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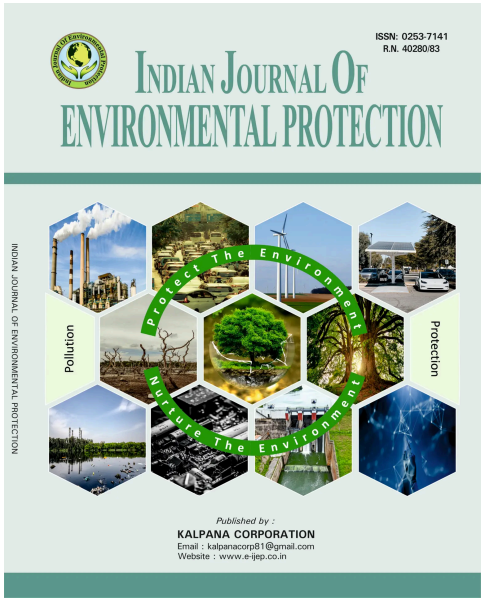

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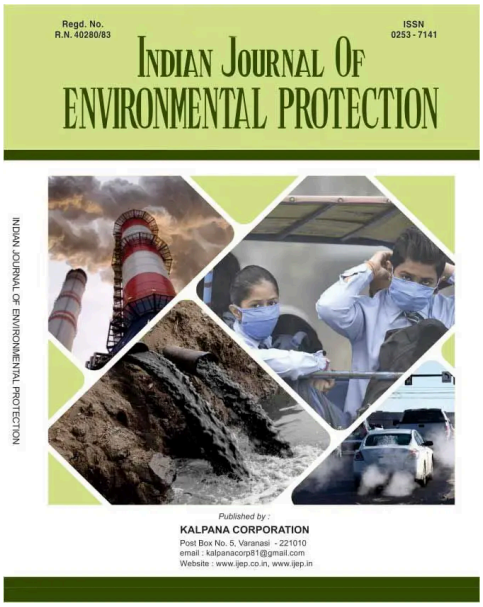

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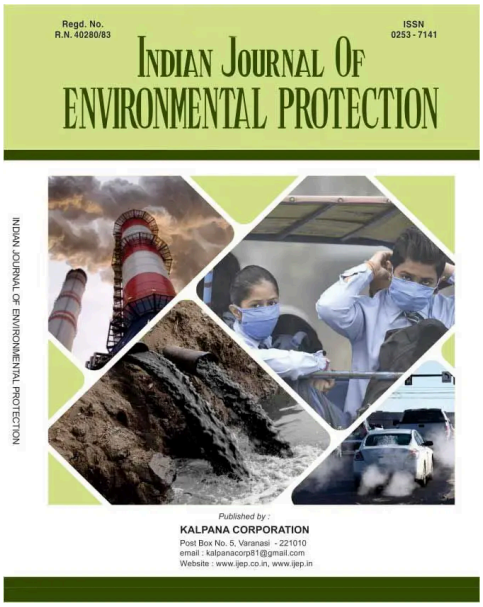

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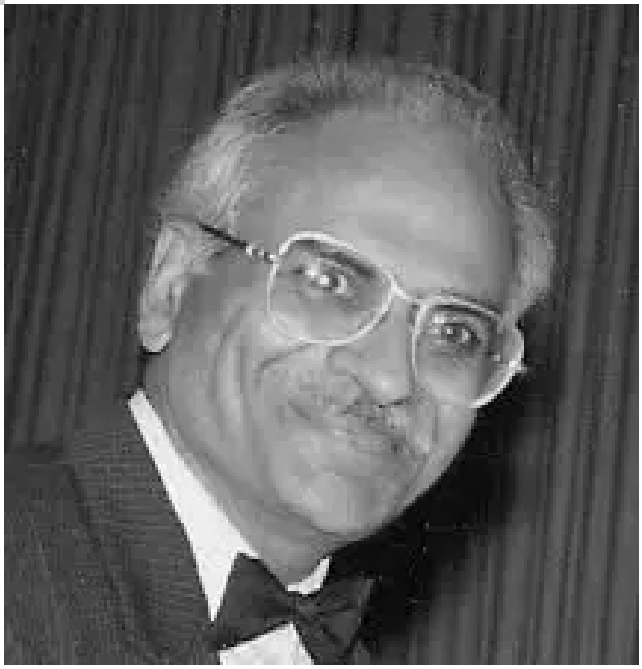

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IJEP 42 (14) : 1742-1746 (2022) (ISSN : 0253-7141)

Chronic Encephalopathy due to the Long-Term Exposure to Carbon Disulphide: Literature Review

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Carbon disulphide (CS_2) is widely used for numerous purposes, especially in the viscose rayon industry. Encephalopathy is a type of central nervous system (CNS) impairment due to CS_2 poisoning, which is usually slowly progressive. Acute, stroke-like episodes may occur, with manifestations ranging from hemiparesis, speech disturbance, neuropsychiatric changes and others, suggesting vascular events. Brain morphological changes have been documented in these patients, showing lesions in basal ganglia, corona radiata and brainstem; diffuse lesions in the white matter, which indicate central demyelination; decreased regional central blood flow (CBF) and prolonged regional cerebral vascular mean transit time (MTT) in subcortical white matter and lacunar infarction. Currently, the occupational exposure limit to CS_2 has been set within the range of 1-10 ppm for an 8 hr time-weighted average (TWA). TWA in Indonesia itself has been set at 10 ppm. Data regarding health impacts of CS_2 exposure are primarily available from past studies with higher exposure levels, with studies evaluating low-dose, long-term exposure being comparatively scarce. Further studies evaluating encephalopathy and other CNS disturbances from chronic CS_2 exposure in modern workplace settings in environmental and occupational health talks are necessary to gain more updated information regarding CS_2 toxicity.

KEYWORDS

Chronic encephalopathy, Carbon disulphide, Occupational exposure, Neurotoxicity

1. INTRODUCTION

Encephalopathy may result from damage to the white matter tracts or direct assault on neurons themselves, severing the communication between neurons. Diffuse encephalopathy with axonal polyneuropathy, Parkinsonism features, pyramidal tract symptoms, cerebellar ataxia, cognitive impairment and psychiatric symptoms are to be prompted by the chronic exposure to low-dose carbon disulphide (CS_2) [1,2]. Although the pathogenic mechanisms have not been elucidated, evidence showing vasculopathy, toxic demyelination and impaired brain perfusion have been mainly proposed. Neurora-diological studies and their associated cognitive dysfunction in CS_2-induced encephalopathy have remained abstruse and not well documented [3,4]. Widely used in the textile industry and industrial appliances, namely in manufacturing clothes (viscose rayon), food packaging (cellophane), dyes, tires and other rubber products, the usage of CS_2 is being controlled by government regulation. It is also highly volatile, flammable and has a very low flashpoint in the form of a colourless to faintly yellow liquid. Considering its various negative impacts on health, CS_2 intoxication in viscose rayon manufacturing has been relatively obscure compared to other chemical exposure health issues, such as lead or asbestos in-home appliance industry, despite its tremendous health impact among those

employed.

Since the last few decades, there has been growing evidence of CS_2 neurotoxicity, substantially in the talks of environmental and occupational health. As carbon disulphide serves as one of main compounds required in the rayon industry and poses an increasingly major health problem, the occupational exposure limit has changed over the past decade to a lower level, which was set at 20 ppm several decades ago, upto current limit set in the range of 1-10 ppm for a time-weighted average (TWA) of 8 hr. The first published occupational exposure limit was set based on prolonged exposure of 50-250 ppm CS_2 on animals and showed no effect [5,6]. Based on Ministry of Manpower and Transmigration of Indonesia Regulation in 2011, the TWA is 10 ppm [7]. Although manufacturers were bound to follow regulations to ensure the health of their workers, intoxication due to low-dose, long-term exposure has been well-sighted. While cutting short the exposure aids as the primary solution, careful investigation in differentiating the carbon disulphide toxic encephalopathy and other encephalopathy is crucial [8]. In this review, we focus on chronic exposure to CS_2 and its properties in the development of toxic encephalopathy.

2. MATERIAL AND METHOD

A literature search was performed using bibliographic databases, including PubMed, Google Scholar and Science Direct, regarding the clinical effects of long-term exposure to carbon disulphide, particularly on central nervous system.

3. RESULT AND DISCUSSION

3.1 Carbon disulphide

3.1.1 Substance properties and their uses: This compound is colourless, volatile and evaporates at room temperature, with its vapour twice the weight of air. It is highly flammable, with the heat of a light bulb sufficient to ignite its vapour [9]. Carbon disulphide is manufactured through a reaction of sulphur and charcoal or methane at really high temperatures, combining sulphur and carbon. Primarily, it is used to manufacture viscose rayon, cellophane film, xanthogenates, electronic vacuum tubes and carbon tetrachloride [6,9]. Human exposure mainly occurs in occupational settings via vapour inhalation or contact with skin and liquid contact. The general population may be exposed through inhalation of surrounding air and ingestion of foods containing CS_2 [6,9].

3.2 Carbon disulphide encephalopathy

3.2.1 Proposed mechanism of action: Although the CNS has a protective mechanism against toxic exposure to some degree, it does not entirely erase its vulnerability from certain chemicals in our surrounding environment. In fact, with neurons mainly composed of lipids and having a high metabolic rate, organic solvents with properties of non-polar and lipophilic would have the fewest difficulties in accessing the CNS. Lipophilic toxins can easily damage both the white and grey matter of the brain [8]. Specifically speaking of carbon disulphide, its mechanisms of toxicity had still been dubious but were thought to be the result of its metabolites formation, namely dithiocarbamates and/or derivatives, capable of inactivating metalloenzymes by chelation of metal ions [10]. Acute high-dose exposure may result in no substantial delay onset of adverse effects due to its rapidly metabolized nature once absorbed [8]. Cerebral cortex was more sensitive to these toxins than the brain stem and hence as consciousness falls, the brain stem function mostly remains intact. It, of course, depends on the exposure level- the greater the exposure, the greater the dysfunction it would cause [1]. A single neurotoxin may induce multiple neurological symptoms. High-dose acute exposure to carbon disulphide might cause psychosis. Meanwhile, low-dose chronic exposure might demonstrate vascular encephalopathy. The nervous system has limited capability in regenerating compared to other organs; hence the removal of causal neurotoxin might still leave sequelae after that [8].

Diffuse decrease of brain regional blood flow was demonstrated in CS_2 exposure, thus thereupon leading to central demyelination, markedly in the perivascular regions compatible with cerebral vasculopathy changes. Relative loss of myelinated fibres, degeneration of axon and myelin and decreased fibre density were noted in patients. The pathological mechanism of vasculopathy in carbon disulphide toxicity is still unclear. It is thought that it partakes in formation of initial lesions in atherosclerosis pathogenesis. Alterations in lipid metabolism, fibrinolytic function, derivatization and cross-linking of neurofilaments are found after exposure to CS_2. It also demonstrates cross-linking of low-density lipoprotein apolipoprotein B (LDL apoB), hence altering the uptake of macrophages and accelerating the process of atherosclerosis [1,11,12]. Despite the explanation few studies reported, the evidence is still rather insufficient. Diffuse encephalopathy is thought to be due to small-vessel ischemia.

3.2.2 Clinical manifestations: Depending on dose and duration of exposure, CS_2 intoxication may result in rapid onset of severe neurological symptoms or relatively slowly progressive neurological symptoms. Death upon exposure may occur, in part, due to respiratory paralysis. Upon high-dose acute inhalation oral or dermal exposure of carbon disulphide, patients may develop nausea, dizziness, headache, manic-depressive psychosis, blurred vision, convulsion, delirium and coma. A few reports demonstrated the development of psychosis, hallucinations and even suicidal attempts in subacute exposure for a few months. Clinical features include lowered vigilance, insomnia, nightmares, mood lability, paranoia, slurred speech and excessive sexual behaviour [13-16]. Repeated history of indicative acute intoxication symptoms (nausea, dizziness, headache) is often accompanied by neurological deficits and morphological changes in brain imaging [8]. However, as most reported cases with acute symptoms were from workers who had prior exposure to CS_2 for weeks or years, it is possible that these acute intoxication symptoms were superimposed on chronic ones [17].

Low-dose chronic exposure might result in polyneuropathy (for example, impaired sensory in distal areas, muscle weakness and hypo or areflexia of the tendon reflexes), vascular encephalopathy, Parkinsonian features and extrapyramidal syndrome (for example, motor disturbances, such as bradykinesia, rigidity, masked face, tremor and muscle weakness) [15]. Similarities to Parkinson's disease may pose a challenge to diagnosing CS_2 intoxication. There are several things to be taken note of in CS_2 intoxication, as follows: relatively young age, distinguished mental impairment, prevalent coordination disturbances, polyneuropathy and cerebellar dysfunction, not to mention their ineffective response to anti-Parkinsonian agents [1,8]. Several pieces of evidence demonstrated accompanying vascular lesions in basal ganglia as well as subcortical white matter, in accordance to the following clinical manifestations, explaining vasculopathy and small vessel disease in carbon disulphide intoxication [1,3,4,8]. Vascular encephalopathy is thought to develop due to arteriosclerotic changes after long-term exposure to low concentration of CS_2. Neuropsychological tests demonstrate impairments in learning and memory, attention, visuospatial perception, eye-hand coordination and motor speed in patients chronically exposed to CS_2 [12].

3.2.3 Morphological changes in neuroimaging: Multiple lesions were found in several areas, such as the basal ganglia, corona radiata and brainstem, demonstrated in brain CT and MRI scans. Brain MRI may show focal, often bilateral basal ganglia lesions or diffuse brain oedema [18]. One cannot ignore the similarities to Parkinson's disease. Dopamine transporter scan (DaTscan) of single-photon emission computed tomography (SPECT) scan shows normal uptake of dopamine transporter (DaT), thus suggesting different pathophysiology from Parkinson's disease [1]. Central demyelination is also indicated, as diffuse lesions of brain white matter were found in a handful of cases. Decreasing the regional cerebral blood flow (CBF) and prolonging regional cerebral vascular mean transit time (MTT) in subcortical white matter was also demonstrated [1]. The most notable findings frequently found in imaging studies are hyperintensity of white matter and lacunar infarction. However, its prevalence also increases with age. With the increasing age, CBF gradually decreases, thus initiating atherosclerotic plaque formation. Although comorbidities could accelerate this, such as diabetes, hypertension or other cardiovascular risk factors the patients have studies have also shown CS_2 exposure role in accelerating atherosclerosis, notably in the aorta, cerebral, coronary and renal arteries [3,11,13,18].

3.2.4. Clinical importance: In developing a diagnosis of CS2 intoxication, careful acquisition of exposure and occupation history is necessary. Many cases may go unrecognized, which may bring more harm to patients and other people exposed to the compound. There are several things to be noted before establishing toxic encephalopathy of carbon sulphide intoxication, which are: (1) exposure, sufficient dose or prolonged exposure; (2) compatible symptoms evolution through time course; and (3) exclusion of other neurological disorders in similar terms [8,19,20]. It is essential to differentiate carbon sulphide encephalopathy from other metabolic, inflammatory and degenerative nervous system diseases, or even psychiatric diseases, as they may also overlap and be found in one individual patient. Central nervous system (CNS) dysfunction symptoms from long-term exposure to carbon disulphide usually manifest slowly yet gradually progressive. Due to the carbon disulphide exposure, chronic encephalopathy typically has vascular disturbance as the primary underlying mechanism, with stroke-like episodes. These episodes may occur with presenting symptoms, such as speech disturbance and hemiparesis and maybe initially misdiagnosed as cerebrovascular attacks [8,21]. Vascular lesions in basal ganglia and subcortical white matter findings are in line with the hypotheses of vasculopathy and small vessel disease in carbon disulphide intoxication [1,3,4,12]. Therefore, carbon disulphide poisoning should be considered a differential diagnosis of vascular encephal-

opathy, particularly in high-risk populations (for example viscose industry workers) [8,12]. Moreover, it does not deny that age is also a variable that should also be considered carefully.

Even after cessation of occupational exposure, encephalopathy may get worse for 1-2 years. Partial recovery may subsequently ensue; had the damage been not too extensive, recovery might even be nearly complete [22]. By identifying CS_2 as the culprit, interventions may take place, including terminating the patient's exposure to the substance, potentially finding similar manifestations in their co-workers and evaluating their respective workplaces regarding exposure limit to CS_2. As the impact is pertinent to nation's working population, it is imperative to approach the issue in a sustainable effort, as issued in sustainable environmental assessment (SEA) and regulated in Governmental Regulation Number 46/2016, although successful integration is still limited. Indonesia's SEA needed to integrate multiple hazards or activities interactions, systemic risks and clear spatial information, thus built based on the existing regional mid-term development plan.

4. CONCLUSION

Long-term exposure to carbon sulphide, which predominantly occurs in occupational settings, has numerous deleterious effects on human health, including encephalopathy. Encephalopathy due to CS_2 intoxication should be considered a differential diagnosis, especially in workers of the viscose rayon industry or other workplaces involving the utilization of CS_2. The encephalopathy is typically vascular, owing to the atherosclerotic changes in blood vessels caused by CS_2 poisoning. Occupational exposure has currently been limited to 1-10 ppm per 8 hr TWA, which is effective in minimizing health risks for the exposed workers. Meanwhile, reports of the effects of low-dose, long-term exposure to CS_2 from more recent studies are comparatively scarce. Further studies evaluating carbon sulphide encephalopathy in current workplace settings are imperative.

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Chronic Encephalopathy due to the Long-Term Exposure to Carbon Disulphide: Literature Review

By Donna Adriani

WORD COUNT 2637
TIME SUBMITTED 18-JUN-2026 11:39AM
PAPER ID 122184535

International Conference on Environmental and Sustainability Context (ICoESCo) on August 24, 2021 by Environmental Research Group (EnSi-RG), Diponegoro University, Indonesia

IJEP42 (14): 1742-1746 (2022) (ISSN: 0253-7141)

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3. RESULT AND DISCUSSION

3.1 Carbon disulphide

3. 1.1 Substance properties and their uses: This compound is colourless, volatile and evaporates at room temperature, with its vapour twice the weight of air. It is highly flammable, with the heat of a light bulb sufficient to ignite its vapour [9]. Carbon disulphide is manufactured through a reaction of sulphur and charcoal or methane at really high temperatures, combining sulphur and carbon. Primarily, it is used to manufacture viscose rayon, cellophane film, xanthogenates, electronic vacuum tubes and carbon tetrachloride [6,9]. Human exposure mainly occurs in occupational settings via vapour inhalation or contact with skin and liquid contact. The general population may be exposed through inhalation of surrounding air and ingestion of foods containing cs2 [6,9].

3.2 Carbon disulphide encephalopathy

3.2.1 Proposed mechanism of action: Although the CNS has a protective mechanism against toxic exposure to some degree, it does not entirely erase its vulnerability from certain chemicals in our surrounding environment. In fact, with neurons mainly composed of lipids and having a high metabolic rate, organic solvents with properties of non-polar and lipophilic would have the fewest difficulties in accessing the **CNS**. Lipophilic toxins can easily damage both the white and grey matter of the brain [8]. Specifically speaking of carbon disulphide, its mechanisms of toxicity had still been dubious but were thought to be the result of its metabolites formation, namely dithiocarbamates and/or derivatives, capable of inactivating metalloenzymes by chelation of metal ions [10]. Acute high-dose exposure may result in no substantial delay onset of adverse effects due to its rapidly metabolized nature once absorbed [8]. Cerebral cortex was more sensitive to these toxins than the brain stem and hence as consciousness falls, the brain stem function mostly remains intact. It, of course, depends on the exposure level- the greater the exposure, the greater the dysfunction it would cause [1]. A single neurotoxin may induce multiple neurological symptoms. High-dose acute exposure to carbon disulphide might cause psychosis. Meanwhile, low-dose chronic exposure might demonstrate vascular encephalopathy. The nervous system has limited capability in regenerating compared to other organs; hence the removal of causal neurotoxin might still leave sequelae after that [8].

Diffuse decrease of brain regional blood flow was demonstrated in CS_2 exposure, thus thereupon leading to central demyelination, markedly in the perivascular regions compatible with cerebral vasculopathy changes. Relative loss of myelinated fibres, degeneration of axon and myelin and decreased fibre density were noted in patients. The pathological mechanism of vasculopathy in carbon disulphide toxicity is still unclear. It is thought that it partakes in formation of initial lesions in atherosclerosis pathogenesis. Alterations in lipid metabolism, fibrinolytic function, derivatization and cross-linking of neurofilaments are found after exposure to CS_2. It also demonstrates cross-linking of low-density lipoprotein apolipoprotein B (LDL apoB), hence altering the uptake of macrophages and accelerating the process of atherosclerosis [1, 11, 12]. Despite the explanation few studies reported, the evidence is still rather insufficient. Diffuse encephalopathy is thought to be due to small-vessel ischemia.

3.2.2 Clinical manifestations: Depending on dose and duration of exposure, CS_2 intoxication may result in rapid onset of severe neurological symptoms or relatively slowly progressive neurological symptoms. Death upon exposure may occur, in part, due to respiratory paralysis. Upon high-dose acute inhalation oral or dermal exposure of carbon disulphide, patients may develop nausea, dizziness, headache, manic-depressive psychosis, blurred vision, convulsion, delirium and coma. A few reports demonstrated the development of psychosis, hallucinations and even suicidal attempts in subacute exposure for a few months. Clinical features include lowered vigilance, insomnia, nightmares, mood !ability, paranoia, slurred speech and excessive sexual behaviour [13-161. Repeated history of indicative acute intoxication symptoms (nausea, dizziness, headache) is often accompanied by neurological deficits and morphological changes in brain imaging [8]. However, as most reported cases with acute symptoms were from workers who had prior exposure to CS_2 for weeks or years, it is possible that these acute intoxication symptoms were superimposed on chronic ones [17].

Low-dose chronic exposure might result in polyneuropathy (for example, impaired sensory in distal areas, muscle weakness and hypo or areflexia of the tendon reflexes), vascular encephalopathy, Parkinsonian features and extrapyramidal syndrome (for example, motor disturbances, such as bradykinesia, rigidity, masked face, tremor and muscle weakness) [15]. Similarities to Parkinson's disease may pose a challenge to diagnosing CS_2 intoxication. There are several things to be taken note of in CS_2 intoxication, as follows: relatively young age, distinguished mental impairment, prevalent coordination disturbances, polyneuropathy and cerebellar dysfunction, not to mention their ineffective response to anti-Parkinsonian agents [1,8]. Several pieces of evidence demonstrated accompanying vascular lesions in basal ganglia as well as subcortical white matter, in accordance to the following clinical manifestations, explaining vasculopathy and small vessel disease in carbon disulphide intoxication [1,3,4,8]. Vascular encephalopathy is thought to develop due to arteriosclerotic changes after long-term exposure to low concentration of CS_2. Neuropsychological tests demonstrate impairments in learning and memory, attention, visuospatial perception, eye-hand coordination and motor speed in patients chronically exposed to CS_2 [121.

3.2.3 Morphological changes in neuroimaging: Multiple lesions were found in several areas, such as the basal ganglia, corona radiata and brainstem, demonstrated in brain CT and **MRI** scans. Brain MRI may show focal, often bilateral basal ganglia lesions or diffuse brain oedema [18]. One cannot ignore the similarities to Parkinson's disease. Dopamine transporter scan (DaTscan) of single-photon emission computed tomography (SPECT) scan shows normal uptake of dopamine transporter (DaT), thus suggesting different pathophysiology from Parkinson's disease [1]. Central demyelination is also indicated, as diffuse lesions of brain white matter were found in a handful of cases. Decreasing the regional cerebral blood flow (CBF) and prolonging regional cerebral vascular mean transit time (MTT) in subcortical white matter was also demonstrated [1]. The most notable findings frequently found in imaging studies are hyperintensity of white matter and lacunar infarction. However, its prevalence also increases with age. With the increasing age, CBF gradually decreases, thus initiating atherosclerotic plaque formation. Although comorbidities could accelerate this, such as diabetes, hypertension or other cardiovascular risk factors the patients have studies have also shown CS_2 exposure role in accelerating atherosclerosis, notably in the aorta, cerebral, coronary and renal arteries [3, 11, 13, 18].

3.2.4. Clinical importance: In developing a diagnosis of CS2 intoxication, careful acquisition of exposure and occupation history is necessary. Many cases may go unrecognized, which may bring more harm to patients and other people exposed to the compound. There are several things to be noted before establishing toxic encephalopathy of carbon sulphide intoxication, which are: (1) exposure, sufficient dose or prolonged exposure; (2) compatible symptoms evolution through time course; and (3) exclusion of other neurological disorders in similar terms [8, 19,20]. It is essential to differentiate carbon sulphide encephalopathy from other metabolic, inflammatory and degenerative nervous system diseases, or even psychiatric diseases, as they may also overlap and be found in one individual patient. Central nervous system **(CNS)** dysfunction symptoms from long-term exposure to carbon disulphide usually manifest slowly yet gradually progressive. Due to the carbon disulphide exposure, chronic encephalopathy typically has vascular disturbance as the primary underlying mechanism, with stroke-like episodes. These episodes may occur with presenting symptoms, such as speech disturbance and hemiparesis and maybe initially misdiagnosed as cerebrovascular attacks [8,21]. Vascular lesions in basal ganglia and subcortical white matter findings are in line with the hypotheses of vasculopathy and small vessel disease in carbon disulphide intoxication [1,3,4, 12]. Therefore, carbon disulphide poisoning should be considered a differential diagnosis of vascular encephal-

opathy, particularly in high-risk populations (for example viscose industry workers) [8, 12]. Moreover, it does not deny that age is also a variable that should also be considered carefully.

Even after cessation of occupational exposure, encephalopathy may get worse for **1-2** years. Partial recovery may subsequently ensue; had the damage been not too extensive, recovery might even be nearly complete [22]. By identifying CS_2 as the culprit, interventions may take place, including terminating the patient's exposure to the substance, potentially finding similar manifestations in their co-workers and evaluating their respective workplaces regarding exposure limit to CS_2. As the impact is pertinent to nation's working population, it is imperative to approach the issue in a sustainable effort, as issued in sustainable environmental assessment (SEA) and regulated in Governmental Regulation Number 46/2016, although successful integration is still limited. Indonesia's SEA needed to integrate multiple hazards or activities interactions, systemic risks and clear spatial information, thus built based on the existing regional mid-term development plan.

4. CONCLUSION

Long-term exposure to carbon sulphide, which predominantly occurs in occupational settings, has numerous deleterious effects on human health, including encephalopathy. Encephalopathy due to CS_2 intoxication should be considered a differential diagnosis, especially in workers of the viscose rayon industry or other workplaces involving the utilization of CS_2 The encephalopathy is typically vascular, owing to the atherosclerotic changes in blood vessels caused by CS_2 poisoning. Occupational exposure has currently been limited to 1-10 ppm per 8 hr TWA, which is effective in minimizing health risks for the exposed workers. Meanwhile, reports of the effects of low-dose, long-term exposure to CS_2 from more recent studies are comparatively scarce. Further studies evaluating carbon sulphide encephalopathy in current workplace settings are imperative.

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