Ethylene Oxide and Cancer: Digging for the Truth

Yanjia li*

College of Literature, Science, and The Arts University of Michigan, Ann Arbor, Ann Arbor, Michigan, USA

Abstract. Multiple studies have shown a relationship between EO exposure and an increased risk of cancer in humans, but the results have been inconsistent. Nonetheless, the association between EO and human cancer risk, especially in terms of dose-response, is poorly understood. Examining whether or not EO exposure is linked to increased cancer risk in the basic adult population in the U.S. was the primary focus of this study. The study included data from both the 2013–14 and 2015–16 waves of the National Health and Nutrition Examination Survey (NHANES), for a total of 3,448 people. Data including demographic characteristics, medical history, and serum EO biomarkers were retrieved from Serum EO biomarker (hemoglobin adduct of EO (HbEO)) concentrations evaluated. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined by multiple logistic regression. The result shows that EO with the highest concentration between 1340 and 1780(OR = 19.12, 95% CI: 1.73-211.47) is statistically significant.

1. Introduction

The chemical intermediate role played by EO within the creation of antifreeze, polyesters, detergents, adhesives, textiles, solvents, pesticides, and many other products has led to its mass production around the world.[1][25] It is also commonly used for fumigating food (such as spices and nuts) and cosmetics to kill any harmful bacteria[25]. Factory and warehouse environments, among others, can pose a risk of occupational exposure to EO because of the presence of these substances in their production and usag[1]. This is how EO gets out into the world and into the bodies of the general public: through the use of common commercial products. Several studies demonstrate a linear correlation between HbEO (N-[2-hydroxyethyl]valine) levels in workers and their exposure to airborne EO on the job.[2][11][16][33][19]

According to toxicology, ethylene oxide has a moderate level of toxicity. Using rats as a model, the typical fatal dose is 330 milligrams per kilogram. Some research has indicated that even moderate exposure to ethylene oxide can cause significant lethal and mutagenic consequences in rats.

EO exposure limits have been established for both continuous contact and limited exposure uses. No more than 0.1 mg of EO per day is recommended for patients using permanent-contact devices. As an added precaution, no single dose of EO should be more than 20 mg, no 30-day total of EO should be more than 60 mg, and no lifetime total of EO should be more than 2.5 g.

The maximum recommended EO dose for prolonged-exposure devices is 2 mg per day. In addition, a patient should not be exposed to more than 60 mg of EO in the first 30 days, with no more than 20 mg given in the first 24 hours.[37]

Numerous studies have shown that EO is harmful to human health. Animal investigations have demonstrated that long-term exposure to EO causes inflammation in multiple organs, decreases levels of the intracellular antioxidant glutathione, and stimulates hepatic lipid peroxidation[21][29][30]. Additionally, The International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) have both suggested that EO is a carcinogen (USEPA). The primary epidemiological evidence linking occupational EO exposure to increased cancer risk was published in 1979 (ref). Studies on humans in the workplace have linked EO exposure with an increased risk of malignancies including but not limited to breast cancer in females, leukemia, and gastric cancer[26][35].

Recently, the EPA's Toxic Substances Control Act warrants re-evaluation of the EO carcinogenicity. Twenty-four preliminary research on animals or humans and over fifty mechanistic studies have been reviewed (ref). Information on the environment is organized according to the International Organization for Standardization (IOM) standard. Results regarding the association of EO exposure with gastrointestinal, mammary, and lymphoid-hematopoietic malignancies was culled from epidemiological, animal, and mechanistic studies. Twenty occupational cohorts, nine population-based cohort studies, two case-control studies, and a review of the literature on population pilot studies were analyzed. Cohort studies have looked at a wide variety of

* liyanjia@umich.edu

malignancies, and the vast majority have found no link to EO.[30]

The study's goal is to determine whether or whether high levels of EO in the environment are related to an increased risk of cancer.[1]-[37]

2. Method study population

The NHANES is a study of the general population of the United States that is designed to be representative of the country as a whole and to assess their health and nutrition. The CDC's National Center for Health Statistics is responsible for carrying out the National Health and Nutrition Examination Survey (NHANES)[10]. The Institutional Review Board at the National Institute of Health Statistics gave their approval for the NHANES project, and all participants provided their written consent. Some extra resources may provide supplementary dat[9]. This research makes use of NHANES data from both the 2013–2014 and 2015–2016 cross-sections. A one-third subsample (n = 3448) was used to obtain an EO estimate, and this sample was representative of the entire study population.

3. Variable evaluation

Adducts of hemoglobin, the biomarker HbEO (N-[2-hydroxyethyl]valine) in the blood can be used to measure how much EO a person has been exposed to. When EO binds to valine in hemoglobin, HbEO is produce. Evidence suggests that HbEO is a sensitive and practical biomarker for EO exposure assessment[4]. The main variables are collected as part of a household questionnaire, but combining them with Mobile Examination Center (MEC)test results requires using the weights from the MEC test data. Households were surveyed by mail-in questionnaires to determine things like average age, gender distribution, racial/ethnic background, level of education, frequency of alcohol use, number of cigarettes smoked per week, number of people in poverty, frequency of exercise, health concerns, and drug usage. The formula for determining a person's body mass index (BMI) is as follows: (kg-height) (meters squared). If your body mass index (BMI) is 30 or higher, you are considered obese, per the World Health Organization. The question, "Ever told you had cancer or malignancy?" is crucial since it reveals whether or not the person actually developed cancer. In addition, NHANES employs several techniques to verify the accuracy of the results from third-party laboratories. In "dry run" sessions, the MEC takes a random sample of people without revealing their identities. Furthermore, the contract laboratory will replicate 2% of all samples by randomization.[1][2][36][33][34]

4. Statistical Analysis

We accounted for sample weights, clustering, and stratification where applicable because NHANES employs a sophisticated sampling approach[8][10]. First, we log2 the EO concentration. Also using multiple imputations for missing values, ten complete datasets were obtained, all of which were used for logistic regression to see if there was an association between EO and cancer. In logistic regression, we first did unadjusted logistic regression, and then we put other control variables in logistic regression, including age, hypertension (with or without hypertension), gender (men or women), race (Hispanic, non-Hispanic whites, blacks, etc.), educational attainment (attending high school, not attending high school or above high school), household income (below the poverty line, above the poverty line), smoking status (never, occasional, daily), and alcohol use (non-drinkers, past drinkers) were adjusted OR, to determine whether different concentrations of EO are associated with cancer risk. Finally, in order to explore the non-linear relationship, we made a GAM model, and finally used GAM graphing to show the non-linear relationship.

5. RESULT

Data on the sample population of whether they have cancer or not are presented in Table 1.

Of 3448 adults, 2168 have had cancer (62.88%). Participants with cancer were 60-80 group (228(70.37%)) more likely to be female (168 (51.85%)), White (214 (66.04%)), had attained high school or higher level of education (270 (83.33%)), and had higher Blood pressure (190 people (58.64%)). People with Cancer were also more likely to be nonsmokers (111 (34.26%)). Participants with poverty were more likely to experience cancer(3.05 vs 2.75). In addition, compared to those without cancer, participants cancer had higher mean concentrations(91.06). The associations between the concentration of EO and cancer are presented in Table 2. statistically significant associations of highest EO concentration quartile (OR = 19.12, 95% CI: 1.73-211.47). After controlling for other covariates, the highest quartile was still observed as statistically significant (OR = 19.65, 95% CI: 1.32-291.81)Moreover, Fig. 1 presents the associations between EO concentration at each level and cancers in the GAM model. Briefly, when EO concentration exceeded certain levels, we observed an elevated risk for cancers and the risk increased exponentially as the EO concentration increases. The overall P value for the non-linear relationship is 0.03.

Table 1. Characteristics of the study population whether they have cancer or not.

Variable	Cancer (NO)	Cancer(YES)
Did not have Alcohol	814(26.06%)	89(27.47%)
Had Alcohol in past	2024(64.79%)	218(67.283%)
Alcohol missing number	286(9.15%)	17(5.25%)
Age20-40	1204(39.03%)	19（5.86%）
Age40-60	1065(34.52%)	77（23.77%）
Age60-80	816(26.45%)	228（70.37%）
Male	1540(49.30%)	156（48.15%）
Female	1584(50.70%)	168（51.85%）
Dont attend high school	334(10.69%)	27（8.33%）
High school	377(12.07%)	27（8.33%）
Above high school	2411(77.18%)	270（83.33%）
Education missing number	2(0.064%)	0（0%）
No high blood pressure	1441(46.13%)	105（32.41%）
High blood pressure	1439(46.06%)	190（58.64%）
High Blood pressure missing number	244(7.81%)	29（8.95%）
Hispanic	864(27.66%)	48（14.81%）
Non-Hispanic White	1131(36.20%)	214（66.05%）
Black	644(20.61%)	41（12.65%）
Other	388(12.42%)	11（3.40%）
Race missing number	97(3.105%)	10（3.09%）
Smoking everyday	480(15.37%)	50（15.43%）
Not smoking every day	142(4.55%)	10（3.09%）
Don’t smoke	708(22.66%)	111（34.26%）
Smoke missing number	1794(57.43%)	153（47.22%）
Mean of Poverty	2.485226	2.598967
IQR of Poverty	3.05	2.75
Mean	90.55561	91.06321
Median	33.42000	31.87000

Table2. Unadjusted and adjusted results.

	Unadjusted			Adjusted		
Term	Odd Ratio	95% Confidence Interval	P.value	Odd Ratio	95% Confidence Interval	P.value
lbxeoa(452,895]	0.60291443	(0.2784,1.3055)	0.1993	0.527924499	(0.2266,1.2298)	0.1387
lbxeoa(895,1340]	0.956054843	(0.1220,7.4932)	0.9659	1.232557156	(0.1365,11.1337)	0.8523
lbxeoa(1340,1780]	19.1210534	(1.7289,211.4742)	0.0161	19.64761585	(1.3229,291.8091)	0.0305

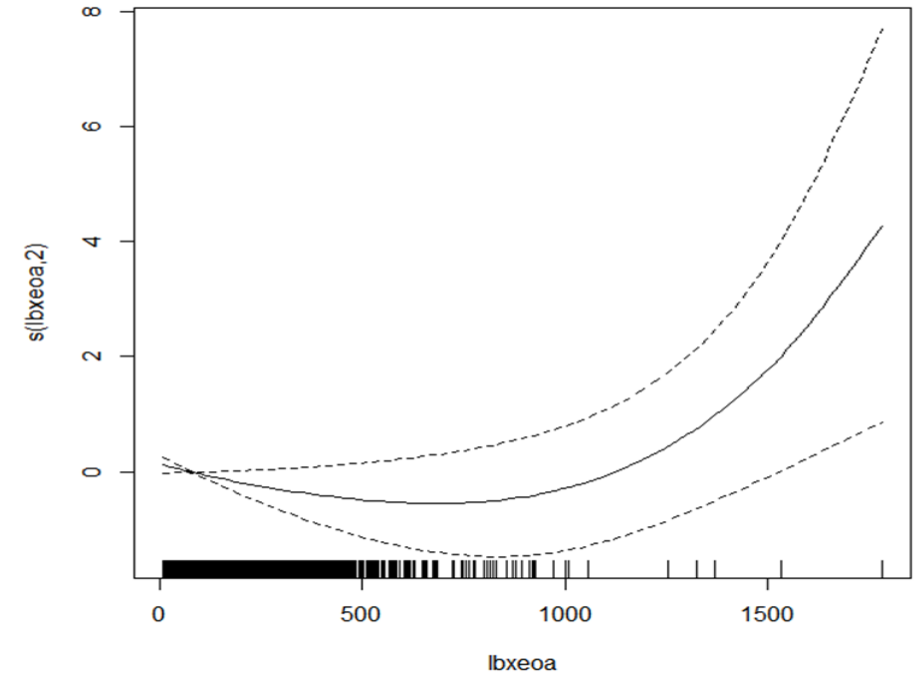

Figure 1. the graph of the effects of EO on cancer.

6. Discussion

The first epidemiological studies showing a link between EO and cancer risk were published as early as 1979. By following a specific group of Sweden's population, an important rise in the number of leukemia and gastric cancer cases was reflected, all of which included small production groups with mixed exposures such as EO exposure to low levels of EO is also carcinogenic, according to toxicological and epidemiological studie.

Recent research employing the EPA's TSCA framework examined a population pilot study with 20 occupational cohorts, nine separate occupational cohort studies, and two case-control studies. Researchers looked at people who produced EO but weren't necessarily involved in sterilization (9 studies), people who had been sterilized (10 studies), and hospital staff (3 research). Cohort studies have looked at a wide variety of malignancies, and the vast majority have found no link to EO. Nonetheless, Lymphoma patients (2347) and controls (2463) were collected from six European countries for this case-control study. Although industrial hygienists evaluated interview replies for exposure to 35 distinct chemicals, only 31 lymphoma cases and 27 control cases were found to had been exposed to EO. Gastric cancer (12 studies), breast cancer (9 studies), and lymphohematopoietic malignancies (15 studies) were the only ones with promising findings. However, further researches failed to uncover sufficient epidemiological evidence linking EO to either gastric or breast cancer in humans, or to show that LHM alone or in combination causes cancer in humans. A further potential source of error is that the study only focused on the three most common types of cancer. To further investigate whether or not EO played a role in the onset of the experimental population's condition, researchers tracked their progress over time. Instead, we used a connection analysis based on preexisting cancer to randomly choose participants to test the hypothesis that EO affects cancer. We separated EO into four distinct strengths. we discovered that greater EO levels were independently related to an elevated risk of cancer in the general population, albeit other factors were also important. For instance, compared to people of other races, whites obviously have a far higher chance of potentially developing cancer; Similarly, compared to people who have never smoked, people who have never smoked have a much higher risk of developing cancer. Alternatively, those people with more education tend to develop cancer more frequently. Another key contributor to cancer incidence is hypertension.

However, this study has many shortcomings that need to be addressed. First, a cross-sectional design cannot determine cause and effect. In the near future, the cohort should be prospectively studied. There is no specific way to identify different types of cancer, and some cancers may not matter at all. The tracking collection of data is not very complete, this cross-sectional study is only for 2013-2014 and 2015-2016, because the population tracking time is not long enough, the results may be uncertain. In conclusion, residual and/or unmeasured confounders and chance may have played a role in this study. In observational studies, it is impossible to completely rule out this possibility.[1]-[30]

7. Conclusion

Using a nationally representative US population sample for the first time, we were able to find that higher concentrations of EO were significantly associated with increased cancer incidence. The results showed that the highest concentration of EO was between 1340 and 1780 (OR = 19.12, 95% CI: 1.73-211.47) with statistical significance. This is a reference for those who have been exposed to the EO environment for a long time. Although their daily amount cannot reach 1340, through accumulation, the boundary of 1340 should be taken seriously. However, more prospective studies are needed to confirm these findings. In addition, further trials are needed to determine whether different amounts of EO really do not matter, and which specific malignancies are associated with exposure to EO.

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