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Ethylene Oxide Gas Sterilization: A Systematic Review of Carcinogenicity, Toxicity And Occupational Exposure.

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ABSTRACT

Background: Ethylene oxide gas is a colorless gas that is used to sterilized all the items that are moisture, heat, and radiosensitive. 25ppm was the minimum amount of ethylene oxide gas that does not affect the patients and workers. Its overexposure has harmful effects on the human central nervous system, reproductive system, and peripheral nervous system.
Methodology: Web of Science, Science Direct, PubMed, Google Scholar, and Scopus websites are used to collect articles with relevant abbreviations.
Results: Firstly, 116 articles were selected, then after reviewing the title and the abstract, 15 articles were finalized. After this reading methodology, discussion, and conclusion finalized 10 articles were finalised that were completely relevant to the study.
Conclusion: This study showed that ethylene oxide gas sterilization was the best choice for sterilizing surgical instruments. Its high exposure can affect the central nervous system, reproductive system and in some cases, cancer and even death. Proper PPEs and attention are required while using ETO.

Key words: Ethylene oxide, Sterilization, Toxicity of ETO, Surgical instruments, Cancer, Neurogenic issues

INTRODUCTION

Sterilization is a process that removes or deactivates all forms of life, such as bacteria, fungi, spores, eukaryotic organisms, and other biological agents, placed on any surface, fluid, or object [1]. It was a process of making something free from bacteria or other living organisms like unicellular eukaryotes, fungi spores, etc. It was also defined as the process where all the living microbes, including bacteria or spores, are killed. Sterilization has many applications in the industrial, medical, and surgical fields. Sterilization was carried out by a physical method or a chemical method. In the chemical method, sterilizing agents were known as chemisteriliants [2].

Nowadays, Ethylene oxide gas has gained more popularity in the medical and pharmaceutical fields. It was also a sterilizing agent and was used to sterilized the surgical items that are used during surgical procedures [3]. Its worldwide production was 5.5 million tonnes and in the United States, its production was 3 million tonnes [4, 5]. Due to its reactive nature, ethylene oxide was a major industrial chemical. Its toxicity was comparable to ammonia. It was a colourless liquid and had a boiling point of 10.7 °C. It was an inflammable gas with the characteristics of the simplest epoxide compounds and a potent biocide. If the concentration of ethylene oxide is higher than 3% it becomes explosive and moderately toxic. The 12% mixture of ethylene oxide with carbon dioxide and freons was not inflammable [6]. Ethylene oxide was an alkylating agent potent biocide and an active epoxide agent. In the chemical industry, it was most widely used.

Ethylene oxide was a famous sterilizing agent that was used to carry out the sterilization process of all medical instruments and equipment that were resistant to heat, moisture, and radio waves [7]. It has the ability to kill bacteria, viruses, and spores. It was widely used due to its effective characteristics and compatibility with most materials. On the other hand, ethylene oxide has many disadvantages. It is carcinogenic and mutagenic in nature if it is not properly handled [8]. Ethylene oxide covalently and irreversibly binds to deoxyribonucleic acid and can cause mutations. Due to over-exposure and its alkylating ability, it can cause a spectrum of chromosomal damage. It was toxic to the reproductive system and could cause infertility in both males and females. EO can cause serious burns on the skin if it is used carelessly. The reaction of ethylene oxide was highly exothermic. The vapours of ethylene oxide can become explosive if the temperature is higher. At a temperature of 400 °C, the gaseous ethylene oxide starts to decompose into carbon monoxide and methane [9]. In the decomposition, the first step was the isomerization of ethylene oxide into acetaldehyde.

Amount of ethylene oxide gas near the working area

Annually, 75000 Healthcare workers are exposed to ethylene oxide in the United States. Exposure to ethylene oxide was high in healthcare facilities and hospitals as compared to the chemical industries. In 1978, the survey was conducted by the National Institute for Occupational Safety and Health in healthcare facilities (NIOSH). They concluded that ethylene oxide near the improperly designated equipment area was 100 ppm for a brief period. 50 ppm was the safe limit for breathing in the hospital [10].

The amount of ethylene oxide gas was 0.1ppm near the sterilizer before turning on and this amount was detected by the ethylene oxide gas monitor. Before opening the door of the sterilizer, the amount of gas in the sterilizer was in the range of 0.10- 2 4.56 ppm this amount was below the detection limit. After that, when the door of the sterilizer was opened for the placement of the instruments into the sterilizer for sterilization, the amount of ethylene oxide gas near the door was 1.71 ppm. After that, when the cycle started, no amount of ethylene oxide gas was detected in the unit. After completing this cycle, when the door was opened, the range was 2.10-2.73 ppm and when the door was closed, the residual amount was in the range of 0.5 - 0.57 ppm [11]. These values showed that the person near the sterilizer unit has a risk of exposure to ethylene oxide gas for 15 minutes during the instrumentation transfer. The 2-ppm residual amount of ethylene oxide gas was still present in sterilized instruments after 24 hours of aeration time. These findings showed that the person who used these instruments also has a risk of exposure [12].

Personal exposure limit

Exposure to ethylene oxide at the workplace was regulated by OSHA standards 29 CFR 1910. 1047. The International Standard Organization ISO 10993-7 (2008) gives a specific limit for ethylene oxide gas residual and its by-products [13]. It was formed by ethylene oxide gas reaction with Hydrochloric acid and Sulfuric acid aqueous solution. Ethylene oxide gas

in this reaction was not produced only by water. If the residual amount of Ethylene oxide gas is not properly aerated, it can cause irritation to the skin and Eyes, and in severe cases, it can cause burns to the skin and mucosa. Ethylene gas toxicity was 10 times greater than ethylene chlorohydrin. 25ppm was the minimum amount that did not affect the patients and workers[14]. Acute exposure can caused irritation to the mucous membrane, depression in the central nervous system, nasal discharge, and lacrimation [15]. 6 to 8 hours of exposure can cause diarrhea, nausea, lung edema, paralysis, and in some cases, it can cause even death.

MATERIALS AND METHODS

A systematic review was conducted according to PRISMA 2020 guidelines to ensure the originality of data. The aim of this systematic review was to find out the toxic effects of ethylene oxide gas in humans. All observational, case-control, Cohort, cross-sectional studies, case reports, and experimental studies were included in the study. Studies that included human subjects were included in the study. Animal-based studies, opinions, and those studies that lack qualitative and quantitative data on exposure to human health were also excluded from the study.

Five websites were used to collect relevant articles. Web of Science, Science Direct, PubMed, Google Scholar, and Scopus were used to fetch articles from sites. Key search terms that were used to collect articles were Ethylene oxide gas, sterilization techniques, EO sterilization techniques, toxicity of ethylene, toxic effects of ethylene oxide gas on humans, exposure limits of ethylene oxide gas, exposure limit of EO near the working area, benefits of ethylene oxide gas sterilization, disadvantages of ethylene oxide gas sterilization, mechanism of action of ethylene oxide gas sterilization, and usage of ethylene oxide gas in medical field. Firstly, I collected 116 articles from these websites. After these two independent observers reviewed and screened articles by reviewing the title, abstract, which showed the relevance of toxicity of ethylene oxide in humans, and its exposure limits in the working area, and finalized fifteen articles. Read these fifteen articles, thoroughly studied methodology, results, discussion, and conclusion sections, and finalized ten articles that were completely relevant to the study. After selecting articles, data was extracted from the articles and authors' names, study design, sample size, and key findings were noted, and a table was created based based on the findings.

RESULTS

Table 1.1 Study Findings of Previous Literature

Name of Author	Study Design	Sample Size	Findings of The Study
Breuer et al	Case control study	12	Out of 8, 7 employees have allergic reactions to one percent epichlorohydrin
Bryant et al	Case series	165	Allergic reactions and neurological issues have been significantly associated with ethylene oxide gas exposure
Estrin et al	Case control study	20 (10 added into the exposed patient group and 10 added into the control group)	The exposed patient group has neurological symptoms with P value (P= 0.009)

Feitosa et al	Case report	1	The patient developed neurological symptoms
Gresie- Brusin et al	Cross-sectional study	98 (19 has higher exposure, while 79 has low exposure from ETO)	Pregnancy loss and spontaneous abortion risk increased with higher exposure to ETO
Kiran et al	Case control study	4810 cases, 2347 lymphoma cases and 2463 controls	Lymphoma cases increased to four times with higher to medium exposure of ethylene oxide gas sterilization (P= 0.003)
Lin et al	Case report	1	Patients develop neurological symptoms with exposure to ETO
Park et al	Cohort study	7185	Lung cancer and breast cancer are significantly associated with ethylene oxide gas exposure

A case-control study was conducted by Breuer et al. He took 12 patients for the study who had exposure to ethylene oxide gas. He noticed that out of eight, seven patients had allergic reactions. Another case series was reported by Bryan et al. He takes 165 patients and reports that allergic reactions and neurological issues have a significant association with ethylene oxide gas sterilization. Fstrin et al conducted a case-control study on 20 patients. He added ten patients to the control group and 10 to the exposed group. He noticed that neurological symptoms have a significant association with ethylene oxide gas exposure. A study was conducted by Park et al. He conducted a Cohort study on 7185 patients. He noticed that lung cancer and breast cancer have a significant association with ethylene oxide gas exposure. (Table 1.1)

DISCUSSION

This systematic review described details of the harmful effects of ethylene oxide gas in humans. Although it was a very useful gas for sterilization but it has very dangerous, long-lasting effects on the human population. It was a carcinogenic gas that has been found to have an association with the development of different types of cancers and many other long-lasting effects. All eight studies concluded that ethylene oxide has harmful effects on human health. Its normal exposure cannot pose a significant threat in humans, but its higher exposure can cause skin burn, bruises, skin irritation, leukemia, lymphoma, cytotoxicity, lung cancer, breast cancer, chromosomal damage, pregnancy issues, abortion, and in some cases, even death may occur.

Breuer et al and Bryant et concluded in their research that those workers who have exposure to ethylene oxide gas are more prone to allergic reactions as compared to others [16, 17]. A similar study was conducted by Cloth et al, which showed ethylene oxide has a significant association with skin irritation, itchy skin, and breathing difficulties. There was a very low chance of these issues; these studies are not like previous studies. Another study showed that high exposure to ETO can cause blisters, bruises, eye pain, and breathing difficulties [18]. These findings of previous literature showed that there is a strong association between ethylene oxide gas exposure and its toxic effects. Estrin [19], Bryan Lin, and Feitosa et al concluded in their research that overexposure to ethylene oxide can cause neurological symptoms[20]. A similar study concluded that neurological symptoms have a significant association with ethylene oxide gas sterilization [21]. Those workers who routinely worked near ethylene oxide gas are more prone to the risk of headaches, loss of memory, and unconsciousness. Another parallel study describes the issues of high exposure to ETO that showed that those workers who are more prone to exposure to ETO developed neurological symptoms as compared to those who have no exposure to ethylene oxide gas. A parallel study conducted by Jones et al showed that those workers who have prolonged exposure to ETO develop neurological issues [18].

These comparable trends suggest that those workers who develop neurological symptoms have a high chance of ethylene oxide gas exposure.

A study conducted by Gresie-Brusin et al showed that loss of pregnancy and spontaneous abortion may increase with high exposure to ethylene oxide gas [22]. A parallel study showed that exposure to ethylene oxide gas can cause abortion and pregnancy issues in female workers. A similar study showed that ethylene oxide gas has a significant association with reproductive system impairment [15]. Kiran et al conducted a study on lymphoma patients, and they observed that the chances of lymphoma may be increased four times with high and moderate exposure to ethylene oxide gas [23]. Park et al conducted a cohort study. He concluded in his research that the chances of lungs and breast cancers increased with high exposure to ethylene oxide [24]. A similar study finding concluded that ETO caused mutations and suppressed genes that result in tumor formation [25]. A cross-sectional study was conducted in Egypt that showed gene mutations were detected in patients who had been exposed to ethylene oxide gas [25]. Another study showed that ethylene oxide has a significant correlation with breast cancer and lymphoma issues. Their chances increased with higher exposure [26]. Another study revealed that the risk of breast cancer increased with exposure to ethylene oxide but non-Hodgkin's lymphoma may not increase with exposure [27]. A parallel study showed that exposure to ethylene oxide gas has carcinogenic effects in humans [28]. A study was conducted by Park et al that concluded the chance of malignancies was increased with a higher dosage of exposure to ethylene oxide gas [15]. These research findings were consistent with previous literature that has reported the same carcinogenic effects with exposure to ethylene oxide gas. That showed the reliability of these research findings.

A study was conducted in the USA that showed exposure to ethylene oxide gas was not associated with breast cancer and lymphoma. This study was not parallel to previous findings because they studied the mechanism of action of ethylene oxide gas effects in the body and stated the results. This study was conducted in the USA, so there might be a chance of bias due to the high standards of healthcare facilities. A study conducted by Jain et al showed that blood cancer has no significant association with ethylene exposure [29]. There might be a chance of biases or workers working in a state-of-the-art institution. Where proper guidelines are followed and aeration is done in a well-ventilated environment. So, the chances of ethylene oxide gas exposure are very low.

The key findings of this systematic review give a brief detail that there was a strong association present between ethylene oxide gas exposure and carcinogenicity, genotoxicity, and toxic effects in humans. This result highlighted the importance of strict adherence to SOPs during usage and regulatory control measures are necessary to protect the environment and healthcare workers.

CONCLUSION

From all the above discussions, it was concluded that ethylene oxide gas sterilization was the best available sterilization method for all the sensitive and weird items. However, some precautions must be considered to reduce damage to healthcare providers. Clinically, all Healthcare workers, especially the sterilization supply department, must be aware of the fact that ETO sterilization can be dangerous if precautions are not followed during its usage. 25 PPM was the normal range of exposure. If exposure increases from this limit, it can cause breathing difficulties, skin rashes, chromosomal damage, and cancer. So, during the usage of ethylene oxide gas, wearing PPEs and proper attention were required to minimized its effects.

RECOMENDATIONS

Add more articles to conduct a more comprehensive study. Research on the health impacts of moderate and high exposure levels of ethylene oxide gas should be done separately. Examine the harmful consequences that ethylene oxide gas has on animals. Demographic variables that indicate which age group and gender are more vulnerable to the harmful effects of ethylene oxide gas can be investigated further. The effects of ethylene oxide gas on the environment can be explored because there are currently few studies available in this area.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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