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REVIEW PAPER

Krzysztof Sieja[1]
Jarosław von Mach-Szczypiński[2]
Joanna von Mach-Szczypiński[3]

HEALTH EFFECT OF CHRONIC EXPOSURE TO CARBON DISULFIDE (CS_2) ON WOMEN EMPLOYED IN VISCOSE INDUSTRY

[1] University of Applied Sciences in Wałcz, Wałcz, Poland
Faculty of Physical Culture

[2] Private Praxis in Gynecology and Obstetrics, Kościerzyna, Poland

[3] Martin-Luther Hospital, Berlin, Germany
Obstetrics and Gynecology Department

Abstract

Many women are exposed to carbon disulfide (CS_2) hazards at work every day. Working with CS_2 may cause some women to experience abnormalities in their reproductive health. Until now obtained data is generally concentrated on the health effects of CS_2 observed in the viscose industry. To date, CS_2 has not been studied precisely for its potential to have damaging effects on female reproductive system, especially the frequency of menstrual disturbances and the course of menopause. The aim of the study was to sum up female reproductive health hazards amongst women chronically exposed to CS_2 in their workplace in the viscose industry. In order to study the effect of CS_2 in the contemporary viscose industry, exposure measurements should be collected in prospective or cross-sectional studies. In conclusion, reproductive health hazards for women chronically exposed to CS_2 in the workplace in the viscose industry are the following: 1) menstrual disorders essentially are more frequent than in the case of the healthy women, 2) for women chronically exposed to CS_2 the average menopausal age is statistically earlier, as compared to healthy women, 3) complex disturbances in neurohormonal system for women exposed to CS_2, resulting from toxic influences of CS_2, which cause the secretion of estrogens and progesterone in ovaries and dehydroepiandrosterone sulfate in the adrenal gland to diminish. Med Pr 2018;69(3)

Key words: estrogens, menstrual disturbances, carbon disulfide, premature menopause, female reproductive health, chronic exposure

Corresponding author: Krzysztof Sieja, University of Applied Sciences in Wałcz, Faculty of Physical Culture, Bydgoska 50, 78-600 Wałcz, Poland, e-mail: siejakrzysztof@wp.pl
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INTRODUCTION

Human beings are exposed to several thousand exogenous chemicals which are hazards to the reproductive health of men as well as women. The issue of reproduction and hazards to reproductive health have become prominent issues in recent decades after reports of adverse effects of certain chemicals on reproductive function [1]. Carbon disulfide (CS_2) is a high-production-volume chemical industrially used for more than one century. It is mainly used as a reagent in the viscose production. At the workplaces of this industrial process, employees are exposed to CS_2, often for many years and occasionally to very high concentrations [2]. Due to its physical properties, CS_2 may enter the employees' body via both lung and skin, which complicates effective prevention of exposure [3].

Carbon disulfide is known for its high acute as well as chronic toxicity. A number of workers are exposed to risk factors every day. Some substances produce disturbances in sexual and reproductive health. The female reproductive system is also vulnerable to persistent chemicals or pollutants but there is less of such data than male reproductive impairment data. Women's health is the area that is gaining attention along with the awareness that men's and women's bodies react differently to environmental agents. The number of women in the workforce is increasing worldwide and a considerable proportion of them are of reproductive age. Therefore, special attention is required to note the reproductive dysfunctions, due to occupational exposure, among others, CS_2 [1,2].

In the viscose production industry, exposures are multitudinous and have given rise to several occupa-

tional health concerns, among others, cardiovascular disease, deterioration of intellectual and psychomotor function, nervous system dysfunction and reproductive disorders. Many women are exposed to CS_2 hazards at work every day. Working with CS_2 may cause some women to experience abnormalities in their reproductive health. To date, CS_2 has not been studied precisely for its potential to have damaging effects on female reproductive system. Until now, obtained data is generally concentrated on the health effects observed in the viscose industry [4,5].

METHODS OF REVIEW

The review of references was performed on the international medical bibliographical services. Reviewed articles were assessed using bibliographic bases Medline, PubMed and informational data Ebsco Discovery Service (EDS). The presented paper includes all the articles connected with the influence of chronic exposure to carbon disulfide in the case of women employed in the viscose industry. Particular attention needs to be paid to the influence of chronic exposure of carbon disulfide on the fertility and the course of pregnancy. A special subchapter was dedicated to the problem of premature menopause among women exposed to CS_2, who were employed in the viscose industry.

English was the main language in which the articles were reviewed. The reports from 1980 until 2016 were taken into consideration.

RESULTS OF REVIEW

Occupational exposure to CS_2

Carbon disulfide is an important pollutant affecting female reproductive function. Until now the effect of CS_2 in terms of the aspect of the impairment of the reproductive system of women has not been sufficiently investigated. Carbon disulfide is a colorless, liquid organic solvent, with an odor of decaying cabbage at room temperature. Carbon disulfide is volatile and flammable. It is highly soluble in blood and fat and moderately soluble in urine and water. In human and experimental studies, CS_2 is easily absorbed via inhalation, oral or skin route, and is distributed throughout the body due to its affinity in lipid rich tissues and organs. The absorbed CS_2 is concentrated in red cells [4–6].

We have reviewed several reports to estimate if there is scientific justification for the current threshold limit value (TLV) of concentration of CS_2, that is 10 ppm, as recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) [7–9]. The TLV ranged worldwide from 1 to 10 ppm. In Poland the current permissible exposure limit (PEL) is 4 ppm, and TLV – below 12,5 ppm [10–14]. According to the reports, some authors claim that the reproductive capacity of female workers may not be adequately protected at the exposure of 10 ppm [15–18]. Amongst workers of the viscose industry, long exposure causes chronic toxicity varying between 40–80 ppm.

The exposure specificity in the viscose industry is governed by long and high exposure in the past decades, high peak exposure, former analytical procedures, which underestimate the exposure and shift work. Data generally supports the occupational exposure limit of 10 ppm. The results of Swedish authors show that rubber workers in the contemporary rubber industry are exposed to low levels of CS_2 (≈ 0,05 ppm) [18]. Exposure to CS_2 is largely driven by specific circumstances in factories. Therefore, biological monitoring of CS_2 in the viscose industry, by assessing levels of 2-thiothiazolidine-4-carboxyl-acid (TTCA) as a metabolite of CS_2 in urine seems to be a reasonable approach [12]. It seems, therefore, that in order to study the effect of CS_2 in the contemporary viscose industry, the exposure measurements should be collected in prospective or cross-sectional studies.

Neuro- and cardiotoxicity of CS_2

Carbon disulfide is one of the harmful agents which have great importance in the impairment of central and peripheral nervous system. Neurological and neurophysiological studies indicate that the function of the central and peripheral nervous system may be impaired when exposed to CS_2. Sex exerts an effect on biological activity of xenobiotics in human beings [19,20]. Carbon disulfide has an especially harmful effect on women's organisms when taking into consideration that metabolism in the case of women is different in comparison to men. Basal metabolism in the case of women weighing 60 kg carries out about 1400 kcal/day. In the case of a man weighing 70 kg, the basal metabolism is about 1700 kcal/day [19]. Physical efficiency of women should be determined as 83% of physical efficiency of a man's organism [19]. Women have slower basal metabolism and longer time of processing food into energy during rest [21]. The basal metabolism rate affects the oxygen consumption. In the case of men, the total lung capacity is about 4 l, in the case of women – only 3 l [13]. The total lung capacity for women is about 25% lesser than for men. Maximal oxygen uptake (VO_2max),

is usually higher in the case of men than women [21]. Slower detoxication of CS_2 among women results from lesser oxygen consumption.

Psychophysical and physic-chemical properties of women are different from those typical for men and should be taken into consideration in cases of women working in the viscose industry [2,6,13,14,19]. In the case of women, intoxication of CS_2 is quicker and more serious than in the case of men because a woman's organism contains less water and more fat than a man's [19–21]. Mean content of fat in a woman's body is 26%, however, in a man's body – 14%. Women also have smaller muscles mass [13–15]. The above-mentioned differences result from the activity of hormones. Higher levels of estrogens in the case of women contribute to greater content of fat [19,21]. Higher concentration of hemoglobin in men's blood enhances the capacity of oxygen transportation. Moreover, the production of erythrocytes in a man's organism is 20% greater than in a woman's [20,21].

It is also important that the structure of the nervous system differs between men and women. Men's brain is 15% greater than women's. Great exposure of the organism to CS_2 accelerates the loss of nervous tissue in the brain [4,14]. The difference between women and men in terms of CS_2 toxicity is connected with the transformation of microsomal enzymes regulated by ovarian hormones [4,7,8,12,14]. It must be stressed that detoxication capacities of a woman's liver against industrial poisons are 5 times smaller than men's. Moreover, women's organisms produce less detoxication enzymes [1,16,20].

There are explicit differences in the cardiovascular system between sexes. The differences in functional parameters of the cardiovascular system and in the environmental stress reactivity could be the cause of more serious effects of CS_2 activity on the cardiovascular system in the case of women than men [21]. Due to smaller heart volume, the stroke volume of a woman's heart is smaller, which leads to deterioration of muscles' blood supply [21]. One of the more serious effects of CS_2 are changes in the cardiovascular system connected with arteriosclerosis leading to coronary disease and arterial hypertension [1,16].

Chronic exposure to CS_2 may induce polyneuropathy, Parkinson and neuro-psychological symptoms [18]. Long-term exposure to high concentrations of CS_2 could lead to the damage of nervous system, elevate blood pressure and promote the development and progression of hyperlipemia and atherosclerosis [22].

Effects on the cardiovascular system belong to the most important toxic effects of chronic CS_2 exposure [16]. Increased mortality rate among CS_2-exposed employees suffering from coronary heart disease (CHD) had been revealed in epidemiological studies. Moreover some new comparisons showed increased coronary artery disease mortality among long-term workers exposed to carbon disulfide and shift work for 4 years or more [2,3]. Long-term exposure to CS_2 may lead to increasing mortality due to coronary artery diseases [18].

Further studies indicated that atherosclerosis might be a major process in the field of CS_2-stimulated CHD. Elevated levels of biochemical risk factors for atherosclerosis, e.g., cholesterol and low density lipoprotein cholesterol (LDL), were found in the case of CS_2-exposed workers. Moreover, this study shows an increase in intima-media thickness (IMT) especially in the case of workers with high and long-term exposure. Intima-media thickness of the carotid arteries (IMT) represents an established marker of atherosclerosis and a reasonable surrogate marker for cardiovascular risk. Intima-media thickness was examined in a large cohort of CS_2-exposed workers and the association with cumulative CS_2 exposure was analyzed [22].

2-Thiothiazolidine-4-carboxyl-acid in urine has been generally applied as a useful biomarker of CS_2 exposure. The level of urinary TTCA may reflect the exposure of the day. There was a linear correlation between TTCA values in urine and the CS_2 values in the atmosphere [22].

Influence of CS_2 on female physiological and reproductive functions

Working with CS_2 may cause some women to experience abnormalities in their reproductive health. The majority of reviewed papers on female fertility concerns the alterations of menstrual cycle and pregnancy complications rather than occupational exposure-induced female infertility. The literature supports the hypothesis that, in general, working women have a tendency of higher risk of unsuccessful reproductive outcomes, although the existing data is not sufficient [23–26].

To date, CS_2 has not been studied precisely for its potential to have damaging effects on female reproductive system, especially menstrual disturbances and menopause. The aim of the study has been to sum up female physiological and reproductive health hazards for women chronically exposed to CS_2 in their workplace in the viscose industry.

Carbon disulfide and reproductive health

Carbon disulfide may lead to spontaneous abortion and very early pregnancy loss among women exposed in the workplace, but the mechanism remains unclear [23,24].

Carbon disulfide has reproductive toxicity but the mechanism remains unclear. Chinese authors investigated the effect of oxidative stress and deoxyribonucleic acid (DNA) damage on embryo implantation of mice exposed to CS_2 at peri-implantation [24–31]. According to the study performed by Wang et al. [31] CS_2 directly induced DNA damage in endometrial cells and enhanced the action through oxidative stress, both of which were responsible for CS_2-induced embryo loss. Studies indicated that DNA damage and apoptosis of endometrial cells might be one of the mechanisms due to which CS_2 resulted in the failure of blastocyst implantation [25–28].

These findings suggest that the decreased protein and messenger ribonucleic acid (mRNA) level of integrin β3 in the uterine tissue after mice exposure to CS_2 might be relevant to the underlying mechanism of embryo implantation disorders, but DNA methylation of integrin β3 does not contribute to this action [23]. Carbon disulfide exposure during peri-implantation may reduce the estrogen receptor α (ER-α) expression in the uterus and the serum level of estradiol (E_2) in the case of pregnant mice, which may be one of the mechanisms of embryo toxicity of CS_2 [29,30].

Some studies showed that the rate of very early pregnancy loss, confirmed by detecting the level of human-chorionic gonadotropin in the urine of each menstrual cycle, was 48.7% in the CS_2-exposed group as compared with 26.3% – in the healthy group [25]. These results indicated that the period of early embryo development was sensitive to CS_2-exposure. The increased incidence of spontaneous abortion was found by some other authors [24,28,30,32].

Carbon disulfide and menstrual disturbances

Physiological conditions of women undergo great changes during their physiological menstrual cycle. The physiology of a woman's menstrual cycle is especially easily disturbed by the chronic influence of neurotoxins [31–33]. The studies reveal that this occupational risk is especially high in the case of younger women because the development of their neural system is not completed [16]. Based on the results of the reports presented here we can make the conclusion that the consequences of excessive exposure to CS_2 should be studied especially meticulously in the case of women [13,16,27,28, 31–34].

Menstrual problems, pregnancy/birth outcome, and teratology of occupational exposure to CS_2 (≥ 1–15 years) among females were examined by Liang et al. [35]. Female viscose rayon factory workers (N = 337) in China exposed to CS_2 at 1.0 ppm, 2.08 ppm and 4.74 ppm (range: 0.54–4.74 ppm) from 1970 to 1985 (< 3.2 ppm in the factory since 1980) and non-exposed subjects (N = 397) were examined by means of a questionnaire about menstrual history and related questions. Married female exposed (389 pregnancies) and non-exposed workers (293 pregnancies) as well as wives of exposed (293 pregnancies) and non-exposed male workers (203 pregnancies) were interviewed for pregnancy progression and outcome. No associations between exposure at < 3.2 ppm and effects on the course and outcome of pregnancy occurred, although a higher rate of overdue delivery was observed among wives of the exposed male workers. There was an increased risk (relative risk (RR) = 1.92) of menstrual disturbances (painful, profuse, and/or irregular, or too little bleeding) among female workers (35%) with an average 7-year exposure to ≥ 2.08 ppm (no-observed-effect-level (NOEL) ≈ 0.992 ppm).

According to the study by Zhou et al. [32] at higher CS_2 levels, an exposure–response relationship was found. A retrospective cohort study performed in China examined menstrual status, term and outcome of pregnancy among 265 female factory workers exposed to CS_2 and 291 non-exposed female workers as well as 530 pregnancies (off-site women). Carbon disulfide concentration to which the workers had been exposed for 15 years before the study had been an average of 0.992 ppm, 2.08 ppm, and 4.74 ppm (range: 0.54–4.74 ppm). The results showed that exposed females had a higher incidence rate of menstrual disturbance (irregular cycle or unusual bleeding) than the non-exposed women (35.9% vs. 18.2%, RR = 2, $p < 0.01$), and an exposure–response relationship between the CS_2 level and the incidence rate of menstrual disturbance was revealed. Data indicates that exposure to CS_2 at about 4.74 ppm may affect the function of the female reproductive system (NOEL ≈ 2.08 ppm) [33].

In some studies CS_2-exposed women have a threefold greater frequency of menstrual disturbances as compared to healthy women [13,14]. The results revealed that menstrual disturbances in the case of healthy women in the reproductive age were found at the level of 7.5%. However, in the case of women with occupational exposure to CS_2 in the viscose industry, the level of 21.4% was found [13]. These results are in

accordance with the data reported from China [33]. Moreover, it was found that carbon disulfide might lead to early menopause and reduction of serum concentration of estrone (E_1), E_2, progesterone (P), 17-hydroxyprogesterone (17-OH-P) [7]. In the urine the daily excretion of adrenaline (8.06±1.7 mcg/day vs. 6.53± 0.87 mcg/day), and noradrenaline (22.03±2.97 mcg/day vs. 17.92±1.28 mcg/day) was essentially lower as compared to the urine of healthy women [13].

Carbon disulfide and premature menopause

There is deficiency of entire evaluation of the relationship between menopause and chronic exposure to CS_2. Nonetheless this problem has been studied by some authors [13,14,30,34,35]. Based on the neurohormonal state of women exposed to CS_2 in the viscose industry, Pieleszek and Stanosz [14] addressed the issue of the influence of this exposure on functional changes in their reproductive system. The above-mentioned authors carried out a comparative study of women chronically exposed to CS_2, who were employed in the viscose factories, as compared to healthy ones. The concentration of CS_2 ranged from 9.36 μg/m^3 to 23.4 μg/m^3 (3–7.9 ppm). The average concentration in the air was 13.98±3.46 μg/m^3 (4.48±1.1 ppm). A hormonal profile included assays of prolactin (PRL), folitropin (FSH), lutropin (LH), E_1, E_2, 17-OH-P, total testosterone (TT) and dehydroepiandrosterone sulfate (DHEA-S). Moreover, the concentration of dopamine (DA), serotonin (5-HT) in blood serum was tested. Daily excretion of adrenaline and noradrenaline in urine was estimated. The influence of the exposure to CS_2 on climacteric symptoms, functionality and the quality of life of women was studied [13].

This quality of life was assessed by means of Kupperman index (IK) [36]. In 1953 Kupperman and colleagues described an index for the evaluation of the effect of menopausal symptoms. This index in a modified form, which is adopted for use by patients, is the most widely used instrument for evaluation of menopausal symptoms [13] The frequency, the appearance of climacteric symptoms such as fatigue, depression, insomnia, tachycardia, hot flushes, headache, weight gain, loss of libido and scores, according to the index of Kupperman, were significantly higher for women exposed to CS_2 as compared to the control group of women with no exposure to CS_2 [13,14,37,38].

Especially interesting is the examination of CS_2 exposure in relation to the appearance of menopause. The average age of menopause for women exposed to CS_2 in the viscose industry, was 43.9±3.7 years old, and in the healthy control group of women – 48.1±2.4 years old [13]. Carbon disulfide exposure could change the reported age of menopause by an alteration of endocrine feedback loops and alternations of circulating hormone levels. CS_2 could specifically induce the estrogen metabolizing enzymes [2,37–39]. The precise mechanism of CS_2, inducing hormonal changes, is still unclear. The data suggests that the involvement of the hormonal system may be due to abnormalities of the peripheral nerves and their effects on the central nervous system (CNS) [27,30,32]. For most patients, the onset of CNS manifestations is insidious and the course is slowly progressive. Studies revealed chronic encephalopathy and microangiopathy in CNS after prolonged CS_2 exposure [5,13,34].

The activity of dopamine β-hydroxylase in the serum of CS_2-exposed women, working in the viscose industry, was essentially lower as compared to the healthy women in the control group [39]. The above-mentioned result correlates with the essentially lower levels of DA concentration in serum of CS_2-exposed women [13]. Moreover, the essential lowering of DA concentration in serum could be connected with the data that indicates a presynaptic dopaminergic damage of the nigrostriatal pathway [34]. The results of the study reported in "Neurotoxicology" indicate an abnormal presynaptic dopaminergic pathway for patients with chronic CS_2 intoxication which induces parkinsonism [34]. The exact mechanism is not provided [5,34].

The above-mentioned results indicate that CS_2 affects not only ovaries but also the activity of adrenals, causing suppression of their activity [4,5]. The consequences of this influence are: diminishing concentrations of progesterone, 17-hydroxyprogesterone, total testosterone and dehydroepiandrosterone sulfate in the serum of CS_2-exposed women [13].

The observed essentially more frequent menstrual disturbances and early menopause in CS_2-exposed women could also be connected with disturbances of secretion neurohormones on hypothalamus-hypophysis axis [30,32]. This hypothesis indicates essentially higher concentrations of 5-HT and prolactin in the serum of CS_2-exposed women [1,13,39]. These agents diminish the activity of the hypothalamus-hypophysis-ovarian axis. Essential decrease in DA in the serum of CS_2-exposed women causes the increase in PRL with all clinical consequences.

Disruption of ovarian function by CS_2 greatly affects women's reproductive and endocrinal health. Carbon

disulfide, as an environmental factor, may affect the female endocrine system and thus play an important role in the increasing problem of infertility [1,4,13,14,37,39].

CONCLUSIONS

In conclusion, reproductive health hazards for women chronically exposed to CS_2 in the workplace in the viscose industry are the following:

1. Menstrual disorders essentially more frequent than among healthy women were found.
2. The average menopausal age was statistically earlier as compared to healthy women.
3. Complex disturbances in neurohormonal system, resulting from toxic influences of CS_2, which cause diminishing secretion of estrogens and progesterone in ovaries and dehydroepiandrosterone sulfate in the adrenal gland.

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