vision and contrast sensitivity.

Method of Visual Evoked Potential (VEP):

pattern-reversal VEP was recorded following international society of clinical electrophysiology of vision (ISCEV) last updated 2016. The active electrode was placed over the occipital cortex, reference electrode at a non-visual area and a ground electrode over the mastoid bone. Dark and white checkerboard of equal size were presented as pattern reversal generated on a screen at a distance about 50 cm. Check size was 600 of retinal arc, contrast was 0.95. They were filtered with cutoff frequencies of 0.5 and 1 Hz. The latencies of N75, P100, N145 and peak-to-peak amplitudes were measured.

Method of Electroretinogram (ERG):

Full field or maximal combined flash and pattern ERG responses were performed and recorded binocularly following international society of clinical electrophysiology of vision ISCEV last updated 2015. Patients were dilated with 1.0% and dark-adapted for at least 20 min before testing. The flash response was done using the Ganzfeld white bowl, while the pattern response was recorded using pattern reversal checker board.

The active electrode was a filament type electrode [gold foil electrode] suspended on the lower lid after application of topical anesthesia. Reference electrode was a silver chloride electrode placed on the patient's forehead and a ground electrode placed 2 cm from the ipsilateral outer canthus.

Color vision testing:

Color vision was assessed with the Lanthony D15d test which is a desaturated adaptation of the Farnsworth D15 and is comprised of 15 chips covered by Munsell papers of fixed saturation and variable hues. Each chip has 1.5 degrees of visual angle when viewed at 50 cm. The test was performed under consistent lighting conditions. Color Confusion Index (CCI) was used to express the results.

Contrast sensitivity testing (CS):

The contrast sensitivity data were collected using video display channel in which letter targets are presented on screen based on Pelli Robson principle with the best possible optical correction in place at normal room illumination, which is approximately 30–70 foot-lamberts. Contrast sensitivity letter targets subtend an angle 2–6 degree with different levels of contrast. The test was performed monocularly with the eye in the undilated state at a distance of 2.5 m. With the manifest prescription in place, the participant was asked to identify the letter targets in each column. Typically, the test measures the minimum contrast threshold at which a target can be resolved by an observer. The contrast level of the last correct response was recorded as the contrast threshold. Contrast sensitivity was expressed as the reciprocal of the minimum resolvable contrast, and this value is then transformed to a logarithmic scale.

Environmental monitoring

Organic solvents used mainly by the painters were tetrachloroethylene, benzene, toluene and xylene. These solvents have comparable and occasionally synergistic effects on the human body, so to evaluate the level of exposure to the mixture of organic solvents, we used the equation used by Cohen, 2007 and considered the ACGIH-TLVs (American Conference of Governmental Industrial Hygienists Threshold Limit Values, which are standard values established annually for chemical substances and physical agents) as the standard for permissible levels: $Em = C_1/L_1 + C_2/L_2 + \dots + C_n/L_n$

Where Em , C and L stand for equivalent concentrations of the mixture of the organic solvents, mean concentration of organic solvents in the workplace air and permissible levels of exposure to organic solvents; respectively. $Em > 1$ was considered as exposure to more

than permissible levels of a mixture of organic solvents in the workplace after determining the mean concentration of each solvent and using the formula.

Environmental monitoring of organic solvents present in the workplace was done at the workers' breathing zone. Air samples were collected on charcoal tubes with constant flow [100 ml/min] pumps [SKC 226-01]. Three samples were taken from each worksite and the mean readings of all sample was calculated. Air monitoring was performed during working hours. Afterward, gas chromatography was used to analyze the samples, and the mean concentration of each solvent was identified. All these steps were done by qualified personnel from the air pollution department in the national research Centre, Cairo, Egypt.

Statistical analysis of the collected data was done using statistical package for social science (SPSS) version 20 (SPSS Inc. Released 2011. IBM SPSS statistics for windows, version 20.0, Armonk, NY: IBM Corp.). Student's t-test was used for comparing quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Pearson correlation was used to correlate two continuous normally distributed variables while Spearman correlation was used for not normally distributed ones. It was assumed that statistical significance was verified when the P-value was less than 0.05 (two-tailed).

Results:

Forty eyes of twenty exposed subjects were compared to eighty eyes of healthy controls not occupationally exposed to any known organic solvents who were matched for the same gender and age. All the participants were males. The mean age was 35.40 ± 4.0 in the exposed group and 34.82 ± 8.06 in the non-exposed group [$p = 0.80$], the mean duration of work for the exposed workers was 22.6 ± 5.4 .

All waves of the pattern-reversal VEP response had significantly longer latency in the exposed group than the non-exposed group ($p = 0.002$, <0.01 and <0.01 for N75, P100 and N135; respectively), while the amplitude of P100 and N135 was significantly higher in the exposed group ($p < 0.01$ in both waves), table 1.

The mean color confusion index (CCI) in the exposed group was 1.30 ± 0.21 which was significantly higher than the non-exposed group (1.10 ± 0.12) with p value <0.001 . Most of the workers in the exposed group had confusion in arranging colors in blue-yellow spectrum suggesting early Tritan defect, table 1.

The exposed group had significantly lower contrast sensitivity function as their LogCS was 1.90 ± 0.04 while the non-exposed group had 1.93 ± 0.04 mean Log CS ($p < 0.01$) as shown in table 1.

Full field ERG response did not differ significantly between both group. There was no significant difference in a-wave latency, a-wave amplitude and b-wave latency or b-wave amplitude between the exposed and non-exposed groups. Pattern ERG showed no significant difference between both groups except the latency of P50 which was longer in the exposed

group with $53.35 \text{ (ms)} \pm 2.94$ than non-exposed group with $51.85 \text{ (ms)} \pm 2.00$ (p value <0.01), table 2.

In the exposed group, P100 and P50 latencies had significant positive correlation to work duration and CCI, but significant negative correlation to Log CS. also, work duration had significant positive correlation to CCI but negative to Log CS and finally CCI and Log CS were negatively correlated to each other. This is illustrated in table 3.

The workers were exposed to a mixture of organic solvents. Table 4 shows with the mean concentration (PPM) and ACGIH-TLVII (PPM) for each one. In this study, Em was 8.4 which means that the concentration of the organic solvents mixture in the painting workplaces was higher than the permissible levels.

Discussion

Many industries and occupations depend on organic solvents as the principal materials needed for the formulation of the final products or itself is the final product. These occupations include - but not limited to - paints, adhesives, surface cleaning, dry cleaning, printing, and in the plastics, pesticide and chemical industries.

The VEP response in the exposed group in this study showed significant delay in the latency of all the waves and greater amplitude of P100 and N135. The delay in P100 which is considered the main wave of VEP response which refers to demyelination of the nerve fibers and could be attributed to the long-term exposure to low-levels of organic solvents which are known to affect the nervous tissues' lipid structure found principally in the myelin sheath of the axon and cell membrane as stated by WHO 1985 and other authors like Gilmore 1988, Rosenberg 1989, Niedermayer 1987.

Vrca et al., 1995, compared 49 workers exposed to Toluene to 59 workers not occupationally exposed to any known neurotoxic substance and found that N75, P100 and N 145 waves of the reversal pattern VEP in the exposed group had significantly higher greater amplitude than non exposed group with longer latency in P100.

Increase in VEP wave latencies was also observed in cases of acute exposure to low-level organic solvents. Altmann et al., 1990 demonstrated the effect of acute exposure to low-level tetrachloroethylene (Per) on total of 22 healthy adult male volunteers. In the group exposed to 50ppm Per, they observed increase in the peak latencies of VEP waves (N75, P 100 and N150) during the inhalation period. The comparison of the 2 groups revealed statistically significant differences of these latency changes during Per exposure. Also, during the exposure to 50 ppm Per, they observed shift of the peak latencies of waves N 75, P 100 and N 150 towards higher values in comparison to the control day. The increase in the latency was more obvious for P 100 and N 150 components which represents the delayed components than for N 75 which represents the early component and it was more evident for the last exposure days.

ERG response reflects the functions of different components of the retina. In the full field ERG response, the a-wave originates from the photoreceptors and b-waves originates from

the bipolar cells. In this study, the exposed group was nearly like the non-exposed group in all components of full field ERG response.

The pattern ERG response goes deeper to show the function of the ganglion cell layer represented in the P50 and N95 waves. The exposed group in this study showed significantly longer latency of P 50 than the non-exposed group. This draws attention to the possible effect of organic solvents exposure on the retinal ganglion cells.

There is paucity of the clinical studies that demonstrate the effects of organic solvents on the retinal ganglion, however an experimental animal study done by Boyes et al., 2016 to examine the visual function by recording VEP and ERG responses from four groups of rats repetitively exposed to toluene. They found no significant induced change in the VEP amplitudes caused by toluene exposure. In the group of rats previously exposed to 1000 ppm toluene, b-wave amplitude of the dark-adapted ERGs were significantly reduced at high stimulus luminance values. The other 2 groups of rats which were exposed to Toluene for 4 weeks did not show any statistically significant reductions of ERG b-wave amplitude. In ERG a-wave amplitude, a-wave latency, b-wave latency, UV- or green-flicker ERGs, or in photopic flash ERGs, there was no significant change in. However, a reduction of b-wave amplitude was observed in the group exposed to toluene for 13 week, they had reduction which persisted for 1 year. They concluded that repeated exposure to toluene may lead to minor persistent changes in visual function.

In this study, the increase in P100 and P50 latencies was significantly positively correlated to the work duration ($r=0.55$ and 0.74 respectively and $p < 0.001$ for both), while the amplitude of both waves did not [$p > 0.05$]. CCI had also significant positive correlation with the latencies of both P100 and P50 ($r= 0.43$ and 0.60 respectively, $p 0.005$ and <0.001 respectively), while Log CS had significant negative correlation with both [$r= -0.38$ and -0.50 respectively, $p 0.01$ and 0.001 respectively).

The optic tract and retinal ganglion cells are not only concerned with the function of acuity of vision, but also concerned with the fine details of vision as color vision and contrast sensitivity. These latter functions can be effected even earlier than the acuity of vision in cases of organic solvents toxicity. The color vision in the studied group showed some defects evidenced by the significantly higher CCI when compared to the non-exposed group. The main confusion was in the blue-yellow spectrum. This reflects defects in the optic nerve/ tract which is the target of organic solvents. Contrast sensitivity was also affected in the exposed group as they had significantly lower LogCS than the non-exposed group.

This agreed with Semple et al., 2000 who argued that, exposure to mixed solvents is associated with impairment in color vision and the risk increases with increasing exposure. Gong et al., 2003 reported that the color confusion index (CCI) values of subjects exposed organic solvents were significantly higher than that of the age-matched controls ($P < 0.01$), while their contrast sensitivity values were significantly lower than those in the controls at spatial frequencies of 6 and 12 cycles per degree (cpd) [$P < 0.01$ and <0.05 , respectively]. However, they found no abnormal data of the VEP test in the exposed subjects

who were found to have impaired CV and CS. They assumed that a low concentration of the mixed organic solvents might affect the retina and optic nerve.

The results of decreased contrast sensitivity in the exposed group in this study goes with the results of Boeckelmann and Pfister 2003, who studied the visual contrast sensitivity in a group of subjects occupationally exposed to organic solvents [in a printing industry] using the Vistech VCTS 6500 chart. They divided the exposed workers into low exposed, middle and high exposed groups. Abnormal contrast sensitivity results were higher in the exposed than non-exposed groups and conclude that contrast sensitivity is abnormal in workers exposed to organic solvents and can be used as an indicator of visual defects induced by organic solvents exposure.

Even the infant born to mothersexposed to organic solvents were also affected as shown in the study done by Till et al., 2005 who studied a sample of 21 infants born to women who were occupationally exposed to solvents during pregnancy and compared them to 27 non-exposed age-matched control infants. Their results have shown a significant reduction in the contrast sensitivity in the low and intermediate spatial frequency range in solvent-exposed infants compared to non-exposed ($p < 0.001$). Also, color vision was affected in 26.3% of infants in the exposed group versus 0% of the non-exposed.

Some studies however, reported no significant effects of organic solvents on color vision, like a study done by Schaper et al., 2004. They repeatedly investigated the possible effects of long-term occupational exposures to toluene in workers of a printing industry on color vision in a follow-up study over 4 years with three repeated examinations. After repeated analyses and multiple regressions, their results did not show any significant effects of toluene with respect to intensity or duration of current or long-term exposure. They explained this by the controlled and monitored exposure in the studied environment.

Conclusion:

from the research that has been conducted we can conclude that participates who have long-term occupational exposure to organic solvents had significantly longer latency and higher amplitude of most VEP waves especially P100, higher CCI and lower contrast sensitivity. No significant difference between exposed and non-exposed participants in full-field flash ERG response but significantly longer latency of P 50 of pattern ERG was observed in the exposed group.

Recommendations:

color vision and contrast sensitivity testing can be used as a rapid and cheap screening of worker occupationally exposed to organic solvents to detect early neuro-ophthalmological affection and any worker with abnormal test result should have electrophysiological testing because they are significantly correlated.

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Table 1:

VEP results in the studied groups:

	Exposed (n=40 eyes) Mean $\pm$ SD	Non-exposed (n=80 eyes) Mean $\pm$ SD	P value
N75 latency (ms):	78.33 $\pm$ 10.21	85.06 $\pm$ 10.94	0.002
N75 amplitude (μ v)	6.75 $\pm$ 5.71	7.92 $\pm$ 5.64	0.42
P 100 latency (ms):	103.65 $\pm$ 7.11	99.97 $\pm$ 6.34	<0.01
P100 amplitude(μ v):	22.36 $\pm$ 8.60	17.49 $\pm$ 7.71	<0.01
N135 latency (ms):	142.18 $\pm$ 9.44	133.45 $\pm$ 13.15	<0.01
N135 amplitude (μ v):	21.63 $\pm$ 11.56	15.04 $\pm$ 6.40	<0.01
CCI:	1.30 $\pm$ 0.21	1.10 $\pm$ 0.12	<0.001
LogCS	1.90 $\pm$ 0.04	1.93 $\pm$ 0.04	<0.01

Table 2:

ERG results in the studied groups:

	Exposed (n=40) Mean $\pm$ SD	Non-exposed (n=80) Mean $\pm$ SD	P value
Full field Flash ERG			
a-wave latency (ms):	19.85 $\pm$ 3.56	20.90 $\pm$ 3.62	0.13
a-wave amplitude (μ v)	34.77 $\pm$ 15.66	35.18 $\pm$ 19.21	0.28
b-wave latency (ms)	42.50 $\pm$ 3.72	40.58 $\pm$ 8.61	0.09
b-wave amplitude (μ v):	149.55 $\pm$ 64.90	142.47 $\pm$ 83.56	0.63
Pattern ERG			
N35 latency (ms)	37.00 $\pm$ 2.07	36.95 $\pm$ 1.55	0.88
N35 amplitude (μ v)	0.48 $\pm$ 0.07	0.46 $\pm$ 0.07	0.43
P 50 latency (ms)	53.35 $\pm$ 2.94	51.85 $\pm$ 2.00	<0.01
P 50 amplitude (μ v)	7.67 $\pm$ 1.26	7.48 $\pm$ 1.07	0.40
N 95 latency (ms)	98.62 $\pm$ 2.78	97.68 $\pm$ 2.19	0.06
N95 amplitude (μ v)	3.95 $\pm$ 0.67	3.86 $\pm$ 0.77	0.54

Table 3:

Color confusion index (CCI) and Log contrast sensitivity (Log CS) among exposed:

Wave	Work duration (y)		CCI		Log CS	
	r	P value	r	P value	r	P value
P100 lat.	0.55	<0.001	0.43	0.005	-0.38	0.01
P100 amp.	-0.24	0.13	-0.26	0.10	0.09	0.56
P50 lat.	0.74	<0.001	0.60	<0.001	-0.50	0.001
P50 amp.	0.07	0.65	-0.26	0.09	0.10	0.50
CCI	0.32	0.04	-----	-----	-----	-----
Log CS	-0.59	<0.001	-0.37	0.01	-----	-----

Table 4:

results of environmental monitoring of the work environment for different types of organic solvents:

Solvent	Mean concentration (ppm)	ACGIH-TLVII (ppm)
Tetrachloroethylene	38	25
Benzene	2.43	0.5
Toluene	56	50
Xylene	90	100