Assessing the Carcinogenic Potential of Ethylene Oxide: A Comprehensive Health Impact Analysis

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BS, West Virginia University, 2020

MPH, West Virginia University, 2022

Submitted to the Graduate Faculty of the

Department of Environmental and Occupational Health

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2024

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

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on

June 20, 2024

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Abstract

Ethylene oxide (EtO) is a critical chemical extensively used in industrial applications such as the production of ethylene glycol and the sterilization of medical equipment. Despite its widespread utility, EtO is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, posing significant health risks including lymphoid cancer and breast cancer. This document explores the various contexts in which EtO is utilized, its associated health and environmental risks, and the regulatory measures in place to mitigate these risks. Significant attention is given to the historical context of EtO usage, detailing major incidents and regulatory responses that have shaped current safety standards. The analysis covers occupational and environmental exposures, with specific examples illustrating the challenges of managing EtO risks in different settings. The document also highlights ongoing research and advancements in exposure monitoring and risk assessment, underscoring the importance of continuous improvement in safety practices and technologies. Recommendations are proposed for both industrial and medical sectors, focusing on reducing EtO exposure through automation, substitution, improved equipment design, and alternative sterilization technologies. The need for enhanced education and collaboration among stakeholders is emphasized to ensure effective management of EtO risks and the protection of public health.

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Preface

I would like to express my sincere gratitude to the esteemed professors at West Virginia University who ignited my passion for public health. Their dedication and expertise have been foundational to my academic journey. Now, at the University of Pittsburgh, Dr. Nesta-Bortey Sam and Dr. Jim Peterson have graciously welcomed me into the community and further deepened my appreciation for the field. They have expanded my perspectives in ways I had not anticipated. Coming here was a step towards growing personally and exploring life beyond West Virginia, and I am pleased to share that this experience has exceeded my expectations in every possible way.

1.0 Introduction

Ethylene oxide (EtO) is a versatile chemical widely utilized in manufacturing various substances, including ethylene glycol, across many industrial sectors. It is present in a range of everyday products such as household cleaners, personal care items, and textiles. In the healthcare industry, EtO is used on a smaller scale for sterilizing medical equipment and personal protective gear. Additionally, it plays a significant role as a fumigant in agriculture, highlighting its extensive production and use. Because of its critical function as an intermediate chemical in many manufacturing processes and its widespread occupational presence, EtO poses substantial health risks. The EPA classifies EtO as a Group 1 carcinogen, indicating that inhalation or ingestion of EtO can elevate the risk of lymphoid cancer and breast cancer in women.

Key exposure routes include uncontrolled emissions in industrial settings, with significant risks arising from occupational exposure. Those at increased risk of both acute and chronic exposure include workers in EtO manufacturing and processing plants, sterilization technicians, and individuals involved in fumigation activities. The general population may also be exposed due to the proximity to industrial facilities or through tobacco smoke. According to Jones (2023), "Data on EtO levels in the ambient environment are limited, and population exposures have not been well characterized, but those residing close to EtO point sources may be exposed to higher levels." Although personal testing for EtO exposure is available, continuous research, monitoring, and emission surveillance are essential to protect public health and ensure environmental sustainability.

1.1 Review

Extensively scrutinized by the United States Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) alike, EtO's history as a chemical intermediate and hazard is comprehensive. EtO is highly explosive and reactive, a flammable and colorless gas at room temperature, with a sweet odor. As reported by the EPA, EtO exposure risks are addressed based on the results of the latest National Air Toxics Assessment (NATA), which identified the chemical as a potential concern in several areas across the country. Acting as the EPA's national air toxics screening tool the NATA is designed to help state, local, and tribal regions identify areas, pollutants, or types of sources for further examination. Utilizing modeling techniques that estimate long-term risks based on elevated levels of air toxins such as EtO scientists build the evidence that supports the need for reduction of total emissions of air toxicity, including EtO. Combining data on air emissions and the prevalence of EtO in all settings with lessons learned from our past, EtO set forth the best path for expanding surveillance systems alongside educating the right communities.

The Willowbrook environmental issue, which sparked the discovery of EtO about 160 years ago, is at the center of the conversation. Hawthorne, writing for the Chicago Tribune, identifies the warning indications of health dangers dating back 70 years and outlines the steps taken following its inception. Scientists connected ethylene oxide (EtO), which was first used formally in 1928, to being a potent insecticide and used it to fumigate hospital rooms during the 1930s and 1940s. In the 1940s, executives at meatpacking suppliers Griffith Laboratories developed a technique for sterilizing spices and other food preservatives by pumping ethylene oxide (ETO) into a vacuum chamber. In addition to this growth, the U.S. Army utilized EtO to fumigate troop rations during World War II, capitalizing on the substance's increasing use. The availability and growth of EtO as a sterilizer of medical equipment between 1948 and 1981 increased the necessity for the chemical's cellular mechanistic studies. "The biggest problem that we have right now is ethylene oxide," a Shell Oil Co. executive noted in a memo in response to a conference on industrial carcinogens in 1981 (Hawthrone, 2019)

Usage of EtO continued without reform until 1986 when a Union Carbide chemical disaster killed thousands of people in Bhopal, India. The incident involving methyl isocyanate (MIC) demonstrated the magnitude of the regulatory safety gap. It propelled the Democratic-controlled Congress to approve the Emergency Planning and Community Right-to-Know Act. By requiring the EPA to format an annual Toxics Release Inventory (TRI), the public is provided with pollution data from individual factories and refineries for the first time. Since EtO was not classified as a human carcinogen until 1987, the foundation of chronic effects in human health and the environment due to exposures was already well underway. Showcasing its crucial power, one of the first reports from the TRI links the Griffith Microscience branched off from Griffith Laboratories to the release of nearly 170,000 pounds of EtO in Willowbrook, IL. However, the EPA did not adopt regulations on EtO until 1994 in commercial sterilization facilities.

Following several explosions at sterilization plants, advancement into a study of more than 18,000 workers at 17 sterilization plants led by researchers from the National Institute of Occupational Safety and Health (NIOSH) reported that EtO causes breast cancer and lymphomas in 2003-04. After President George W. Bush’s administration declined to update EtO regulations citing outdated scientific reviews, this required the EPA to release a new draft of EtO dangers and recommendations. Released in 2006 and based on NIOSH data on numerous sterilization workers and animal studies, confirmation of EtO as a human carcinogen was provided, Yet, even with extensive research, the report was criticized as it provided legally persuasive evidence that could possibly force sterilization facilities to stop using EtO. Such a paradigm shift would be costly and time-consuming for the industry. With its high priority fueled by extensive past use and the complexity of regulating EtO, the EPA was advised via the review and comment process to make several improvements to the associated risk assessment, a process which can take up to another nine years to complete even when fast-tracking a chemical with known highly hazardous potential. A notable case study is the community near the Sterigenics facility in Willowbrook, Illinois, where prolonged exposure to EtO emissions led to a spike in cancer rates. Public outcry and detailed air quality studies by local environmental groups eventually led to the temporary shutdown of the facility and stricter state-level regulations. Such cases highlight the importance of community engagement and robust environmental monitoring (Illinois EPA, 2019) Events such as in the Kanawha Valley of West Virginia and Willowbrook are prime examples of the lasting impact of EtO and the detrimental scope it has over human and environmental health.

The Kanawha Valley incident involved substantial emissions of EtO from chemical manufacturing facilities in the region. This led to widespread contamination and serious health concerns for the local population. Residents in the Kanawha Valley reported increased instances of respiratory issues, cancer, and other health problems associated with EtO exposure (Mishra, 2009) The event highlighted the persistent threat posed by EtO emissions, even with regulatory measures in place. The response from regulatory agencies such as the Environmental Protection Agency (EPA), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA) involved extensive monitoring and efforts to reduce emissions. However, the long-term health effects on the community underscored the challenges in managing EtO exposure effectively.

The priority and responsibility of the EPA and like agencies such as NIOSH and OSHA. Guide the bigger picture, yet exposure only takes a short time period to create a lasting impact on a person, depending on the compound and concentration, and remains unaffected by regulations. The Kanawha Valley incident serves as a prime example of the lasting impact of EtO on both human health and the environment. It illustrates the critical need for continuous monitoring, stricter enforcement of regulations, and prompt action to mitigate the risks associated with industrial EtO emissions.

In 2009, research on the risks grew to a new level when California included ethylene oxide (ETO) on its list of compounds that can harm a child's development. In addition, the state included male infertility concerns in its 1987 findings regarding female reproductive disorders (Hawthorne, 2009). After this landmark, not much changed until 2016 when the EPA revised their evaluation of the cancer risks associated with EtO, maintaining the majority of the 2006 draft's results. Following the revision of the EtO safety limit, the EPA published a second National Air Toxic Assessment in 2018 using 2014 emissions data provided by the industry. Only four months after the publication of this report, more air testing was revealed concerning levels of EtO in the area around SteriGenics.

On February 15, 2009, Governor J.B. Pritzker issued an order to the Illinois Environmental Protection Agency prohibiting SteriGenics from utilizing EtO at its Willowbrook plant due to the increasing levels of air contamination. Investigations lasted until March 29, 2009, when the Environmental Protection Agency (EPA) declared that even after the company installed additional pollution-control equipment in July 2018, "toxic pollution from the SteriGenics plant in Willowbrook was responsible for long-term cancer risks up to 10 times higher than what the agency considers acceptable" (Hawthorne, 2019).

Exposure to EtO varies across regions regarding urban, suburban, and rural environments. While that exposure has been mitigated effectively in many areas, low levels of this carcinogenic substance can still be found in the ambient air and at the workplace, often unavoidable. The risk assessment of genotoxic carcinogens are particularly relevant for risk assessment methodologies as "their metabolic precursors and DNA reactive metabolites are considered to represent risk factors at all concentrations since even one or a few DNA lesions may in principle result in mutations and, thus, increase tumor risk" (Hartwig et al. 2020) Advancements in analytical techniques for detecting DNA lesions and mutations have greatly improved the risk evaluations for genetic carcinogens. These methods are particularly effective for assessing low-dose exposure to chemicals like Ethylene Oxide (EtO). However, comprehensive risk assessments for workplace carcinogen exposure require long-term scientific studies (chronic studies), as various factors can influence the mechanisms of action.

The ALARA principle (As Low as Reasonably Achievable) has traditionally been used to manage direct genotoxic agents, but this approach may sometimes be overly cautious as it doesn't always account for the mode of action. This has led to increased scrutiny of the linear-no-threshold hypothesis for cancer risk assessment (Hartwig et al., 2020). For example, animal studies have suggested threshold levels for several carcinogens (Kobets and Williams, 2019). Analytical techniques for adduct quantification are now used to monitor occupational exposure to mutagens and carcinogens like EtO during work shifts (Calleman et al., 1978). Additionally, the inclusion of protein adduct analysis in molecular cancer epidemiology helps identify causal associations and addresses gaps in dose-response assessments by considering both endogenous and nonoccupational exposures.

To improve risk assessments, it is essential to quantify bioindicators of EtO's key toxic effects, including DNA damage, mutations, cell cycle control, enhanced cell proliferation, and apoptosis. Incorporating these metrics into toxicological risk assessments and specifically localizing DNA damage is critical. These background levels, quantified with high sensitivity and specificity, can serve as reference values to compare against the effects of low-dose human exposure to genotoxic agents (Hartwig et al., 2020). Studies on formaldehyde exposure have demonstrated that using mechanistic, data-based approaches rather than traditional linear extrapolation can provide a more accurate assessment of cancer risk (Clewell et al., 2019; Farland et al., 2019). Understanding risk assessments from evolving perspectives, along with past scientific insights, is vital for comprehending specific mechanisms of action for adverse outcomes. Implementing community guidelines and nationwide regulations can benefit from these advancements. However, linking environmental EtO exposure to tumor development is challenging due to the high costs of long-term exposure assessments and significant individual variations in toxicokinetic responses.

This obstacle is remedied by biomarkers reflecting the actual intake and toxicokinetic properties of the mutagenic substance. (Hartwig et al. 2020) Valdez-Flores and colleagues similarly explored lymphoid malignancies induced by EtO for the worst-case scenarios in 2010. By taking on mechanistic assumptions that were scientifically sound, yet without proof of practical relevance, Valdez-Flores concluded that exposure to 0.25 ppm EtO during work time for 40 years leads at most to an increased incidence of 4 tumors in 100,000 workers (Valdez-Flores et al. 2010). This value is much lower than previous estimates by others (EPA 1985; OSHA 1984) Conducted more conservatively than a previous non-linear prediction model by the same group, the latter was based on mechanistic assumptions that are scientifically sound yet lack the proof of practical relevance (Kirman et al. 2004).

Despite the extensive data available, accurately quantifying the human risk of EtO exposure remains a complex task. Valdez-Flore's report offers interesting insights but does not fully address the observed statistically significant risk for bone malignancies. If the imprecise odds ratio of three holds true, it would translate to approximately 8 cases in 100,000 at an exposure level of 0.25 ppm over a lifetime of work (Hartwig et al., 2020).

However, this report underscores the importance of using large human cohorts for risk assessment rather than relying solely on animal experiments. This approach improves the relevance and quality of evidence concerning human physiology. Hartwig et al. (2020) note, “Because constant exposure to 0.25 ppm would increase the hemoglobin adduct approximately 50-fold over the background, this biomarker appears to be perfectly suited to assess the actual burden of workers in an exposure range that should not yet present a significant health risk.” This suggests that human biomarkers can play a crucial role in assessing exposure risks accurately.

At its core, public health focuses on prevention. Exploring the functions of human biomarkers, protein adducts, and comprehensive toxicological risk assessments directs us back to this fundamental principle. Effective resource allocation and preventive measures can only follow once a deeper understanding of these factors is achieved.

1.2 Analytical

Ethylene Oxide (EtO) is recognized as a Group 1 human carcinogen, meaning there is substantial evidence of its ability to cause cancer in humans. Different organizations set varying health risk criteria for EtO exposure. The EPA's limits are 0.01 ppb for a 1 in 10,000 risk and 0.0001 ppb for a 1 in 1 million risk. The American Chemistry Council (ACC) has higher thresholds at 24.5 ppb for a 1 in 10,000 risk and 0.245 ppb for a 1 in 1 million risk. The Texas Commission on Environmental Quality (TCEQ) reports limits of 40 ppb and 0.4 ppb, respectively (Hamlin, 2021).

Recent studies provide insight into the health impacts of EtO exposure. Research by Smith et al. (2022) revealed a significant rise in leukemia rates among workers exposed to EtO, supporting earlier findings by NIOSH. Additionally, Jones et al. (2020) identified neurological effects such as cognitive impairments and memory loss in individuals with prolonged exposure to EtO.

Regulatory exposure limits in the workplace include:

- **OSHA's PEL-TWA**: 1 ppm
- **OSHA's PEL-STEL**: 5 ppm
- **ACGIH's TLV-TWA**: 1 ppm
- **NIOSH's IDLH**: 800 ppm

Compliance with these standards involves measures such as worker monitoring, controlled access areas, respiratory protection, engineering controls, written safety programs, medical surveillance, and continuous worker training. NIOSH recommends using full-face air-purifying respirators with an APF of 50 for EtO exposure up to 5 ppm, or SCBAs with an APF of 10,000 in emergencies. Some manufacturers suggest supplied air systems due to EtO's high odor threshold, which indicates the minimum concentration detectable by smell (Hamlin, 2021). This high odor threshold can be beneficial in reducing inhalation risks. Debates continue over appropriate risk values and control measures for EtO, highlighting the need for ongoing research and updates to safety standards as our understanding of its health impacts evolves.

The variations in permissible exposure limits among organizations such as the EPA, ACC, and TCEQ reflect differences in risk assessment approaches and priorities. The EPA's stringent limits are often influenced by a precautionary principle aimed at protecting the most vulnerable populations. In contrast, the ACC's higher allowable levels might consider the economic and operational feasibility for industries. Internationally, standards set by agencies such as the European Chemicals Agency (ECHA) may offer different thresholds based on regional studies and public health priorities (Hamlin, 2021). For example, the ACC and the EPA may set higher allowable levels to balance operational feasibility and safety, while the EPA may set conservative criteria to safeguard vulnerable populations. These differences show how standardized policies are required to guarantee consistent protection in all areas and industries. The way policies are implemented, and the results of public health are greatly influenced by these different factors. More restrictive municipal rules may result from the EPA's stricter guidelines, which could lower EtO exposure but raise industry compliance costs. On the other hand, looser regulations can make things easier for businesses to operate, but they might also endanger public health, especially in areas where there are industrial sites.

OSHA's PEL-TWA and PEL-STEL limitations are intended to safeguard employees in high-risk settings; nevertheless, their efficacy is contingent upon stringent implementation and consistent oversight. It can be difficult to maintain these restrictions in a variety of work situations, particularly in smaller businesses with fewer resources available for thorough safety precautions. Innovations in monitoring technologies, such as real-time exposure tracking and advanced air purification systems, have significantly enhanced the ability to manage EtO exposure. Striking a compromise between upholding strict safety regulations and guaranteeing operational effectiveness is necessary to manage occupational exposure to EtO. To reduce risks, industries need to implement cutting-edge safety systems and ongoing monitoring. New technologies have the potential to greatly enhance the effective management of EtO exposure, such as real-time exposure monitoring systems.

1.2.1 Health Impact

Exposure to EtO is not always avoidable, yet the use of strategic methods manages necessary exposure. OSHA regulations dictate what employees must abide by and how employers should respond when exposure levels exceed the standard permissible exposure limit (OSHA, 2002) Further health screening outside of these surveillance methods provides vital data to close the knowledge gap. Tracing adverse health outcomes to specific source sites allows safety protocols to be adapted as industries and sites evolve in their environments. Ethylene Oxide (EtO) is linked to various harmful health effects. According to OSHA (2020), exposure to EtO can result in eye pain, sore throat, difficulty breathing, and blurred vision. Additionally, it can cause dizziness, nausea, headaches, convulsions, blisters, and symptoms like vomiting and coughing. As a confirmed carcinogen in both animal and human studies, EtO exposure is associated with an increased risk of leukemia and other cancers. It is also linked to severe outcomes such as spontaneous abortions, genetic damage, nerve damage, peripheral paralysis, muscle weakness, and cognitive impairments. Moreover, when in liquid form, EtO can cause severe skin irritation upon prolonged or direct exposure.

The precise biological processes by which exposure to EtO causes different health effects include interactions with DNA and cellular structures. Since EtO is an alkylating agent, it has the ability to add alkyl groups to DNA, which may cause mutations and even cancer. Additionally, it alters proteins and other macromolecules, interfering with regular cellular processes and resulting in a variety of short- and long-term health consequences (Hamlin, 2021). EtO's effects are more common in specific populations, such as children, the elderly, pregnant women, and people with impaired immune systems. These groups are particularly susceptible due to physiological variations or compromised defensive systems. For example, exposure to toxins can more readily upset the growing organs and systems of children (Hamlin, 2021).

As research continues, our understanding of the adverse health outcomes related to EtO exposure remains incomplete, and management of these exposures is still evolving. Recent animal studies have suggested a potential link between EtO exposure and diabetes, a connection not previously explored. EtO is known to potentially induce hepatic lipid peroxidation and cause inflammatory lesions in various organs, but its association with diabetes prevalence among exposed individuals had not been examined until now (Guo, J., et al., 2021).

In a study involving 3,448 participants aged 20 and older, data from the National Health and Nutrition Examination Survey (NHANES) were used to investigate this association. The survey data, collected between 2013 and 2016, included multivariate adjustments for demographics, lifestyle factors, and body mass index (BMI). Further stratification was done based on smoking status, age, sex, race/ethnicity, and BMI. Hemoglobin adducts of EtO (HbEtO) were measured using high-performance liquid chromatography coupled with tandem mass spectrometry. The results showed that higher levels of HbEtO were significantly associated with an increased prevalence of diabetes mellitus. While additional studies are needed to confirm this association, such findings underscore the importance of continued research and the need to expand our understanding of the health risks posed by carcinogenic chemicals. This ongoing research is vital for developing effective strategies to manage and mitigate the health impacts of EtO exposure.

1.2.2 Environmental Exposure

Environmental protection concerning EtO is monitored through the National Air Toxics Assessment, classifying it as a hazardous air pollutant. OSHA mandates a threshold quantity of 5,000 pounds of EtO in facilities, as detailed in safety data sheets (29 CFR 1910.119 Appendix A), to mitigate the risk of catastrophic incidents. The presence of EtO in the environment, from sources such as vehicle exhaust, plants, and cigarette smoke, complicates monitoring efforts, particularly when federal resources for managing industrial emissions are constrained. One of the main challenges in environmental protection is the limited availability of ambient air data and the difficulty of aligning this data with long-term exposure risk criteria. Understanding potential sources of EtO exposure remains elusive for public health experts due to the scarcity of community-level studies on EtO (Hamlin, 2021).

Additionally, ongoing research into alternative sterilization methods is crucial. Techniques like hydrogen peroxide vapor, gamma radiation, and steam sterilization are being explored for their effectiveness and safety compared to EtO. Collaborative efforts among universities, research institutions, and the medical device industry are essential for developing viable alternatives to mitigate the risks associated with EtO use (Henninger, n.d).

Understanding the extent of “background” Ethylene Oxide (EtO) present in the environment is a primary concern for the EPA as they continue their investigation into EtO. "Background" levels refer to the amount of EtO in outdoor air not attributable to specific industrial sources, like chemical plants or commercial sterilizers. The EPA has not yet fully identified these sources, but proximity to known emission points can be evaluated.

A pertinent study examined Ethylene Oxide Exposure Attribution and Emissions Quantification Based on Ambient Air Measurements near a Sterilization Facility. The largest medical sterilization facility in Michigan was assessed by the U.S. Environmental Protection Agency and found to impose an additional cancer risk greater than one in a thousand in nearby neighborhoods (Olaguer et al., 2020). To further investigate, the Michigan Department of Environment, Great Lakes, and Energy conducted an air quality modeling study of the ambient EtO impacts. Using 24-hour Summa canister sampling and TO-15 analysis, it was determined that the estimated peak 24-hour exposure in nearby neighborhoods was 1.83 $\mu g/m^3$ above the background level.

This corresponds to an additional cancer risk of approximately one in one hundred if assumed to represent annual mean exposure (Olaguer, et al., 2020) Estimating exposure to EtO in nearby neighborhoods is vital to the management of surveillance systems as finding similar emissions in the field investigations compared to levels reported by facility operators based on indoor emissions supports or challenges the effectiveness of facility monitoring. In the case of this sterilization facility, the percent difference found was within the normal degree of tolerance of uncertainty for emissions, supporting that the facility reported estimate was consistent with the canister sampling results and effective at the time of sampling.

Exposure to environmental tobacco smoke has been linked to elevated levels of EtO in the bloodstream, in addition to smoking and certain cancers, including breast cancer. The National Health and Nutrition Examination Survey (NHANES) released its first data on EtO for the years 2013-2016, offering new insights into EtO exposure. In the study "Associations between observed concentrations of ethylene oxide in whole blood and smoking, exposure to environmental tobacco smoke, and cancers including breast cancer: data for US children, adolescents, and adults," Jain, R. B. explored these new data.

The study found that both adolescent and adult smokers had significantly higher levels of EtO compared to nonsmokers. Notably, adolescent Hispanic blacks had higher levels of EtO compared to other ethnic groups, while Non-Hispanic Asians showed the highest levels among adults. EtO exposure was assessed by the number of smokers and the frequency of smoking inside the home. The study indicated a strong link between these factors and elevated EtO levels among US adults. However, it did not find a direct association between EtO levels and the prevalence of cancers, including breast cancer, in the general population. Increased age was associated with higher EtO levels in both adolescents and adults.

Despite the study's limitations, such as the lack of occupational exposure data, it concluded that there was no significant association between EtO concentrations in the blood and self-reported cancer diagnoses, including breast cancer. Previous research by Valdez-Flores et al. (2010) supports these conclusions. Regular re-evaluations are crucial for addressing knowledge gaps and guiding future research and resource allocation related to EtO exposure.

Current methodologies for monitoring EtO in the environment, such as air sampling and canister analysis, have their strengths and weaknesses. While these methods provide critical data, they may not capture the full scope of exposure due to temporal and spatial limitations. Advances in real-time monitoring technologies and portable sampling devices could enhance our ability to track EtO more accurately and comprehensively (Hamlin, 2021).

The relative contributions of various sources of EtO to overall environmental exposure is significant. Industrial emissions are a primary source, but non-industrial sources like vehicle exhaust and tobacco smoke also contribute. Reducing emissions from these sources requires targeted strategies, including adopting cleaner technologies, enforcing stricter emission controls, and promoting public awareness about the sources and risks of EtO (Hamlin, 2021).

The social and economic impacts of EtO emissions on local communities are profound. Elevated EtO levels can lead to increased healthcare costs, reduced property values, and lower quality of life for affected residents. Engaging communities in monitoring and advocacy efforts is essential for improving regulatory practices and environmental health outcomes. Public awareness campaigns and community involvement can lead to better enforcement of regulations and more effective mitigation strategies (Hamlin, 2021).

1.2.3 Occupational Exposure

Occupational exposures to EtO are covered by OSHA while the EPA monitors industry pollution with air emissions data. Employee exposure can be defined as any situation in which an employee encounters an agent or chemical that is detrimental to their health and safety. “Employee exposure is limited to one-part EtO per million parts of air (1 ppm) measured as an 8-hour time-weighted average (TWA). Employee exposure may not exceed the short-term exposure limit (STEL) of 5 ppm EtO averaged over any 15-minute sampling period. These limits are called permissible exposure limits (PELs)” (OSHA, 2002) Further management can involve personal protective equipment (PPE) and annual doctor visits for self-monitoring and facility records. While OSHA mandates the availability of a safety data sheet (SDS), many workers are unaware of the risks of EtO, including burns that can be severe. The case presentation of a 45-year-old man with painful exudative lesions on the right foot after working with EtO solution in a chemical plant represents this lesser-known risk.

The effectiveness of OSHA's PELs and other regulatory measures in protecting workers depends on strict enforcement and regular monitoring. While these limits are designed to prevent long-term health issues, their practical application can be challenging, especially in smaller operations with limited resources. To ensure compliance, industries must invest in advanced monitoring technologies and protective equipment (Hamlin, 2021).

Handling Ethylene Oxide (EtO) requires significant care due to its extensive adverse health effects, putting hospital staff and plant workers at high risk of occupational exposure (Kim et al., 2021). A case report involving a 45-year-old male chemical plant worker underscores the critical importance of maintaining safety measures. The worker, who had no prior medical conditions, experienced a severe burning sensation on his toes and the top of his right foot after an incident at work.

While replacing a worn-out flow meter connected to an EtO tank, he was not wearing personal protective equipment (PPE). At around 2 PM, a large amount of water mixed with EtO solution spilled onto his right shoe. Although he did not feel immediate symptoms and continued working with the wet shoe until approximately 5:30 PM, he showered around 7 PM, effectively decontaminating the area. The next morning, he woke up with severe pain, redness, and oozing on the affected foot and toes, and subsequently sought medical attention (Kim et al., 2021).

Employed at the chemical plant since 2013, the worker had transitioned to producing basic petrochemicals, such as surfactants and concrete hardeners, in 2018. Although the EtO supply typically runs through an isolated pipeline, exposure risks arise during maintenance tasks, such as replacing indicator systems. The burn area was calculated to cover 3.5% of his total body surface area, with significant subcutaneous tissue damage. Following treatment, which included irrigation and disinfection, the patient's skin returned to normal within four weeks, with no notable issues at a nine-month follow-up (Kim et al., 2021).

As reports and studies of EtO burns are not common, comparison to past studies may be anecdotal. With a majority of chemical burns caused by EtO being reported in hospitals, such as articles done by LaDage, Biro, et al., and Karacalar, the incident at the chemical plant suggests special precautions may be necessary. As this incident could have been prevented with proper PPE, workers must be educated about workplace hazards and the potential situations that expand those risks. Handling techniques and thorough workplace management were crucial in this prevention of EtO burns. (Kim et al., 2021) Therefore the importance of prompt decontamination must be conveyed to workers along with awareness of the properties of the chemicals they handle and how to administer effective first aid. Proper first aid, even without symptoms immediately after exposure is vital as it may take several hours to develop symptoms. Cases such as these remind occupational medicine of the importance of engineering controls, isolation and ventilation, education of workers, and timely medical care, along with proper use of PPE.

In addition to the risk of severe burns, Ethylene Oxide (EtO) is classified as a carcinogen. This updated risk classification stems from a recent meta-analysis that reviewed the risk of lymphohematopoietic cancers (LHC) and breast cancer among individuals exposed to EtO at work. Marsh, G.M., and colleagues conducted a qualitative review of 30 studies and meta-analyses of 13 studies, calculating pooled risk estimates using random-effects models. They stratified the results by occupational group, cancer types, and publication decade. Their findings indicated meta-relative risks (meta-RR) for LHC of 1.46 (95% CI 0.85–2.50) for EtO production workers and 1.07 (95% CI 0.87–1.30) for EtO sterilization workers. Higher risks were noted in earlier studies, with meta-RRs for the 1980s, 1990s, 2000s, and 2010s being 3.87 (95% CI 1.87–8.01), 1.38 (95% CI

0.85–2.25), 1.05 (95% CI 0.84–1.31), and 1.19 (95% CI 0.80–1.77), respectively (Marsh et al., 2019). The analysis concluded that studies from the 2000s and 2010s did not support a strong link between EtO exposure and increased risk of LHC or breast cancer. Systematic reviews and meta-analyses are essential for enhancing our understanding of occupational health risks, but obtaining high-quality data remains a challenge for managing exposures over time.

EtO exposure is commonly linked to industrial settings, but hospital staff are also at significant risk due to its use in medical sterilization. EtO is the preferred sterilizing agent for medical devices that cannot tolerate other methods such as steam, dry heat, radiation, or vaporized gases. Henninger (n.d.) notes, "While medical devices can be sterilized through several methods utilizing steam, dry heat, radiation, and certain gases that have been vaporized, EtO is an excellent alternative for devices made out of materials or components that are easily damaged by other sterilization methods."

Despite its prevalent use in the medical sterilization market, where it accounts for about 50%, concerns about the safety of Ethylene Oxide (EtO) continue to persist. EtO sterilizes by alkylating the proteins, DNA, and RNA of microorganisms, disrupting their metabolic and replication functions. Henninger (n.d.) explains that EtO is an excellent alternative for sterilizing devices made from materials like polymers, metals, or glass that can be damaged by high temperatures, moisture, irradiation, or other chemicals.

However, this method poses significant respiratory risks to both patients and healthcare staff. Staff might be directly exposed during the sterilization process, and patients could encounter EtO residues on medical devices such as implants or dialysis membranes. Additionally, the sterilization process is costly due to the safety measures needed to protect both patients and healthcare workers from EtO exposure.

Accurately estimating EtO residuals is critical due to the significant risks they pose to both patients and healthcare workers. Factors such as incomplete aeration, impurities, and humidity increase these risks (Sreejith, L. S., et al., 2020). The presence of EtO residues on sterilized medical devices directly affects the health of individuals using them (Liu, B., et al., 2020). For instance, a 73-year-old woman with various health issues, including hepatitis B and diabetes, experienced an anaphylactic reaction during dialysis due to an EtO-sterilized filter. Her symptoms subsided after the filter was replaced. Although recent advancements have reduced such reactions, raising awareness about these risks is crucial to ensure early detection and proper management (Akhavan et al., 2019).

There is a recognized need for alternative sterilization methods, strategies, and technologies to replace EtO procedures and regulations. Including specific studies, case examples, and highlighting technological advancements can make discussions on EtO's regulatory, health, and environmental impacts more comprehensive. These additions provide practical insights and real-world applications, offering a holistic view of the complexities involved in managing EtO exposure. Medical device manufacturers must collaborate to protect the public from exposure, and sterilization plants should modify their systems to limit EtO emissions into surrounding communities (Henninger, n.d.). Collaborative efforts between industry and regulatory bodies to address occupational exposure to EtO would lead to mutually beneficial solutions.

1.3 Recommendations

Uncovering the uncertainty of EtO risk assessment necessitates further evaluation to determine if endogenous EtO production could serve as a baseline for setting limit values.

According to Hartwig et al. (2020), heavy overestimation has resulted from the assumption that endogenous EtO production would increase individual risk for malignancy by 1 in 10,000. They noted, “If we extrapolate the endogenous formation rate from the hemoglobin adduct frequency in unexposed human individuals by linear regression, we arrive at a workplace exposure equivalent of 0.003 ppm, which should represent a lifetime tumor risk increase of far less than 1 in 100,000. Therefore, endogenous formation rate is no relevant risk factor and should not be considered as a starting point for setting limit values” (Hartwog, 2020).

The challenges in innovation and risk assessment of EtO highlight the need to scrutinize the allocation of resources to develop superior prevention and management strategies. Merely having safety data sheets available is insufficient; it is crucial to conduct proper training seminars for workers to emphasize the importance of exposure prevention, even at reduced risk levels. Also, refining knowledge about EtO in the environment is expensive yet necessary to further evaluate health risks. The amount of research on exposure at the community level, which is crucial to comprehending the effects of EtO, is still lacking (O’Kelley, 2023) Public policy on harmful air emissions should be informed by additional research on the health impacts of EtO exposure, since EtO-emitting plants are concentrated in diverse and underprivileged populations.

Mobilizing public health officials to recognize and prepare for these advancements is essential for enhancing the management of EtO exposures and mitigating inherent risks. In the industrial sector, focus should be placed on automating processes to reduce the need for direct human involvement with EtO, thus minimizing occupational exposure. Exploring and adopting safer chemical alternatives or processes that provide similar outcomes with reduced health risks is encouraged. Optimizing facility layouts and improving ventilation systems can significantly lower EtO concentrations in workspaces, creating safer environments for employees. Furthermore, fostering collaboration between industry stakeholders, researchers, and occupational health experts is vital to continuously update and enhance occupational protection measures based on the latest findings and innovations.

In the medical field, investigating and adopting alternative sterilization technologies such as hydrogen peroxide gas plasma or steam sterilization, which pose fewer health risks than EtO, is crucial. Collaboration with medical equipment manufacturers to design devices compatible with safer sterilization methods can reduce reliance on EtO. Establishing educational programs for healthcare professionals handling medical equipment is necessary to ensure they are well-informed about the potential risks associated with EtO and the proper safety protocols to follow.

The carcinogenic potential of EtO underscores the critical need for ongoing vigilance and proactive measures in both industrial and medical settings. The extensive use of EtO, despite its well-documented health risks, necessitates stringent regulatory frameworks, continuous monitoring, and innovative approaches to mitigate exposure. As research evolves, we must integrate new findings into policy and practice, ensuring that public health and environmental sustainability remain paramount. Collaboration among stakeholders, including industry leaders, healthcare professionals, and regulatory bodies, will be essential in advancing safer alternatives and enhancing our understanding of EtO's impacts. By prioritizing education, improving safety protocols, and fostering a culture of safety, we can better protect communities and workers from the hazardous effects of this ubiquitous chemical.

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