



Neurobehavioral symptoms and reproductive hormones from paint occupational exposure

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Article published on May 30, 2018

Key words: Neuropsychological symptoms, Occupational exposure, Paint, Prolactin, Reproduction, Testosterone

Abstract

Occupational exposure to paint compounds and the joint action of solvents-metals probably causes effects on neurobehavioral profiles, and reproductive hormones of male workers. We undertook this study to determine relationship between occupational exposure to paint compounds mixture, especially solvents and neurobehavioral perturbations, testosterone and prolactin production. Exposure was estimated in 64 workers from a paint manufacturing plants, North East Algeria. Two exposure groups were formed: and divided into 2 main groups; the control and the exposed groups; the latter was subdivided into three categories of working periods (>10, 10-20, > 20 years of solvent exposure). The Swedish Q16 questionnaire was given to workers, followed by serum testosterone and prolactin concentrations were measured with ELISA. Workers with long period exposure (10-20, > 20 years) showed a significant reduction in testosterone concentration, and a significant increase in prolactin concentration and The average Swedish Q16 questionnaire score in the exposed group (4.6±4.2) is also significantly higher than the non-exposed group (3.4±3.1) (p=0.001). Fertility markers assessed in workers with long solvent exposure were disturbed than in those with a short solvent exposure, long solvent exposure produced high frequency of neuropsychological symptoms.

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Introduction

Millions of worldwide workers are employed in paint manufacture and as construction painters. Thousands of chemical compounds are used in paint products as pigments, extenders, binders, solvents and additives; which paint workers may be exposed, without neglecting the other chemical agents as metals. (Langard and Norseth, 1986; Keogh and Boyer, 2001; Waalkes *et al.*, 2001).

The volatile nature of these products makes workers easily exposed by the respiratory route; causing various symptoms and complications, mainly in the central nervous system CNS (Bleecker *et al.*, 1991). The main effect of solvents is the CNS depression, and it may cause headache, dizziness, fatigue or even loss of consciousness and death (Ridgway *et al.*, 2003). The question of chronic neurobehavioral effects of solvent exposure is still nevertheless controversial. A pilot study has suggested that Chinese printing workers exposed to a mixture of organic solvents have an excess of a wide range of neurobehavioral symptoms (Ng and Lam, 1989). Chemical pollutants may interfere with typical brain development, eventually increasing the risk of either subclinical neuropsychological alterations or manifest clinical conditions, where epidemiological studies have linked maternal exposure to environmental toxicants and neurodevelopmental disorders (Grandjean and Bellanger, 2017; Tran and Miyake, 2017).

In the same way industrial chemicals can contribute to disease and dysfunctions, for example, by interfering with hormonal functions (endocrine disrupting chemicals, or EDCs) (Sharratt *et al.*, 1984; Ahmed *et al.*, 2018). Indeed environmental factors are involved in the alteration of reproduction markers, and several studies have shown the relationship between air pollution and decreased fertility. In Wistar dams rats, epididymal sperm counts were reduced several months after end of exposure to endocrine disrupters (Axelstad *et al.*, 2017), as well as in rodents at adulthood (Faqi *et al.*, 1998b), (Kuriyama and Chahoud 2004).

Furthermore, paint pollution has been reported as a cause of the quantitative and qualitative alteration of human sperm (Fredricsson *et al.*, 1993; Slama *et al.*, 2004; Pant *et al.*, 2010). Nevertheless, there are little information regarding possible correlations between male reproduction dysfunctions and neurobehavioral disorders. Recently a link was made between neurological symptoms and decreased fertility (Kuriyama *et al.*, 2004), in which several reports has shown the existence of a close relationship between neurobehavioral disorders and male infertility in occupational exposure to pollutants. Reproductive toxicity may manifested by alterations in sex hormone levels, diminished libido and potency, menstrual disorders, early or late menarche, impairment of semen quality, ovarian dysfunction, early or late menopause, infertility and adverse pregnancy outcome (Lindbohm *et al.*, 2013).

Diminished libido was reported in painters, where nearly 20% of men have neurological disorders (Tache *et al.*, 1980; CERHR, 2004). Accordingly, abnormal semen analysis, including decreased sperm count, abnormal morphology or impaired motility, has been reported in 90% of men with neurological disorders (Gerendai *et al.*, 1995; Herzog, 2008).

This study therefore aims to evaluate the rate of the two major reproductive biomarkers: prolactin and testosterone workers of a paint factory to provide a first detailed description of their reproductive status, and further study the involvement of different compounds of painting in the neurobehavioral toxicity of painting workers by using the Swedish Q16 questionnaire, which is a screening tool for neurotoxicity symptoms related to organic solvents (Hogstedt *et al.*, 1984; Labbafinejad *et al.*, 2014). To establish a possible relationship between neurobehavioral toxicity and reproductive toxicity in exposed workers.

Materials and methods

A. Study Design

This work was carried out between January 2012 and April 2013 on workers of paint manufacturing plants, North East Algeria.

Two groups of workers were chosen; from the paint maker unit (n=44) and from the administrative personnel (n=20). Only workers who voluntarily participated in the study were interviewed.

Workers' exposure to the solvents was measured quantitatively (internal data of the factory); however in this survey only qualitative data was available. Swedish Q16 questionnaire, was given to male workers from similar socio-economic status this one is a screening tool for neurotoxicity symptoms related to organic solvents in workers. It is considered as a valid questionnaire, consisting of 16 short yes/no questions and dealing with the symptoms widely expressed by the solvent-exposed workers.

Those respondents, who give positive answers to more than 6 questions, have to be referred to a physicians or psychiatrists for further examinations to exclude the possibility of organic brain damages (Hogstedt *et al.*, 1984; Labbafinejad *et al.*, 2014).

A. Data Collection

A questionnaire was established concerning age, sex, period of employment, position, previous jobs, shift, paint exposure, personal protection methods, the clinical symptoms, and medical history, current use of medication and drug abuse, smoking history. The socio-economic status of workers was considered to be similar. Only workers with approximately similar age and working period were taken from each group, to avoid the effect of these two factors (Table 1). Paint makers, then, were divided into 3 different working period categories (>10, 10-20, > 20 years). Subjects take free daily meal rich with all nutrients and they are supplied with the necessary protective equipment (gloves, eye-goggles, anti-dust mask, and solvent-respirator). Smokers and person with known chronic diseases were excluded from the study.

Table 1. Demographic Characteristics of the Study Groups.

| Designation | Control | Exposed groups |
|----------------------------|-------------|----------------|
| Subjects | n = 20 | n = 44 |
| Age (mean± SD) | 43.47±6.824 | 43.43±9.272 |
| Exposure period (mean± SD) | - | 14.59±7.17 |

B. Laboratory Study

Blood samples were collected at the beginning of morning shift, then serum or plasma testosterone and prolactin levels were measured using the kit "Elecsys de Roche", and the apparatus Elecsys de Roche 1010 Analyser equipment, which is a chemiluminescence immunoassay analysis system (E.C.L.I.A) (Runnebaum and Rabe, 1997).

C. Statistical analysis

Statistical analysis was used by applying Student *t*-test, ANOVA, nonparametric Mann Whitney U test and Chi-square test of independence to compare between the groups of workers. All treatments were performed using the statistical program STATISTICA (Stat Soft, version 8.0). The significance for all statistical analyses was established with 95% confidence intervals.

Results

A total of 64 workers of a paint company included in this study; 34 of whom were exposed to the paint components, and particularly organic solvents and were considered as the exposed group which average age was 43.43±9 years with a working experience in paint units of 14.59±7 years and 20 ones were working in administrative units of the company where there was no exposure to the solvents and they were considered as the control (non-exposed group) which average age was 43.47±6 years with a working experience of 14±8 years. Comparison between the two groups in terms of age, working experience is shown in Table 1. and their Swedish Q16 questionnaire score is shown in Table 2.

As can be seen, the average age and working experience of the exposed groups is significantly higher than the control (non-exposed group) (p<0.05). The average Swedish Q16 questionnaire score in the exposed groups is also significantly higher than the non-exposed group.

Table 2 shows the percentage of positive answers to each question in the Swedish Q16 questionnaire for both groups. As shown here, in most of the questions

like depression, fatigue, anger, difficulty in concentration, feeling of amnesia, decreased sexual desire, and difficulty in comprehension, a significant relationship is recognized in the organic solvent-exposed group. There was no significant difference

between the exposed and non-exposed groups for some questions of the questionnaire including amnesia in others' opinions, feeling of chest pressure, note-taking due to paramnesia, frequent review, and once a week headaches.

Table 2. Frequency of positive answers to each of Swedish Q16 questions in the two studied groups, suffering from Neuropsychological symptoms.

| N° | Questions | Exposed group | Non exposed group |
|----|---|---------------|-------------------|
| 1 | Are you abnormally tired? | 29 | 8 |
| 2 | Do you often have a painful tingling in some part of your body? | 32 | 10 |
| 3 | Do you have heart palpitation even when you don't exert yourself | 19 | 4 |
| 4 | Do you often feel irritated without any particular reason? | 12 | 2 |
| 5 | Do you often feel depressed without any particular reason? | 33 | 7 |
| 6 | Do you have problems with concentration? | 26 | 6 |
| 7 | Do you forget easily? | 33 | 5 |
| 8 | Do you perspire without any particular reason? | 16 | 1 |
| 9 | Do you often have problems with open and close buttons on your dress? | 17 | 3 |
| 10 | Do you generally find it hard to get the meaning from reading newspapers and books? | 13 | 2 |
| 11 | Have your relatives told you have a short memory? | 25 | 8 |
| 12 | Do you feel pressure in your chest? | 14 | 2 |
| 13 | Do you often have to make notes about what you must remember? | 20 | 8 |
| 14 | Do you often have to go back and check things you have done (locked the door ,etc) | 28 | 10 |
| 15 | Do you have headache at least once a week? | 33 | 9 |
| 16 | Are you less interested in sex than what you think is normal? | 5 | 2 |
| | Abnormal test | 11 | |

*: Significant vs the control.

The frequency of the neurobehavioral symptoms in the exposed groups shown in Fig. 1, was significantly higher than the control, indeed results indicated a high frequency of different neuro-psychological symptoms. The highest frequency was for memory loss, followed by headaches and in the same level comes insomnia and poor concentration. However poor coordination, had recorded the lowest percentage. However, only 2 different symptoms were found in the control (headaches and poor concentration).

Furthermore the levels of hormones are shown in fig 2 and 3. A significant decrease of testosterone concentration were observed in category 2

($4.61 \pm 2.005 \text{ ng/ml}$) and category 3 ($4.25 \pm 1.67 \text{ ng/ml}$) of exposed workers (Mann Whitney: $U = 92.5$; $p = 0.1$ and $U = 41.5$; $p = 0.001$, respectively) compared to the control ($6.43 \pm 1.73 \text{ ng/ml}$).

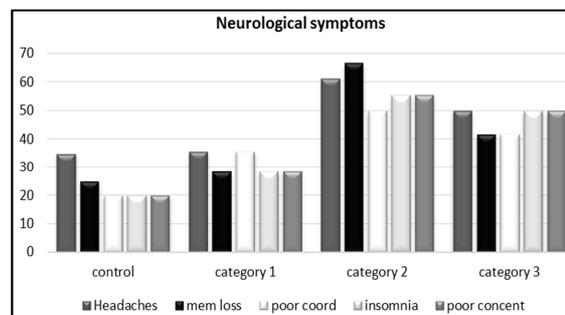


Fig. 1. Neurological symptoms of the control group, and the exposed categories, of different working periods.

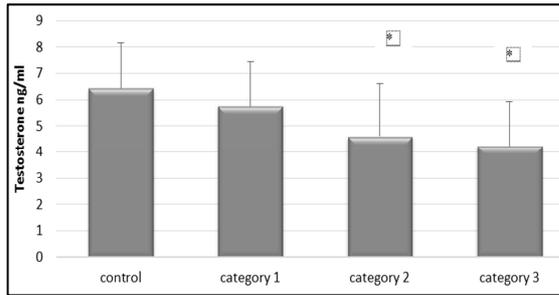


Fig. 2. Testosterone concentration: (mean \pm SD) in (serum or plasma) of control, and the exposed categories of different working period.

*: *: Significant vs the control.

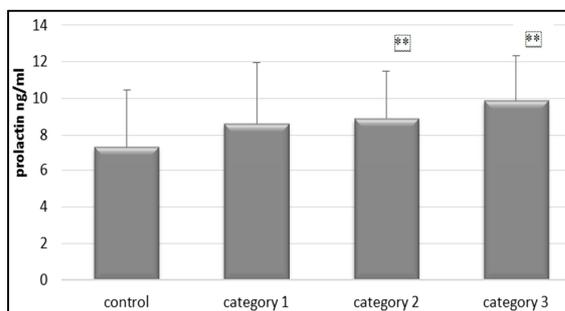


Fig. 3. Prolactin concentration (mean \pm SD) in (serum or plasma) of the control, and the exposed categories of different working periods.

However in the case of prolactin, result showed that in category 2 of exposed workers (10-20 years) the hormone level has significantly increased (9.9 ± 2.43 ng/ml) (Mann Whitney: $U = 59$; $p = 0.01$). ANOVA test ($F = 3.59$; $df = 6$; $p = 0.002$) between the four groups showed a statistically significant differences in prolactin level.

Discussion

Neurobehavioral profiles of the workers

A full clinical examination for the clinical symptoms was used to study the possible effects of different working periods on the paint workers. A consistent evidence was found that the exposed painters especially category 2 (10-20y) and category 3 (>20y) suffer from much more symptoms than those of the control. Even the frequencies of the shared symptoms observed in the exposed painters are higher than those of the control. For all these reasons, it seems that the prolonged occupational exposure to organic solvents is responsible on most clinical disorders.

The results of the Swedish Q16 questionnaire confirmed those of the neurological symptoms, and allowed to demonstrate a large percentage of neurological impairment in the exposed groups. Accordingly, A number of reports, particularly from Scandinavian countries, claim that painters and workers with prolonged occupational exposure to organic solvents develop a type of mental illness characterized principally by impairment of memory and co-ordination and some deterioration of personality. The condition called "organic solvent disease" or "painters' syndrome" is classed as an occupational disease in certain countries (Sharratt *et al.*, 1984). That's why, in the Scandinavian countries, many solvent-exposed workers receive early retirement due to solvent-related neuropsychiatric disorders. (Hogstedt, 1994).

How organic solvents damage the central nervous system remains an unresolved question. Although some authors have suggested that brain dopamine may be a target for solvent toxicity (Mutti *et al.*, 1988). Alteration of synaptosomal membrane function induced by solvent exposure has been reported (Korpela, 1989; LeBel and Schatz, 1989, 1990).

Other mechanism of toxicity is that solvents interact with cells to generate reactive intermediates, which may covalently bind to proteins, lipids, DNA, or RNA, and they may inactivate receptors and enzymes, damage cellular membranes, or initiate mutagenic reactions. Lipid solubility often allows solvents to access to structures of the nervous system, where it produces some effects, such as demyelination, cell death, irreversible effects ...etc (Benignus *et al.*, 2009; Grandjean and Bellanger, 2017).

In the present study, the ages of workers in the two groups were similar, which exclude any age-effect on any physio-pathological changes. Even though, there were no detected major differences between younger and elder Dutch painters in neurobehavioral tests (Wang and Chen, 1993). Moreover, the shifts of each exposed worker's group were 8 hours/day.

Reproductive profiles of the workers

Concerning reproduction profile, significant decrease of testosterone concentration were observed in category 2 (10-20 years of solvent exposure) and category 3 (>20 years). However in the case of prolactin, result showed that in category 2 of exposed workers (10-20 years) the hormone level has significantly increased and according to a recent hypothesis, all abnormalities of the male genital system do have a common cause, namely exposure to endocrine disruptors affecting markers of male reproductive function.

Recently, research on the toxicity of aromatic compounds solvents as toluene and xylene were reported to affect the function of reproductive system stimulating hormones that remarkably decreases the concentration of estradiol and testosterone. Moreover, the exposure to toluene and xylene for a long period provoked endocrine system disruption (Yilmaz *et al.*, 2006).

Reproductive endocrine dysfunction in workers presenting solvent neurotoxicity, have a hypogonadism associated with low serum testosterone level and/or decreased or abnormal sperm production (Tache *et al.*, 1980; Eagleson *et al.*, 2000). It can manifest as diminished sexual desire, potency, fertility, energy, competitive drive, bone and muscle mass, and secondary sexual characteristics with functional hyperprolactinemia (Tache *et al.*, 1980), which explains the results of the Swedish Q16 questionnaire.

Neurobehavioral disorders and psychosocial stress associated with biochemical and hormonal disorders may play an important role in hypofertility (Yilmaz *et al.*, 2001; Moore *et al.*, 2003). From a neuroendocrine perspective, stress response involves the activation of the hypothalamo-pituitary-adrenal (HPA) axis (Eagleson *et al.*, 2000). Factors that increase the activity of the HPA axis interfere with reproductive endocrine secretion as well as reproductive function (Eagleson *et al.*, 2000; Pant *et al.*, 2010; Ahmed *et al.*, 2018).

Neuropsychological disorder increases the release of pro-opiomelanocortin (POMC) the precursor protein that is cleaved to form ACTH and endorphin (Eagleson *et al.*, 2000; Yilmaz *et al.*, 2001), both of which inhibit gonadotropin secretion and reproductive function (Almeida *et al.*, 1998; Girard-Buttoz *et al.*, 2009). Thus, ACTH increases cortisol secretion whilst endorphins boost dehydroepiandrosterone production. Enzyme-inducing stress can directly suppress gonadal testosterone synthesis, increase testosterone binding by the induction of sex hormone binding globulin (SHBG), and increase serum estradiol levels in absolute or relative terms (Eagleson *et al.*, 2000; Girard-Buttoz *et al.*, 2009). Based on results and findings, described previously, and data found in the literature there is a very close relationship between Neuropsychological disorders or Neurobehavioral disorders and decreased fertility, deduction already made by several recent researches. Supporting the actual data, Kuriyama *et al.*, (2004); Axelstad *et al.*, (2017), found that neuropsychological disorders were accompanied by reproductive marker ailments represented with acute rise in prolactin level.

Conclusion

Exposure to paint pollutants revealed a higher prevalence of neurobehavioral disorders and variations in reproductive hormones. The neuromodulatory role of reproductive hormones suggests that a greater understanding of neuroendocrine regulation in solvent toxicity may be important, not only for reproductive function, but also for optimal management of occupational health assessment in paint industry. If the results of the present research can be confirmed by further prospective studies, then the use of Swedish Q16 questionnaire would be helpful in the periodic examinations of the personnel exposed to paint compounds for their occupationally health care.

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