Media Gizi Kesmas
p-ISSN 2301-7392, e-ISSN 2745-8598
10.20473/mgk.v12i2.2023.1095-1106

LITERATURE REVIEW **Open Access**

Efek Vinil Klorida terhadap Metilasi DNA: Tinjauan Sistematis

Effect Vinyl Chloride to DNA Methylation: A Systematic Review

Nabila Azzahra Alifia[1]*, Abdul Rohim Tualeka[1]

[1]Department of Occupational Health and Safety, Faculty of Public Health, Airlangga University, Surabaya, 60115, Indonesia

Article Info

***Correspondence:**
Nabila Azzahra Alifia
nabila.azzahra.alifia-2019@fkm.unair.ac.id

Submitted: 16-03-2023
Accepted: 31-05-2023
Published: 30-11-2023

Citation:
Alifia, N. A., & Tualeka, A. R. (2023). Effect Vinyl Chloride to DNA Methylation: A Systematic Review. *Media Gizi Kesmas*, 12(2), 1095–1106. https://doi.org/10.20473/mgk.v12i2.2023.1095-1106

ABSTRAK

Latar Belakang: *Vinil klorida adalah sebuah gas dengan kandungan bahan kimia beracun dengan ciri khas gas tidak berwarna yang banyak digunakan dalam industri pembuatan plastik. Vinil klorida memiliki berbagai efek yang mengancam kesehatan seperti mengganggu metilasi* deoxyribonucleic acid *(DNA) sehingga menyebabkan hepatoseluler karsinoma (HCC) dan kanker.*
Tujuan: *Tujuan penulisan tinjauan sistematis ini adalah untuk mengetahui hubungan pengaruh antara vinil klorida terhadap metilasi* deoxyribonucleic acid *(DNA).*
Metode: *Desain penelitian ini merupakan artikel tinjauan sistematis dengan menggunakan metode PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses). *Pertanyaan ini disusun dengan memperhatikan 4 tahapan yaitu*: Population Intervention, Comparison, *dan* Outcome (PICO). *Dengan mecari artikel/jurnal sesuai dengan kata kunci di PICO yaitu "vinil klorida" dan "metilasi DNA" secara* online *melalui Google Scholar dan PubMed, diperoleh 74 artikel/jurnal dengan kriteria inklusi yang telah ditentukan pada judul, abstrak, dan* fulltext *sehingga diperoleh 8 artikel/jurnal.*
Hasil: *Berdasarkan hasil tinjauan sistematis, telah ditemukan gambaran hubungan sebab akibat vinil klorida terhadap metilasi* deoxyribonucleic acid *(DNA) pada pekerja industry yang menunjukkan induksi metilasi* deoxyribonucleic acid *(DNA) dengan peningkatan risiko terjadinya kanker dan hepatoseluler karsinoma.*
Kesimpulan: *Terdapat hubungan antara paparan vinil klorida pada metilasi* deoxyribonucleic acid *(DNA) yang menimbulkan efek bahaya kesehatan hepatoseluler karsinoma (HCC) dan kanker. Perlu adanya upaya pencegahan dan pengendalian paparan vinil klorida dalam aplikasinya untuk mencegah paparan terhadap pekerja, misalnya dengan menggunakan APD. Hasil kajian tinjauan iniangat penting digunakan pemerintah sebagai acuan dalam upaya mencegah dan mengendalikan paparan bahan kimia vinil klorida di lingkungan kerja.*

Kata kunci: *Vinil klorida, Metilasi DNA, Hepatoseluler Karsinoma, Kanker, Pekerja*

ABSTRACT

Background: Vinyl chloride (VC) is a toxic chemical hazard which is characterized with colorless gas widely used in the plastics manufacturing industry. Vinyl chloride (VC) has various health threatening effects such as bothering deoxyribonucleic acid (DNA) methylation that can cause hepatocellular carcinoma (HCC) and cancer.
Objectives: The purpose of writing systematic review is to determine the effect vinyl chloride (VC) to deoxyribonucleic acid (DNA) methylation.
Methods: The research design is a systematic review article using PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. This question is structured by taking into account 4 stages, namely: Population, Intervention, Comparison, and Outcome (PICO). By searching for articles/journals that match the keywords in PICO, namely "vinyl chloride (VC)"

and "DNA methylation" online via Google Scholar and PubMed. Through this search, 74 articles/journals were obtained. Then an assessment of the suitability of the inclusion criteria that has been determined in the title, abstract, and content is carried out full text so that 8 articles/ journals were obtained.
Results: Based on the results systematic review, picture of cause and effect relationship vinyl chloride (VC) against deoxyribonucleic acid (DNA) methylation has been found in industrial workers who inhibit deoxyribonucleic acid (DNA) methylation which ultimately causes risk of cancer and hepatocellular carcinoma (HCC).
Conclusions: There is a connection between exposure vinyl chloride (VC) and deoxyribonucleic acid (DNA) methylation that cause health hazardous effects in the form of hepatocellular carcinoma (HCC) and cancer. It's necessary to have efforts to prevent and control exposure vinyl chloride (VC), one of which is the use of Personal Protective Equipment (PPE). Results of this systematic review are very important to be used by the government as a reference in efforts to preventing and controlling chemical exposure vinyl chloride (VC) in the work environment.

Keywords: *Vinyl Chloride, DNA Methylation, Hepatocellular Carcinoma, Cancer, Worker*

INTRODUCTION

Vinyl chloride (VC) is a toxic chemical hazard which is characterized with colorless gas widely used in the plastics manufacturing industry particularly as an organic agent and coolant. Vinyl chloride (VC) will undergo metabolized in liver to become electrophilic metabolites that are chlorethylene oxide (CEO) and chloro acetaldehyde (CAAs). This gas has being quikly absorbed by human body via inhalation. CEO and CAA react with basic deoxyribonucleic acid (DNA) to form mutagenic adducts in bacterial and mammalian cells, including humans (Weihrauch *et al.*, 2001).

Vinyl chloride (VC) has the formula H2C=CHCl which is commonly called organochloride vinyl chloride monomer (VCM). These compounds is a special chemicals for production of polymers polyvinyl chloride (PVC) with finished products such as polymers polyvinyl chloride (PVC) bottles and pipes. Other uses of this compound are as furniture and car coatings, wall coverings, refrigerants, household appliances, and automotive parts. About thirteen million kilograms vinyl chloride (VC) are produced annually. Vinyl chloride monomer (VCM) is on the top 20 petrochemicals in world production. This gas was highly toxic, carcinogenic and flammable which contain sweet smell. Vinyl chloride (VC) is an industrial waste substance or decomposition of chlorinated chemicals that can poison drinking water supplies.

Vinyl chloride (VC) has various health threatening effects such as Raynaud's syndrome and acroosteolysis. The mutagen disruption of this compound has a clastogenic effect that affects the chromosomal structure of lymphocytes. The effects of carcinogens are very diverse, such as: angiosarcoma, brain and lung tumors, malignant hemopoiesis lymphatic tumors, hepatotoxicity, respiratory failure, euphoria and disorientation, decreased male libido, spontaneous abortion, and birth defects. Meanwhile, acute dermal and ocular effects that affect the skin include skin thickening, edema, decreased skin elasticity, local frostbite, blistering, and irritation.

Concentration of vinyl chloride (VC) that exceeds the threshold value with13 mg/m^3 or 5 bds can have various effects, one of it can bothering deoxyribonucleic acid (DNA) methylation. In humans, a causal relationship has been shown in several studies between exposure to vinyl chloride (VC) by deoxyribonucleic acid (DNA) methylation. Body cells contain genetic information which is there are genes might be contain procedures for making specific proteins according to their function in cells. In order for the cell to know what to do or what protein to make according to its function, other genes that are not fit for its function are turned off. One way to activate and deactivate genes are with deoxyribonucleic acid (DNA) methylation process (Weihrauch *et al.*, 2001).

Deoxyribonucleic acid (DNA) methylation is responsible for determining cell function according to the target organ to be formed. Deoxyribonucleic acid (DNA) methylation finished by adding a methyl group to a gene that is unnecessary by the cell so that there is a change in its structure and makes it unable to make protein. Then, what's the point used for protein production is a gene that doesn't have a methyl group or it's called an unmethylated gene. This process causes the shape of the cell to be different even though the genetic it carries the same information. The environment can affect the deoxyribonucleic acid (DNA) methylation process, including the exposure to harmful substances such

as vinyl chloride (VC).

Deoxyribonucleic acid (DNA) methylation is an action-reaction process of a series of deoxyribonucleic acid (DNA) methylation and deoxyribonucleic acid (DNA) demethylation activities. There are three main mechanisms of epigenetic modification, one of which is Deoxyribonucleic acid (DNA) methylation. Deoxyribonucleic acid (DNA) methylation is initiated and defined by one of kind de novo deoxyribonucleic acid (DNA) methyltransferases DNMT3 (DNMT3A and DNMT3B) and is maintained during replication by maintenance deoxyribonucleic acid (DNA). Deoxyribonucleic acid (DNA) methylation involves adding a methyl group to the 5 cytosine pyrimidine ring composition of the CpG dinucleotide, using S Adenosyl-methionine (SAM) as the methyl donor. Active demethylation of methylated cytosine involves hydroxyl methylation by Ten-eleven translocation (TET) enzymes, including Tet 1, Tet 2, and Tet 3, which sequentially convert 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), then to 5-formyl cytosine and finally to 5-carboxytosine (Ye, Siwko and Tsai, 2021).

Research by the Kyoto encyclopedia of genes and genomes (KEGG) and gene ontology (GO) showing three main effects by deoxyribonucleic acid (DNA) hypermethylation and hypomethylation namely cancer, neuronal ligand receptor interactions, and axon guidance. Certain dimethylglyoxime (DMG) depigenetic disorders (BCL2, TJP2, TAOK1, PFKFB3, LIPI, LIPH, BNIP1, and GRPEL2) still connected with deoxyribonucleic acid (DNA) damage from vinyl chloride exposure (Zhao *et al.*, 2022). Other effects that arise due to deoxyribonucleic acid (DNA) methylation reactions are often found related with liver disorders such as liver angiosarcoma (LAS) and hepatocellular carcinoma (HCC) (Weihrauch *et al.*, 2001). Targeted objects of vinyl chloride (VC) exposure which have been shown can increase the risk of liver cancer are workers who's work in factories that use and produce arsenic, cadmium, and several other hepatotoxins (Barsouk *et al.*, 2021).

Weihrauch *et al.* (2001) have reported that workers exposed by vinyl chloride (VC) experienced a higher frequency of p16INK4A hypermethylation causing hepatocellular carcinoma (HCC) compared with unexposed workers. Risk factors which play role in developing hepatocellular carcinoma (HCC) including exogenous factors, such as viral infection and exposure to vinyl chloride. Loss of function of p16INK4A occurs due to promoter methylation, as the beginning of the pathogenesis various tumor. In 2001, hepatocellular carcinoma (HCC) was ranked as the fifth most common solid tumor in the world and the top three leading cause cancer related death. Several studies have shown that aberrant methylation of the 5'-cytosine-phosphoguanine island in the promoter region frequently upregulates the tumor suppressor gene p16INK4A (Weihrauch *et al.*, 2001).

In addition to vinyl chloride, there are several toxins and chemical associated with causing hepatocellular carcinoma (HCC), such as androgenic steroids an aflatoxin B1. Cases of hepatocellular carcinoma (HCC) in men and women or certain racial groups vary depending on the various risk factors received by them and the characteristics of their own body (Ye, Siwko and Tsai, 2021). Methylating agents modify deoxyribonucleic acid (DNA) in many different places resulting in lethal and mutagenic lesions (Sedgwick, 2004). Deviations in the form of deoxyribonucleic acid (DNA) methylation are very dangerous because they can block proteins that will stick to deoxyribonucleic acid (DNA) so that the transcription process or deoxyribonucleic acid (DNA) reading becomes hampered. Study by Wu *et al.* (2013) suggested that aberrant methylation of the MGMT promoter was found in exposed workers vinyl chloride (VC) damaged chromosomes, causing cancer.

Deoxyribonucleic acid (DNA) methylation can be a cause of carcinogenesis. Carcinogenesis is an event of the formation of cancer in which the development or division of body cells occurs abnormally or uncontrollably which can invade other tissues through the blood and lymph vessels. Currently, cancer is one of the seven leading causes of death in the world (Silva *et al.*, 2019). In another study it was stated that deoxyribonucleic acid (DNA) methylation was associated with deoxyribonucleic acid (DNA) damage responses such as cyclin-dependent kinase inhibitor (CDKN)2A, Race association (RalGDS/AF-6) domain family member (RASSF)1A, O6-methylguanine deoxyribonucleic acid (DNA) methyltransferase (MGMT), Kirsten rat sarcoma viral oncogene homolog (KRAS), and tyrosine kinase (SYK) associated spleen and deoxyribonucleic acid (DNA) damage in mouse hepatocytes after exposure vinyl chloride (VC) subchronic (Yu-Lan Qiu *et al.*, 2019).

Currently, the amount of research regarding the harmful effects vinyl chloride (VC) to deoxyribonucleic acid (DNA) methylation is insufficient to describe their relationship. Because of the importance of this topic, it is necessary to do a literature search through systematic review, so that an adequate systematic review can be obtained to analyze the relationship between vinyl chloride (VC) to deoxyribonucleic acid (DNA) methylation. The purpose of writing systematic review is to determine the effect of vinyl chloride (VC) to deoxyribonucleic acid (DNA) methylation.

METHOD

The research design is a systematic review article using PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. References used to write articles review this is obtained beyond line through a systematic search of Google Scholar and PubMed, as illustrated in Figure 1. All the references to creating this systematic review used an article written in English.

At the initial stage, the researcher determines the scientific questions that form the basis of the systematic review formation. This question is structured by taking into account 4 stages, namely: Population, Intervention, Comparison, and Outcome (PICO) and obtained a scientific question, namely "How is the effect vinyl chloride (VC) compared with the time and amount of exposure to deoxyribonucleic acid (DNA) methylation in humans, particularly workers?".

The search for the data in the form of articles or journals is carried out using the method Boolean searching by using the keyword "vinyl chloride (VC)" and "DNA methylation". Then the inclusion criteria were determined which were also adjusted to the previous 4 elements (PICO), so that the inclusion criteria were obtained as follows: (1) population, namely humans; (2) Intervention, which is effect vinyl chloride (VC); (3) comparison, which is targeted gene, amount and time of exposure; and (4) outcomes, namely deoxyribonucleic acid (DNA) methylation. Then the results of the exclusion criteria by the time of publication with a span of the last 5 years, namely 2017-2022 and only focusing on articles using English.

By searching for articles/journals that match the keywords in PICO, namely "vinyl chloride (VC)" and "DNA methylation" online via Google Scholar and PubMed. Through this search, 74 articles/ journals were obtained. Then an assessment of the suitability of the inclusion criteria that has been determined in the title, abstract, and content is carried out full text so that 8 articles/ journals were obtained.

From the total searches, data were obtained in the form of articles/journals regarding vinyl chloride (VC) and deoxyribonucleic acid (DNA) methylation (n=74). The data focused on study and research articles (n=30). From these 30 articles/journals, an analysis was conducted according to the following inclusion criteria: 1) human population, especially workers; 2) without intervention n; 3) without comparison; 4) articles published in 2017-2022; and 5) English.

From the identification of articles or journals with keywords that match this research, obtained 8 articles with a range of the last 5 years (2017-2022). Each article was studied and analyzed according to the inclusion criteria. Article analysis was obtained through the stages of identification, screening, and criteria determination. There were 8 international articles met the criteria and were synthesized and analyzed. The inclusion criteria "outcome" was determined according to the purpose of writing the systematic review, variables were included in the PICOS method so that they could be explored widely, and the effect was clear. vinyl chloride (VC) against deoxyribonucleic acid (DNA) methylation. The following is a table according the results of the articlesused as research material:

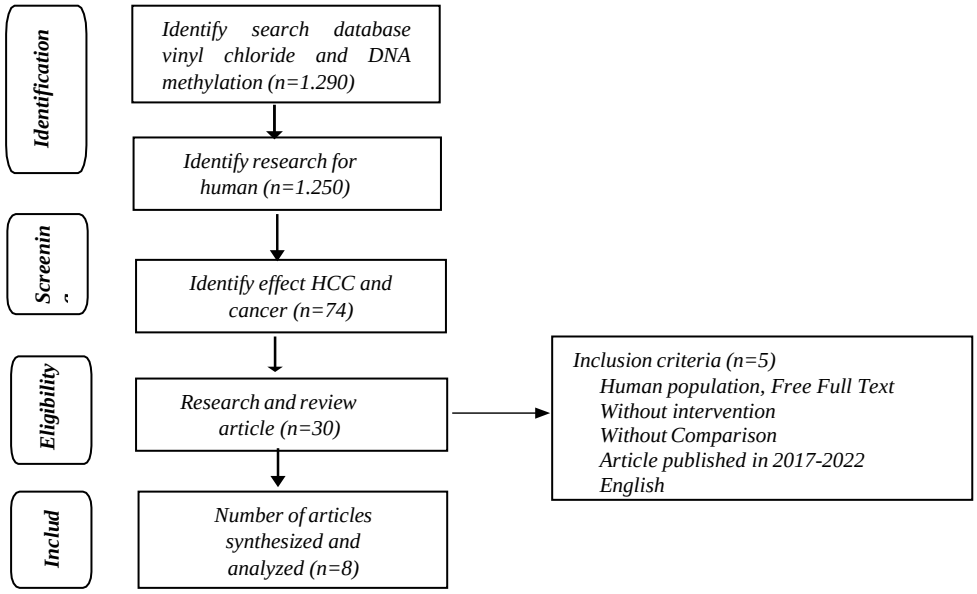

Figure 1. Diagram of the Effect Data Search Process Vinyl Chloride (VC) Against Deoxyribonucleic acid (DNA) Methylation

RESULTS AND DISCUSSUSION

Based on the results systematic review, vinyl chloride (VC) is a chemical that is found often in industry, especially the plastics industry. This gas has a sweet odor, is highly toxic, flammable and carcinogenic. Vinyl chloride (VC) released by industry or formed through the breakdown of other chlorinated chemicals can reach the air and merge with drinking water supplies. Vinyl chloride (VC) enters the human body mostly through the respiratory route (inhalation). This substance has various effects that could be dangerous for health. Therefore, this is the main focus of several researchers with the point of reducing exposure vinyl chloride (VC) on workers.

Based on the results systematic review, deoxyribonucleic acid (DNA) methylation is one of three epigenetic mechanisms whose job is to determine cell function according to the target organ to be formed. deoxyribonucleic acid (DNA) methylation is done by adding a methyl group to a gene that is not needed by the cell so that there is a change in its structure and makes it unable to make protein. Deoxyribonucleic acid (DN methylation is associated with various organ disorders because it interferes with the transcription of amino acids in the body such as liver disorders, cancer, reproductive system disorders, intestinal diseases, asthma, metabolic disorders, and several other diseases. Based on the results systematic review, picture of cause and effect of relationship vinyl chloride (VC) against deoxyribonucleic acid (DNA) methylation has been found in industrial workers who exhibit deoxyribonucleic acid (DNA) methylation induction with an increased risk of liver cancer, hepatic endothelial disorders, portalhypertension and angiosarcoma rare liver malignancy (ASL). Another association was demonstrated by the presence of p16INK4A methylation found in hepatocellular carcinoma (HCC) patients. Exposure to vinyl chloride (VC) has some potential to caused liver cirrhosis leading to hepatocellular carcinoma (HCC) in the late stages due to deoxyribonucleic acid (DNA) damage. Other consequences of exposure vinyl chloride (VC) has the potential to have a carcinogenic effect so that it has an impact on the growth of tumor and cancer cells. This is evidenced by the significant increase in promoter methylation of the CDKN2A, APC, MLH1, BCL2, TJP2, TAOK1, PFKFB3, LIPI, and LIPH genes hypermethylated and the BNIP1 and GRPEL2 methylation levels decreased.

Vinyl chloride (VC) is a hazardous substance that is often found in industry. Based on the article by Barsouk *et al.* (2021). Vinyl chloride monomer (VCM) is a hydrocarbon compound in the plastic industry producing polyvinyl chloride (PVC). Polyvinyl chloride (PVC) is substance whose uses can be found in single day, for example Protective Personal Equipment (PPE) clothing, water pipes, and medical equipments which has harmless properties. However, the substance contains dangerous particle is vinyl chloride monomer (VCM) which is the active monomer of vinyl chloride can threatening adverse effects on thousand workers involved plastic production. In line with this article, research conducted by El-Mougy *et al.* (2014) mentions vinyl chloride (VC) has three entrances in the human body is through inhalation (inhalation), digestion (ingestion), and skin. The route of entry that causes the most cases is inhalation. Reinforcing the previous article, the article by Ye, Siwko and Tsai (2021) mentions that vinyl chloride (VC) is absorbed through the respiratory and metabolized by liver into various mutagenic and carcinogenic compounds such as ethylene dichloride and chloro-ethylene oxide.

Based on the article (Rashed *et al.* 2020) vinyl chloride (VC) is averagely used in manufacturing Dichoro Diphenyl Trichlorethane (DDT). The toxic substance Dichoro Diphenyl Trichlorethane (DDT) is very persistent (long lasting, decades, maybe even 100 years or more), continuos in the environment while poisoning ecosystems without being physically or biologically damage. The use of Dichoro Diphenyl Trichlorethane (DDT) can cause poisoning, contamination of the food chain, and damage to body tissues. In line with the previous article, the article by Habeeb, M., et.al. (2022) vinyl chloride (VC) has a characteristic sweet smell. This gas was highly toxic, carcinogenic and flammable which contain sweet smell. The formation of these compounds was aided by soil organisms when they break down chlorinated solvents. In support of the above systematic review, research conducted by Silva *et al.* (2019) assessed that vinyl chloride (VC) exposes millions of workers worldwide. However, it is sad that the handling of exposure vinyl chloride (VC) can be said to have not been resolved properly. It is proven by the existence of several cases of consequent disease vinyl chloride (VC) chronic, acute, to cause death.

Based on Zhao et al. (2022), deoxyribonucleic acid (DNA) methylation is an epigenetic mechanisms besides histone modification, and non-coding ribonucleic acid (RNA). Epigenetics works by influencinghow a gene is read by the cell and proving whether the cell should produce the relevant protein, for example, the COL1A1 gene in deoxyribonucleic acid (DNA) is present in all cell types then expressed in skin cells to produce the type 1 collagen protein. Based on the article by Ye, Siwko and Tsai (2021)**,** by maintaining deoxyribonucleic acid (DNA) sequences and

altering genomic structure, regulation of expression and genomic stability can be maintained by the presence of epigenetic modifications. It has been found that the key to the formulation of the problem regarding environmental inputs and genetic reactions that initiate several complex diseases such as cancer, hepatocellular carcinoma, and cardiovascular disease.

Ye, Siwko and Tsai (2021) also mentioned that there are two types of enzymatic activity in deoxyribonucleic acid (DNA) methylation catalyzed process, namely the methylation of unmethylated cytosine residues and the addition of new methyl groups to unmethylated cytosine. In the first type, hemymethylation occurs in deoxyribonucleic acid (DNA) strand while deoxyribonucleic acid (DNA) methylation replication occurs. It's then catalyzed by deoxyribonucleic acid (DNA) methylation methytransferase1 (DNMT1) and it's cofactors, such as asubiquitin with PHD and RING 1 (UHRF1) finger domains. Meanwhile, in the type two, type of genes that play a role, namely two de novo deoxyribonucleic acid (DNA) methyltransferases, DNMT3A and DNMT3B, together with their coactivator DNMT3L as a catalyst.

Adding to the previous statement, the article by Barsouk *et al.* (2021), indicates that deoxyribonucleic acid (DNA) methylation can be derived from harmful substances such as arsenic, cadmium, and vinyl chloride (VC). Measurement of deoxyribonucleic acid (DNA) methylation can be done in various ways, one of which is by using a methylation specific polymerase chain reaction (PCR) (MSP) on the p16INK4A gene (El-Mougy *et al.* 2014**).** As for the use of deoxyribonucleic acid (DNA) methylation that has been proven to be mentioned by Rashed *et al.*, (2020), one of them is to detect 363 cases hepatocellular carcinoma (HCC) using whole-exome sequencing (WES). In addition, based on the article by Habeeb and Sugumaran, (2022). Deoxyribonucleic acid (DNA) methylation is beneficial in lipid metabolism functioning by PPARc, the involvement of epigenetic changes including histone methylation, RNA non coding, acetylation, and deoxyribonucleic acid (DNA) methylation have long been promoted as important developments in the progression of liver melanoma. Research conducted by Silva *et al.* (2019) emphasizes that exposure affects methylation levels. Altered deoxyribonucleic acid (DNA) methylation can be used as a potential biomarker for early detection of changes in occupationally exposed individuals.

Based on the results of this systematic review, relationship between vinyl chloride (VC) with deoxyribonucleic acid (DNA) methylation causes so many kinds of health diseases. Two main health problems that havebecome the focus of research by several researchers are leading to problems with the liver, commonly known as liver disease hepatocellular carcinoma (HCC) and cancer. Barsouk *et al.* (2021) mentioned that vinyl chloride (VC) chloride is responsible for a significant burden of liver cancer in certain populations. Vinyl chloride (VC) is one of the chemical risk factors that drives the increased risk of hepatocellular carcinoma (HCC) and other primary liver cancers that are influenced by the presence of deoxyribonucleic acid (DNA) methylation.

Research conducted by El-Mougy *et al.* (2014) shows that vinyl chloride (VC) has been shown to be one of the exogenous risk factors that causes hypermethylation of the p16INK4A gene due to aberrant deoxyribonucleic acid (DNA) methylation mechanisms. Methylation of the promotor region, namely 5' islet cytosine-phosphor guanin, is often found to decrease the function of p16INK4A tumor suppressor gene. Hepatocellular carcinoma (HCC) is a chronic disease caused by chronic infection HBV and HCV viruses. Aberrations in methylation of the p16INK4A tumor gene were found in patients with chronic HBS or HCV disease and also liver cirrhosis. Thus, the chronic hepatitis virus acts as an early stage inductor in methylation process of the p16INK4A promoter in hepatocarcinogenesis.

The article by Ye, Siwko and Tsai (2021) mentions that vinyl chloride (VC) one of the toxins or chemicals in the environment associated with deoxyribonucleic acid (DNA) methylation that causes hepatocellular carcinoma (HCC). In early stages of the process of carcinogenesis, the deoxyribonucleic acid (DNA) methylation machinery play causative roles exhibits neoplasia-associated changes. These methylation changes are associated with widespread of cancer in human body which consists of distinct tumor cell colonies and normal tissues that have not received histologically morphological transformation. Deoxyribonucleic acid (DNA) methylation that occurs as a result of the exposure of vinyl chloride encourages the development of cancer cells through several mechanism including hypermethylation and hypomethylation. First, In hypermethylation mechanism, the promoter inhibits the expression of tumor suppressor genes (TSGs). On the other hand, promoter hypomethylation mechanisms can lead to increased oncogene expression. The role of p16INK4A, Rb, and the von Hippel-Lindau tumor suppressor(VHL) has been shown to silence the aberrant deoxyribonucleic acid (DNA) hypermethylation mechanism in promoter region. Conversely, deoxyribonucleic acid

(DNA) hypomethylation of the RAS oncogene has been reported in hepatocellular carcinoma (HCC).

Second, deoxyribonucleic acid (DNA) hypomethylation suggests that there is a changing landscape that contributes to neoplastic transformation prior to adenoma formation and often seen to be maintained in neoplastic tissue. Deoxyribonucleic acid (DNA) hypomethylation on repeating sequences of elements transposable, such as short interspersed nuclear elements (SINE or Alu elements) or long interspersed nuclear elements (LINEs), can predispose cells to defects and chromosomal rearrangements, leading to genetic instability and oncogenesis. Third, deoxyribonucleic acid (DNA) methylation also increases the likelihood of C-to-T mutations as a result of the spontaneoushydrolytic deamination of 5-methylcytosine at the CpG site (Ye et al., 2021).

The article by Ye, Siwko and Tsai (2021) explains that causes of deaths based on sex/gender-related and race/ethnicity due to cancer and hepatocellular carcinoma are the series of causal relationship with deoxyribonucleic acid (DNA) methylation in neoplastic tissue. That was happened because deoxyribonucleic acid (DNA) methylation aberrations can trigger gene expression that controls cell cycle development in the body's metabolism. Deoxyribonucleic acid (DNA) methylation hypermethylation of seven tumor-associated genes, including APC, WIF1, RUNX3, DLC1, SFRP1, DKK, and E-cad, was found with different CpG methylation between male and female hepatocellular carcinoma (HCC) patients.

In line with the three studies above, the article by Rashed *et al.* (2020) explains that work activities can include occupational exposure to various chemical compounds. Vinyl chloride (VC), an organic compound that increases the risk of hepatocellular carcinoma (HCC) due to deoxyribonucleic acid (DNA) methylation. Deoxyribonucleic acid (DNA) methylation found including TERT promoter mutations, Wnt/β-catenin, cell cycle pathway P53, epigenetic modifiers in histone methylation and chromatin remodeling, mutations on oxidative stress pathways (including NFE2L2 and KEAP1), PI3K/AKT/mTOR pathways, and RAS/MAPK. The article by Habeeb and Sugumaran (2022) mentions that chemical carcinogens, especially viral hepatitis, play the main role in primed for hepatocellular carcinoma (HCC). Carcinogens such as vinyl chloride (VC), aflatoxins, arsenic, tobacco smoke, and other chemicals cause deoxyribonucleic acid (DNA) damage, cause liver cirrhosis, and progress to hepatocellular carcinoma (HCC), either independently or in combination with the virus.

The study conducted by Yu-Lan Qiu *et al.* (2019) proved that administration of intraperitoneal vinyl chloride (VC) injections three times a day for one week was carried out to experimental rats. At the end of the 6^{th} and 12^{th} weeks, eight rats randomly selected from each group were sacrificed comet assay and assessment of deoxyribonucleic acid (DNA) methylation level and mRNA gene expression of associated genes using PCR. As a result, there is a damage to deoxyribonucleic acid (DNA) and increased methylation of the whole genome methylation RASSF1A and MGMT promoters as a results of exposure vinyl chloride (VC) carcinogenic compounds which leads to the growth of tumor cells and cancer.

Another similar study conducted by Zhao *et al.* (2022) stated that the top three genome reaction pathways are cancer, neuroactive ligand receptor interactions, and axon guidance. Then, the top three enriched GO-BP pathways are multicellular organism processes, developmental processes, and anatomical structure development. In conclusion, certain DMG epigenetic disorders (BCL2, TJP2, TAOK1, PFKFB3, LIPI, LIPH, BNIP1, and GRPEL2) as well as in the most enriched DMR pathway (lane in cancer). It was found that BCL2, TJP2, TAOK1, PFKFB3, LIPI, and LIPH hypermethylation in human body are associated with deoxyribonucleic acid (DNA) damage due to exposure of vinyl chloride (VC).

Research conducted by Silva *et al.* (2019) explained that a potential biomarker of cancer risk in exposed workers can be seen from how far the deoxyribonucleic acid (DNA) methylation level in tumor suppressor genes. deoxyribonucleic acid (DNA) methylation in tumor suppressor genes such CDKN2A, APC, and MLH1, as well as in LINE-1 in peripheral blood leukocytes of construction workers is an indicator of exposure harmful effects on human health. Changes in pollutants can be showed altered methylation of the APC, CDKN2A, TP53, RASSF1A, and MGMT genes, and repeated sequences of ALU and LINE-1 suppressed tumors. Workers exposed by vinyl chloride (VC) experienced deoxyribonucleic acid (DNA) hypermethylation, gene promotor repair and increased chromosomal instability, as a measured by evaluating the frequency of MNs. If the frequency of MN increases, then the exposed population experiences a highest risk of cancer than the population doesn't experience an increase frequency of MN.

Table 1. Results of Systematic Review

Author	Title	Design, Sample, and Measurement	Analysis Techniques	Results
Barsouk *et al.* (2021) .	Chemical Risk Factors of Primary Liver Cancer: An Update	This article uses data literature descriptive methods	This article was written based on sources study previously that commonly called with literature review	Factory workers are at risk of exposure to vinyl chloride, arsenic, cadmium, andseveral other hepatotoxins identified in the workplace. While many occupationshave been associated with an increased risk of liver cancer, fewer than a dozen causative agents have been shown to have an association. Occupational chemicals that increase the risk of liver cancer include aflatoxins and DDT in developing farm laborers, vinyl chloride in industrial plants, N-nitrosomines, and industrial solvents in various metalworking, waste disposal, and manufacturing industry. Vinyl chloride monomer (VCM) toxicity has been found to disrupt the hepatic endothelium, cause portal hypertension and angiosarcoma liver malignancy (ASL). These byproducts, such as carbamates, induce DNA cleavage and chromosomal aberrations and are most concentrated in the liver where processing occurs.
El-Mougy *et al.* (2014) .	Aberrant p16INK4 A Methylation Relation to Viral Related Chronic Liver Disease and Hepatocellular Carcinoma	Quantitative, by method statistic parametric. Researching 58 subject; 30 patients HCC; 20 patients cirrhosis; and 8 healthy volunteers. Measurement uses methylation p16INK4A checked use methylation specific polymerase chain reaction (PCR) (MSP).	Comparison quantitative variable between groups study Performed with using Mann- WhitneyU Test for sample independent when not distributed normal. For compare categorical data, Chi-square ($\chi 2$) testing conducted. Test exact used as instead when frequency which less expected of 5.	p16INK4A methylation was found in 6.7% of HCC patients, 5% of liver cirrhosis (LC) patients, and none of the healthy volunteers; 66.67% of thep16INK4A-methylated (2/3) cases were positive for anti-hepatitis C virus(HCV) antibodies (one of them had HCC). All HCC cases with aberrant p16INK4A methylation showed very high serum alpha-fetoprotein (AFP) levels (9,080; 30,000µg/mL). There was no significant relationship between p16INK4A methylation status and tumor size. Hypermethylation of p16INK4A was found to be rare amongEgyptian patients with HCC.
Ye, Siwko and Tsai (2021) .	Sex and Race RelatedDNA Methylation Changes in Hepatocellular Carcinoma	Descriptive method from data literature. The sample came from public China territory, Korean, Japanese, and Europe. Search via PubMed start 1 January 1990 to 3 March 2021 with keywords DNA methylation and heart cancer differentiate between types gender or disparity.	This article was written based onsources study previously that commonly called with Literature review	Several toxins and environmental chemicals are known to be associatedwith HCC, such as aflatoxin B1, vinyl chloride, and androgenic steroids. It is not yet certain which cancer potential of men and women is more dominant based on p16INK4A. Clinical factor analysis revealed that CDKL2 promoter hypermethylation was significantly higher in women (48.0%) compared to men (37.7%) (p=0.037), suggesting that hypermethylation of the CDKL2 promoter may be a contributingfactor to the sex disparity in HCC.

Author	Title	Design, Sample, and Measurement	Analysis Techniques	Results
Rashed *et al.* (2020) .	Hepatocellular Carcinoma (HCC) in Egypt: A Comprehensive overview	Descriptive method. Samplecame from Egyptian society. Measurement not explained in this article.	This article was written based onsources study previously that commonly called with Literature review	The risk factors for HCC in Egypt are very important to report. Risk factors for HCC are risk factors associated with environmental or host/genetic. In recent years, there has been a marked improvement of HCC screening and surveillance strategies in Egypt. The unprecedented national screening campaign launched inlate 2018 is a reflection of this increase. Whereas improvement of HCC prevention requires government health administrations to implement health policies. Although the diagnosis of the Egyptian HCC patients following international guidelines but HCC treatment options are limited in terms of cost. In addition,there are limited Egyptian reports of HCC survival and recurrence. Both basic and clinical HCC research in Egypt is still limited compared to the rest of the world.
Habeeb and Sugumaran (2022) .	Strategies of Cell Signaling and Critical Focus on Etiology of Hepatocellular Carcinoma	This article used study descriptive methods.	Expand existing empathy off track the signaling involved in development and HCC origins, etiology of HCC, with a focus on HCC triggered by liver disease fatty nonalcoholic (NAFLD) and heart disease alcoholic fatty(AFLD), estimate drug targetstherapeutic potential.	Chemical carcinogens, let alone viral hepatitis, play an important role in primed for HCC. Carcinogens such asvinyl chloride, aflatoxins, arsenic, tobacco smoke, and other chemicals cause DNA damage, leading to liver cirrhosisand progression to HCC, either independently or in combination with the virus.
Silva *et al.* (2019) .	Evaluation of DNA Methylation Changes and Micronuclei in Workers Exposed to A Construc tion Environ ment	Research design used are statistics descriptive. Sample comes from Cancer Hospital Barretos with involving 59 workers who exposed environment construction and 49 workers who don't exposed to have qualification that is men over 18 years, worker construction, and ex-smoker more than a yearafter stopping. All workers who smoke, drug user, have a disease infectious or chronic	Distribution parametric and non parametric and Mann-Whitney. Questionnaire for measure profile methylation of the region promoter CDKN2A, MLH1 and APC and the order that repeat LINE-1 exposed workers and not exposed, frequency micronucleus and trace element level in blood, level particle and hydrocarbon polycyclic aromatic (PAH)	Exposed workers showed significantly higher mean promoter methylation levels ofthe CDKN2A, APC, and MLH1 genes and increased LINE-1 hypomethylation compared withunexposed workers (all $p<0.05$).A higher frequency of micronuclei was observed in the exposed group (2±2) compared to the unexposed group (1±1) with $p<0.001$. High particle levels(51–841µg/m3) and some PAHs were found in samples from the construction environment. Increased DNA damage and altered DNA methylation of exposed workers, suggesting that a genomic approach to biomonitoring may be an effective way to predict future cancer risk forconstruction workers.

Author	Title	Design, Sample, and Measurement	Analysis Techniques	Results
Yu-Lan Qiu *et al.* (2019)	Association Between Methylation of DNA damage Response-related Genes and DNA Damage in Hepatocytes of Rats Following Subchronic Exposure to Vinyl Chloride	This article used research design quantitative with cross sectional method. Sample came from Laboratory in China with using 64 healthy mice	Analysis technique is used with measuring VC 5 mg/kg, 25 mg/kg, and 125mg/kg and control group negative that is nottreated	Overall methylation levels in the hepatocyte genome in VC-exposed micewere higher than those in the control group at 6 and 13 weeks (P<0.05), although no difference was observed with respect to dose (P>0.05). After 12 weeks of exposure, differences in methylation of the RASSF1A and MGMT promoter regions were observed between the high-dose group and the other groups (P<0.05), whereas no differences were observed for the KRAS,SYK, and MGMT promoters. CDKN2A (P>0.05).
Zhao *et al.* (2022)	Novel deoxyribonucleic acid Methylation Peturbations in WorkersExposed to Vinyl Chloride	Research article use research design quantitative with method cross-sectional. Sample taken from wrong one chlorine factory alkaline and wrong one factory power plants with involving 193 subject (92 in exposure group VC in alkaline chlorineplant and 101 in Group control that working in power plants) and choose three plug from subjects (exposed and control) for Bisulfit sequencing whole genome (WGBS)	Analysis technique used is with compare control group and group exposed	The rate of micronucleus formation inthe VC exposure group was higher than in the control group (6.05 ± 3.28‰ vs 2.01 ± 1.79‰). A total of 9534 differentially methylated regions (DMRs) were identified by WGBS, 4816 of which were hypermethylated. In the most enriched DMR pathway (the cancer pathway), BCL2, TJP2, TAOK1, PFKFB3, LIPI, and LIPH were hypermethylated and BNIP1 and GRPEL2 methylated levels decreased. The above-mentioned differentially methylated gene (DMG) methylationwas verified by methylation-specific PCR (MSP) and agrosa gel electrophoresis (AGE) in 50 pairs of subjects, where the coincidence ratewas 60-100%.

In addition to these results, a study by Silva *et al.* (2019) found that methylation at this CpG site is involved in chromatin changes associated with regulation gene expression. Environmental exposure such as vinyl chloride (VC) affects the mean methylation levels of MLH1 and LINE-1 genes. This study assessed the deoxyribonucleic acid (DNA) methylation profile of the promoter regions of APC, CDKN2A, and MLH1genes and the CpG sites of LINE-1 peripheral blood leukocytes of construction workers which were found to have potential for cancer cell growth.

Based on research by Rafi'ah, Tualeka and Widajati (2018), there is a connection between behavioral control and the intention of safety behavior of the workers. Plate Cutting Commercial Ship Division of PT. PAL. This shows in efforts to prevent and control exposure vinyl chloride (VC) to workers, appropriate control measures are required. Strengthening this research, there is a study by Ayu, Tualeka and Wahyudiono (2018) which states that there is a relationshipand influence between knowledge and supervision on compliance with the use of personal protective equipment in PT. PAL Indonesia. Therefore, control efforts need to be carried out to prevent work accidents and occupational diseases through the hierarchy of control, namely elimination, substitution, engineering, administration, and the use of Personal Protective Equipment (PPE).

CONCLUSION

There is a connection between exposure vinyl chloride (VC) and deoxyribonucleic acid (DNA) methylation that cause health hazardous effects in the form of hepatocellular carcinoma (HCC) and cancer. Because of limited evidence so this research is carried out to prove the relationship vinyl chloride (VC) and deoxyribonucleic acid (DNA) methylation. It's necessary to have efforts to prevent and control exposure vinyl chloride (VC), one of them is the use of Personal Protective Equipment (PPE). Results of this systematic review much important to assist the government in controlling chemical exposure vinyl chloride (VC) in the work environment.

Acknowledgement

The author would like to thank to Faculty of Public Health, Airlangga University and our lecturers at Occupational Health and Safety Department, Faculty of Public Health, Airlangga University. Also, the author would like to thank to all researchers who have contributed in providing data sources in the form of articles and journals regarding the effects of vinyl chloride (VC) to deoxyribonucleic acid (DNA) methylation which form the basis of this systematic review.

REFERENCES

Ayu, B.F., Tualeka, A.R. and Wahyudiono, Y.D.A. (2018) 'The analysis of factors which are related to the compliance of welder workers in using workplace personal protective equipment in Pt. Pal Indonesia', *Indian Journal of Public Health Research and Development*, 9(5), 47–52. Available at: https://doi.org/10.5958/0976-5506.2018.00410.2.

Barsouk, Adam *et al.* (2021) 'Chemical Risk Factors of Primary Liver Cancer: An Update', *Hepatic Medicine: Evidence and Research*, Volume 12, pp. 179–188. Available at: https://doi.org/10.2147/hmer.s278070.

Chang, L.T. *et al.* (2021) ' Hepatotoxicity caused by repeated and subchronic pulmonary exposure to low-level vinyl chloride in mice. ', *Atmosphere*, 12(5), 596.

Elmaci, I. *et al.* (2022) 'MGMT in glial carcinogenesis. Roles from prevention to treatment.', *European Journal of Cancer Prevention*, 31(6), 568–576.

El-Mougy, F. *et al.* (2014) 'Aberrant p16INK4A methylation: Relation to viral related chronic liver disease and hepatocellular carcinoma', *South Asian Journal of Cancer*, 3(1), 1–4. Available at: https://doi.org/10.4103/2278-330X.126498.

Goodman, S. *et al.* (2022) 'Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: An update of a systematic literature review', *Mutation Research/reviews in Mutation Research*, 789, 108408.

Habeeb, M. and Sugumaran, A. (2022) 'Strategies of cell signaling and critical focus on etiology of hepatocellular carcinoma', *Biointerface Research in Applied Chemistry*. AMG Transcend Association, 5187–5198. Available at: https://doi.org/10.33263/BRIAC124.51875198.

Khodaei, R. *et al.* (2019) 'Voltammetric immunosensor for E-cadherin promoter DNA methylation using a Fe 3 O 4-citric acid nanocomposite and a screen-printed carbon electrode modified with poly (vinyl alcohol) and reduced graphene oxide', *Microchimica Acta*, 186, 1–12.

Liao, X. *et al.* (2021) ' A novel one-pot fluorescence tagging and depyrimidination strategy for quantification of global DNA methylation', *Analytica Chimica Acta*, 34036, 1239.

Luo, B. *et al.* (2022) 'Covalent organic framework nanosheet anchored with highly dispersed Au

nanoparticles as a novel nanoprobe for DNA methylation detection', *Journal of Colloid and Interface Science*, 626, 241–250.

Menezo, Y., Dale, B. and Elder, K. (2019) 'The negative impact of the environment on methylation/epigenetic marking in gametes and embryos: A plea for action to protect the fertility of future generations', *Molecular Reproduction and Development*, 86(10), 1273–1282.

Nishiyama, A. *et al.* (2020) 'Two distinct modes of DNMT1 recruitment ensure stable maintenance DNA methylation', *Nature communications*, 11(1), 1222.

Rafi'ah, Tualeka, A.R. and Widajati, N. (2018) 'A correlation analysis of attitude, subjective norm and behavioral control toward the intention of safety behavior: (A study on plate cutting workers of commercial ships division PT. PAL Indonesia (Persero)', *Indian Journal of Public Health Research and Development*, 9(5), 137–141. Available at: https://doi.org/10.5958/0976-5506.2018.00426.6.

Rashed, W.M. *et al.* (2020) 'Hepatocellular Carcinoma (HCC) in Egypt: A comprehensive overview', *Journal of the Egyptian National Cancer Institute*. Springer. Available at: https://doi.org/10.1186/s43046-020-0016-x.

Rattan, S. *et al.* (2019) 'Prenatal and ancestral exposure to di (2-ethylhexyl) phthalate alters gene expression and DNA methylation in mouse ovaries', *Toxicology and applied pharmacology*, 379, 114629.

Ren, J. *et al.* (2019) 'The prevalence and persistence of aberrant promoter DNA methylation in benzene-exposed Chinese workers', *Plos one*, 14(8), e0220500.

Sanaei, M., Kavoosi, F. and Modaresi, F. (no date) 'DNA methylation of tumor suppressor genes in hepatocellular carcinoma. ', *Iranian Journal of Pediatric Hematology & Oncology*.

Sedgwick, B. (2004) 'Repairing DNA-methylation damage', *Nature reviews Molecular cell biology*, 5(2), 148–157.

Silva, I.R. *et al.* (2019) 'Evaluation of DNA methylation changes and micronuclei in workers exposed to a construction environment', *International Journal of Environmental Research and Public Health*, 16(6). Available at: https://doi.org/10.3390/ijerph16060902.

Sirait, F.A. *et al.* (2018) 'Control of hazardous chemical as an effort for compliance criteria of OHS management system: A cross-sectional study at PT. X Surabaya, Indonesia', *Indian Journal of Public Health Research and Development*, 9(11), 555–559. Available at: https://doi.org/10.5958/0976-5506.2018.01515.2.

Weihrauch, M. *et al.* (2001) 'Frequent k-ras-2 mutations and p16 INK4A methylation in hepatocellular carcinomas in workers exposed to vinyl chloride', *British Journal of Cancer*, 84(7),.982–989. Available at: https://doi.org/10.1054/bjoc.2000.1675.

Wu, F. *et al.* (2013) 'Correlation of chromosome damage and promoter methylation status of the DNA repair genes MGMT and hMLH1 in Chinese vinyl chloride monomer (VCM)-exposed workers', *International Journal of Occupational Medicine and Environmental Health*, 26(1), 173–182.

Ye, W., Siwko, S. and Tsai, R.Y.L. (2021) 'Sex and race-related dna methylation changes in hepatocellular carcinoma', *International Journal of Molecular Sciences*. MDPI. Available at: https://doi.org/10.3390/ijms22083820.

Yu-Lan Qiu *et al.* (2019) 'Association Between Methylation of DNA Damage Response-related Genes and DNA Damage in Hepatocytes of Rats Following Subchronic Exposure to Vinyl Chloride', *Chemosphere*, 227, 323–328.

Zhao, X. *et al.* (2022) 'Novel deoxyribonucleicacid Methylation Peturbations in Workers Exposed to Vinyl Chloride', *Toxicology and Industrial Health*, 07482337221098600. Available at: http://ejurnal.poltekkes-tjk.ac.id/index.php/JK.