Environmental Science and Pollution Research (2024) 31:2802–2812
https://doi.org/10.1007/s11356-023-30712-4

RESEARCH ARTICLE

Impact of hemoglobin adducts of ethylene oxide on the prevalence and prognosis of chronic kidney disease in US adults: an analysis from NHANES 2013–2016

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Received: 11 June 2023 / Accepted: 23 October 2023 / Published online: 8 December 2023

Abstract

Animal experiments have shown that high exposure to ethylene oxide (EO) can cause multiple system damages including the renal system. Recent studies have reported associations between exposure to EO and cancer, dyslipidemia, diabetes, and cardiovascular disease. However, the impact of exposure to EO on the prevalence and prognosis of chronic kidney disease (CKD) in humans is scarcely investigated. The study was designed to investigate the associations between EO exposure and incidence and prognosis of CKD among 2900 US adults. Exposure to EO was measured by detecting the levels of hemoglobin adducts of EO (HbEO). The diagnosis of CKD was made according to an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or a urinary albumin-to-creatinine ratio (UACR) > 30 mg/g. Prognosis of CKD was assessed based on the evaluation system initiated by KDIGO that consists of eGFR and UACR. Survey-weighted generalized linear models and proportional odds models were constructed to assess the associations between HbEO and prevalence and prognosis of CKD, with odds ratios (ORs) and proportional odds ratios (PORs) and their 95% confidence intervals (CIs) reported, respectively. Restricted cubic spline (RCS) function was performed to depict the correlation between HbEO and CKD. The weighted median (interquartile range) of HbEO was 31.3 (23.1–60.3) pmol/g Hb. A total of 491 participants (16.9%) were diagnosed with CKD, and 153 participants (5.31%) were identified to be at high or very high risk. Referred to the first tertile of HbEO, the adjusted ORs (95% CIs) for CKD in the second and third tertile were 1.46 (0.85, 2.50) and 1.69 (1.00, 2.85), and the adjusted PORs (95% CIs) for prognosis of CKD in the second and third tertile were 1.37 (0.94, 1.99) and 1.58 (1.10, 2.26). When HbEO was analyzed as a continuous variable, the adjusted OR (95% CI) for CKD and POR (95% CI for prognosis of CKD were 1.24 (0.97, 1.58) and 1.22 (1.01, 1.47), respectively. RCS analysis revealed a non-linear positive correlation between HbEO and prevalence of CKD (P for nonlinearity < 0.05). Subgroup analysis indicated smoking status had a significant impact on this association, which remained significant among never smokers but lost significance among smokers. Among US adults, increased EO exposure was independently related to increased CKD prevalence and poor CKD outcomes, which was established in never smokers but not among ever smokers.

Keywords Ethylene oxide · Chronic kidney disease · Prognosis · Epidemiology · NHANES

Responsible Editor: Lotfi Aleya

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Introduction

Chronic kidney disease (CKD) is a common disease encountered in clinical practice, which is the consequence of continuous deterioration of renal excretory function caused by various renal diseases. Replacement treatment including dialysis and renal transplant is the ultimate solution. CKD affects approximately 10–15% of the global population (Matsushita et al. 2022), and significantly increases the risk of adverse outcomes, such as stroke, myocardial infarction, and heart failure, constituting the main cause of death from

non-communicable diseases (Webster et al. 2017). Data from the Global Burden of Disease Study 2019 revealed that, in 2019 alone, there were 19.0 million incident CKD patients, 697 million prevalent CKD patients, 1.43 million deaths caused by CKD, and 41.5 million disability-adjusted life years (DALYs) attributed to CKD globally. These numbers represent a significant increase compared to the figures reported in 2010, with incident patients, prevalent patients, deaths, and DALYs rising by 33.9%, 24.7%, 28.8%, and 20.1%, respectively (GBD 2019 Diseases and Injuries Collaborators. 2020). In addition, CKD can exacerbate the symptom burden and seriously jeopardize health-related quality of life (Fletcher et al. 2022).

As a reactive epoxide, ethylene oxide (EO) is mass produced in factories and is widely applied in the production of ethylene glycols, glycol ethers, ethanolamine, ethoxylate, and acrylonitrile. Besides, it is utilized for sterilization of food, fragrances, cosmetics, medical devices, etc. (Kirman et al. 2021). Individuals can access EO through a number of ways. For the general population, endogenous production including gut bacterial synthesis and formation of EO in the liver from ethylene is an important pathway of EO exposure (Bogen et al. 2019). Exogenous pathways, including metabolic production of EO following exposure to exogenous ethylene from various sources, such as tobacco smoke and incomplete combustion of fossil fuels in vehicles, forest fires, fruit and vegetable ripening, and volcanic eruptions, as well as direct exposure to environments containing EO (such as smoking and industrial facilities) are also major sources of EO exposure (Kirman and Hays 2017; Schettgen et al. 2002).

EO is a highly reactive organic substance that can alkylate proteins, RNA, and DNA. Hemoglobin adduct N-(2-hydroxyethyl) valine (HbEO) has been identified as a useful biomarker to characterize total EO exposure of all exposure pathways (Boogaard et al. 1999). Although no definite correlation between EO exposure and malignancies has been found in human epidemiological data, EO has been categorized as a Group I human carcinogen by the International Agency for Research on Cancer based on a thorough evaluation of available scientific evidence, including animal experiments, genotoxicity data, and associated mode of action analyses (Lynch et al. 2022). In the toxicological profile for EO, animal studies revealed that high doses of EO exposure caused damages in multiple systems, including respiratory, hematological, neurological, reproductive, and renal systems (Toxicological Profile for Ethylene Oxide. 2022). Recent analyses from NHANES have demonstrated that high levels of EO exposure are independently associated with metabolic and chronic diseases including dyslipidemia (Zhu et al. 2022), diabetes (Guo et al. 2021), hypertension (Wu et al. 2022), cardiovascular disease (Zeng et al. 2021), and asthma (Li et al. 2023). However, data on the association between HbEO and the prevalence and prognosis of CKD is limited. In this study, we set out to evaluate the impact of HbEO on the prevalence and prognosis of CKD among US adults.

Methods

Study population

NHANES is an ongoing project designed to examine the health and nutritional status of US citizens. It recruits approximately 5000 representative individuals nationwide each year, and the National Center for Health Statistics (NCHS) is responsible for the implementation of the project. Data are collected through face-to-face interviews and physical examinations. The interviews were performed by trained researchers, and the physical examinations were conducted at a mobile examination center (MEC). Detailed information about the NHANES project was available on its website. Participants in the project were informed in detail and signed a written informed consent form. The protocol of NHANES project was reviewed and approved by the institutional review board.

In the present study, data were extracted from NHANES from 2013 to 2016, among which a random selection of study participants who were aged ≥ 6 years was made for the measurement of HbEO, comprising one-third of the total sample ($n = 4860$). After excluding participants who did not meet the inclusion criteria, 2900 participants were included in the study (as illustrated in Fig. 1). The exclusions were

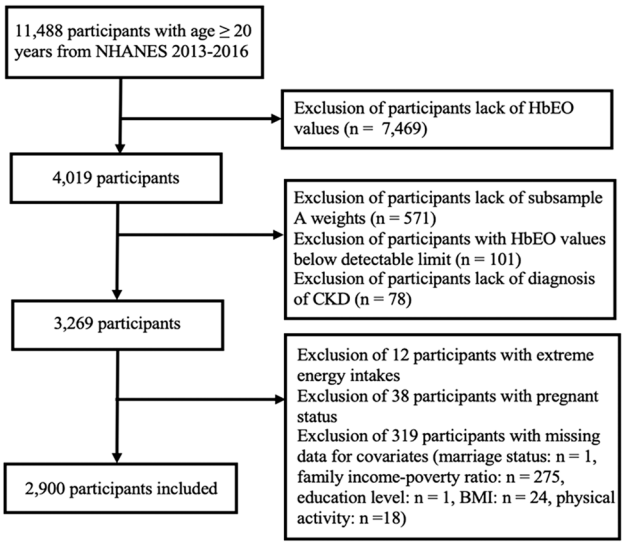

Fig. 1 Study population flowchart. BMI, body mass index; CKD, chronic kidney disease; HbEO, hemoglobin adducts of ethylene oxide; NHANES, National Health and Nutrition Examination Survey

made based on the following criteria: absence of subsample *A* weights ($n = 586$), HbEO values below the detectable limit ($n = 106$), extreme energy intake (defined as daily total energy intake < 500 or > 8000 kcal for males, and < 500 or > 5000 kcal for females ($n = 34$), pregnant ($n = 38$), and missing data for covariates ($n = 540$).

Measurement of HbEO

The collection, processing, and transportation of specimens were performed according to standard procedures. The Division of Laboratory Sciences at the National Center for Environmental Health (NCEH) was responsible for the measurement of HbEO, and detailed information on the laboratory analyses procedures is illustrated in the relevant website. The modified Edman reaction was utilized to test the HbEO levels in whole blood or erythrocytes, with the high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) method applied. The lower limit of detection of HbEO is 12.9 pmol/g Hb, and 109 participants with HbEO values below detectable limit were excluded in this analysis. The accuracy and precision of all assays met the NCEH Laboratory Science Division Quality Control and Quality Assurance Standards (CDC 2023).

Definition of CKD and assessment of prognosis of CKD

The DxC800 modular chemistry analyzer was applied to measure serum creatinine and urine creatinine levels by the Jaffe rate method. Urinary albumin concentrations were determined using the method described by Chavers et al., and it was recommended to use solid-phase fluorescent immunoassay for detection (Chavers et al. 1984). The chronic kidney disease epidemiology collaboration equation was used in this study to calculate the estimated glomerular filtration rate (eGFR) (Levey et al. 2009). CKD was defined as having an eGFR < 60 mL/min/1.73 m^2 or a urine albumin to creatinine ratio (UACR) ≥ 30 mg/g, in accordance with the 2012 clinical practice guidelines for the evaluation and management of kidney disease (Levin et al. 2013). The prognosis evaluation system initiated by KDIGO was used for the assessment of prognosis of CKD, and four risk grades according to the levels of eGFR and UACR were constructed. The calculation formula of eGFR and the scoring system were detailed in Supplementary file 1.

Assessment of covariates

Demographic information (including age, gender, ethnicity), social-economic status (including marital status, education level, household income), health status (including smoking, alcohol use, self-reported health status, physical activity, comorbidities such as diabetes, hypertension, hyperlipidemia, cardiovascular disease, chronic obstructive pulmonary disease, cancer), and dietary habits (energy intake) were determined through standardized questionnaire home interviews. Measurements of blood pressure, body weight and height were conducted at the MEC using standard procedures. In NHANES, dietary intake was assessed via a first 24-h dietary recalls (Stumbo 2008). Energy deficiency is defined as daily energy intake < 2400 kcal/d for adult males and < 1600 kcal/d for adult females (US Department of Health and Human Services and US Department of Agriculture. 2015). Physical activity was quantified in metabolic equivalent (MET) minutes per week and subdivided into insufficient physical activity (< 600 MET min/week) and adequate physical activity (≥ 600 MET-min/week) (Armstrong and Bull 2006). Urinary cadmium was measured using an inductively coupled plasma-mass spectrometry from a single urine specimen.

Statistical analysis

RStudio software (version 2023.03.0 + 386, Posit Software, PBC) was used to conduct statistical analyses, and a 2-tailed P value < 0.05 was statistically significant. As NHANES is designed as a complex, multi-stage, probability sampling study to select representative US individuals nationwide, sample weights, clustering, and stratification must be considered when conducting statistical analysis (Centers for Disease Control and Prevention. 2006). A 2-year weight (2013–2014, 2015–2016) was generated to obtain weighted percentages adjusted to the US adult population.

All participants were grouped into three categories according to tertile of HbEO: T1, 13.2–27.3 pmol/g Hb; T2, 27.3–47.0 pmol/g Hb; T3, 47.0–1781.2 pmol/g Hb. One-way analysis of variance was conducted for comparisons of continuous variables, and the Rao-Scott $\chi 2$ test was performed for comparisons of categorical variables (Rao and Scott 1984). Survey-weighted generalized linear models and proportional odds models were constructed to estimate the influence of HbEO levels on the prevalence and prognosis of CKD, respectively. For these two analytical methods, three models were constructed, respectively: the first model was adjusted for age, gender, and race; the second model was further adjusted for body mass index (BMI), marital status, education levels, household income, smoking, alcohol use, physical activity, energy intake, health status, and urinary cadmium; and the third model was additionally adjusted for comorbidities including cardiovascular disease, hypertension, diabetes mellitus (DM), hyperlipidemia, chronic obstructive pulmonary disease, and cancer. HbEO was natural logarithm transformed and brought into regression models as a continuous variable for analysis. The Akaike

Information Criterion (AIC) values were calculated to estimate the fitting degree of models by using the Rao-Scott approximation to the weighted loglikelihood (Lumley and Scott 2015). Subgroup analyses were performed by age, gender, BMI, race, smoking, and alcohol use. The results of above regression analysis were expressed as odds ratios (ORs) for prevalence of CKD and proportional odds ratios (PORs) for prognosis of CKD, along with their corresponding 95% confidence interval (CIs).

Restricted cubic spline (RCS) analysis was performed to depict the relationship between HbEO levels and CKD. The analysis was based on the third survey-weighted generalized linear models with adjustments for all covariates mentioned above, among which ln-transformed HbEO was included as a continuous variable and CKD was brought into the models as a binary outcome variable. Based on considerations of AIC values, *P* values for nonlinearity tests, and the interpretability of the resulting curves, 3 knots were chosen to depict the curves. RCS analyses were performed by stratifying participants according to smoking status. Sensitivity analyses were conducted to confirm the reliability of our research results. First, to eliminate the potential impact of cancer and premature death on the association between HbEO and CKD, analyses were performed after excluding individuals who had cancer ($n = 269$) or died within first year of follow-up ($n = 12$). In addition, as nicotine metabolites may confound the results, cotinine and hydrocotinine were additionally included in multivariate regression models, to reduce their confounding effects the correlation of HbEO with CKD.

Results

Table 1 illustrates the baseline characteristics of participants. The weighted mean age was 47.7 years, of which 50.3% were male. The weighted median (interquartile range) of HbEO was 31.3 (23.1–60.3) pmol/g Hb. Compared to participants with low HbEO concentrations, those with high HbEO concentrations were younger, more likely to be male, non-Hispanic Black, single, less educated, and had lower income. Besides, they smoked and drank more frequently, and had worse health status.

A total of 491 participants (16.9%) were diagnosed with CKD, and its prevalence rate was notably higher in elevated HbEO groups. Regarding to the prognosis of CKD, 320 participants (11.1%) and 153 participants (5.31%) were identified as being at moderate or high/very high CKD risk, and the proportion of moderate CKD risk was higher among participants with high HbEO levels compared to those with low HbEO levels. In age, sex, and race adjusted generalized linear regression models, compared to the first tertile of HbEO, ORs (95% CIs) for CKD in the second and third tertile were 1.54 (1.08, 2.19) and 1.81 (1.27, 2.57). After adjustment for covariates including BMI, education level, household income, marital status, physical activity, energy intake, smoking, drinking, self-reported health status, chronic diseases, and urinary cadmium, elevated HbEO levels were still notably linked to CKD, and ORs (95% CIs) for CKD in the second and third tertile were 1.46 (0.85, 2.50) and 1.69 (1.00, 2.85). Regarding to prognosis of CKD, after adjustment for covariates in Model 3, elevated HbEO levels were significantly associated with high risk grade, and PORs (95% CIs) in the second and third tertile were 1.37 (0.94, 1.99) and 1.58 (1.10, 2.26), with the first tertile as the reference (Table 2). When ln-transformed HbEO was analyzed as a continuous variable in regression models, the OR (95% CI) for CKD was 1.24 (0.97, 1.58) and the POR (95% CI) for CKD prognosis was 1.22 (1.01, 1.47). Including HbEO in the models can improve the models' goodness of fit (Supplementary 2). Subgroup analysis indicated that smoking status had a prominent influence on the correlation of high HbEO levels with the prevalence of CKD (*P* for interaction 0.01). Among never smokers, the adjusted ORs (95% CIs) of CKD across HbEO tertiles were 1.00 (reference), 1.69 (0.95, 2.68) and 2.00 (1.04, 3.87), respectively, while this association lost significance in never smokers. No significant interactions were noticed in subgroups stratified by age, gender, ethnicity, BMI, and alcohol use (Fig. 2).

The RCS analysis revealed a positive dose-response relationship between HbEO and prevalence of CKD for overall participants (*P* for nonlinearity < 0.05). In never smokers, elevated HbEO levels were linearly correlated with CKD in a positive way (*P* for nonlinearity > 0.05), whereas in ever smokers, the risk of CKD initially increased and then decreased with increasing HbEO levels (Fig. 3). In sensitivity analysis, consistent findings were obtained when excluding individuals who had cancer or died during the first follow-up year (Supplementary file 3). After additional adjustment for hydrocotinine and cotinine, the relationship between high HbEO levels and increased prevalence and adverse prognosis of CKD were maintained (Supplementary file 4).

Discussion

The present study explored the impact of HbEO on prevalence and prognosis of CKD in US adults from NHANES 2013–2016. Our findings are as follows. First, participants with high HbEO levels suffered from CKD more frequently, and the proportion of moderate CKD risk was higher among participants with high HbEO levels compared to those with low HbEO levels. After adjustment for covariates, high HbEO levels were significantly associated with elevated risk of CKD and adverse CKD-related prognosis. RCS

Table 1 Baseline characteristics of participants according to tertile of HbEO[a]

Variables	All participants (n = 2900)	Tertile of HbEO (pmol/g Hb)			P value
		T1 (n = 974)	T2 (n = 960)	T3 (n = 966)	
HbEO, pmol/g Hb	31.3 (23.1, 60.3)	21.3 (18.4, 21.4)	33.0 (30.1, 38.4)	163.4 (77.9, 314.6)	< 0.001
Age, years	47.7 ± 0.5	48.7 ± 0.8	48.9 ± 0.7	45.1 ± 0.7	< 0.001
Male, *n* (%)	1459 (50.3)	447 (46.2)	478 (50.4)	534 (53.3)	0.07
Body mass index, kg/m^2	29.3 ± 0.2	30.1 ± 0.3	29.4 ± 0.4	28.1 ± 0.3	< 0.001
Ethnicity, *n* (%)					< 0.001
Mexican American	429 (14.8)	149 (7.9)	182 (11.5)	98 (6.5)	
Non-Hispanic White	1163 (40.1)	440 (72.5)	329 (61.6)	394 (63.6)	
Non-Hispanic Black	559 (19.3)	142 (7.1)	168 (10.3)	249 (15.4)	
Other	749 (25.8)	243 (12.4)	281 (16.5)	225 (14.5)	
Marital status, *n* (%)					0.003
Married or living with a partner	1754 (60.5)	615 (65.2)	625 (67.1)	514 (55.7)	
Widowed/divorced/separated	590 (20.3)	190 (16.7)	161 (14.5)	239 (22.7)	
Never married	556 (19.2)	169 (18.1)	174 (18.5)	213 (21.6)	
Education, *n* (%)					< 0.001
Less than high school	289 (10.0)	105 (5.2)	101 (5.6)	83 (5.7)	
High school or equivalent	978 (33.7)	264 (22.8)	286 (26.9)	428 (42.2)	
College or above	1633 (56.3)	605 (72.1)	573 (67.4)	455 (52.1)	
Poverty-income ratio	2.97 ± 0.08	3.24 ± 0.10	3.15 ± 0.10	2.44 ± 0.09	< 0.001
Energy intake, kcal/day	2186.4 ± 18.6	2144.1 ± 35.0	2144.5 ± 33.0	2287.5 ± 43.5	0.02
Physical activity, MET-minutes/week	3595.3 ± 147.8	3179.3 ± 198.6	2765.0 ± 171.3	5001.4 ± 303.8	< 0.001
Smoking status, *n* (%)					< 0.001
Never smoker	1625 (56.0)	699 (71.8)	685 (68.8)	241 (20.6)	
Former smoker	680 (23.5)	269 (27.4)	246 (27.9)	165 (18.8)	
Current smoker	595 (20.5)	6 (0.8)	29 (3.3)	560 (60.5)	
Drinking status, *n* (%)					< 0.001
Nondrinker	1840 (63.5)	642 (60.0)	661 (65.2)	537 (50.5)	
Mild to moderate drinker	644 (22.2)	219 (27.6)	196 (23.4)	229 (25.9)	
Heavy drinker	416 (14.3)	113 (12.3)	103 (11.4)	200 (23.6)	
Self-reported health status, *n* (%)					< 0.001
Poor to fair	672 (23.2)	191 (12.6)	201 (15.8)	280 (26.0)	
Good	1102 (38.0)	368 (35.7)	354 (34.4)	380 (37.8)	
Very good to excellent	1126 (38.8)	415 (51.7)	405 (49.8)	306 (36.2)	
Self-reported chronic diseases, *n* (%)					
Diabetes mellitus	544 (18.8)	164 (13.6)	206 (18.6)	174 (14.0)	0.02
Hypertension	1200 (41.4)	410 (40.2)	372 (34.4)	418 (38.1)	0.19
Hyperlipidemia	1989 (68.6)	664 (65.1)	660 (67.1)	665 (69.0)	0.36
Cardiovascular disease	287 (9.9)	84 (6.4)	92 (8.2)	111 (9.9)	0.06
COPD	104 (3.6)	28 (2.6)	21 (2.7)	55 (5.2)	0.04
Cancer	269 (9.3)	98 (10.4)	90 (12.8)	81 (9.3)	0.20
Urinary cadmium, ng/mL	0.17 (0.08, 0.33)	0.14 (0.07, 0.29)	0.15 (0.07, 0.28)	0.22 (0.10, 0.49)	< 0.001

[a]All estimates accounted for sample weights and complex survey designs, and means and percentages were adjusted for survey weights of NHANES. Continuous variables are presented as weighted mean ± standard error or weighted medians and interquartile ranges. Categorical variables are weighed presented as numbers (percentages)

COPD chronic obstructive pulmonary disease, *HbEO* hemoglobin adducts of ethylene oxide, *hs-CRP* high-sensitivity C-reactive protein

analysis indicated a positive correlation between HbEO levels and prevalence of CKD. Second, the above findings were largely affected by smoking status, and the association was prominent in never smokers, but lost significance in ever smokers. Last, the sensitivity analysis confirmed the robustness of our above research findings.

Table 2 Association between HbEO and CKD and prognosis of CKD in US adults participating in NHANES (2013–2016)

	Tertile of HbEO (pmol/g Hb)				Ln (HbEO)	
	T1 (n = 974)	T2 (n = 960)	T3 (n = 966)	P trend	HR (95% CI)	P value
CKD						
Number (percentage)	151 (11.9)	169 (16.9)	171 (15.1)	0.04		
Generalized linear models						
Model 1	Ref	1.54 (1.08, 2.19)*	1.81 (1.27, 2.57)**	0.001	1.23 (1.07, 1.41)	0.005
Model 2	Ref	1.48 (0.98, 2.23)	1.70 (1.08, 2.66)*	0.012	1.26 (1.03, 1.54)	0.03
Model 3	Ref	1.46 (0.85, 2.50)	1.69 (1.00, 2.85)*	0.027	1.24 (0.97, 1.58)	0.07
Prognosis of CKD						
Number (percentage)				0.04		
Low risk	823 (88.5)	791 (83.8)	795 (85.6)			
Moderate risk	97 (7.6)	115 (12.5)	108 (10.7)			
High risk	36 (3.0)	24 (2.0)	39 (2.8)			
Very high risk	15 (1.0)	23 (1.7)	16 (0.9)			
Proportional odds models						
Model 1	Ref	1.44 (1.03, 2.02)*	1.71 (1.20, 2.45)**	0.003	1.22 (1.06, 1.40)	0.005
Model 2	Ref	1.38 (0.97, 1.98)	1.60 (1.09, 2.37)*	0.018	1.20 (0.99, 1.44)	0.060
Model 3	Ref	1.37 (0.94, 1.99)	1.58 (1.10, 2.26)*	0.013	1.22 (1.01, 1.47)	0.037

Model 1: adjusted for HbEO, age, sex, and race

Model 2: additionally adjusted for body mass index, marital status, education level, poverty-income ratio, physical activity, energy intake, smoking, drinking, self-reported health status, and urinary cadmium

Model 3: additionally adjusted for hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, chronic obstructive pulmonary disease, and cancer

CI confidence interval, *CKD* chronic kidney disease, *HbEO* hemoglobin adducts of ethylene oxide, *HR* hazard ratio, *ln* natural logarithm

*P value < 0.05, **P value < 0.001

At room temperature, EO exists in the form of gas, and human exposure to EO is mainly through inhalation. The primary metabolic pathways of EO are glutathione conjugation and hydrolysis, and both pathways are considered to be detoxifying (Filser and Klein 2018). EO is electrophilic by nature and can react with cellular macromolecules including proteins and DNA, to form adducts. HbEO can reflect the cumulative total exposure of all exposure pathways to EO and has been proven to be the best parameter to assess EO exposure (Boogaard et al. 1999). In NHANES, the modified Edman reaction using HPLC-MS/MS method was utilized to test HbEO levels in human whole blood or erythrocytes, which is a well-established method for the detection of EO and ensures the accuracy of the test results. There is rare data on EO exposure levels in the general populations. In a previous study conducted by Szwiec et al. (2020), it was found that residents living near facilities emitting EO had a geometric HbEO level of 35.0 pmol/g Hb, and nonsmokers had a lower HbEO level of 29.7 pmol/g Hb; besides, HbEO levels in nonsmoking participants living in a neighborhood approximately 0.8 km from one of the facilities were significantly higher compared to those living farther away (Szwiec et al. 2020). Our analysis revealed that the weighted median level of HbEO in US adults was 31.3 pmol/g Hb, and the main source of HbEO in this population was endogenous generation rather than inhalation of EO from background ambient air or breath air near EO use/production facilities, as no specific external NO exposures were identified (Kirman et al. 2021). Furthermore, our analysis demonstrated that ever smokers had notably higher HbEO levels compared to never smokers, which provides additional evidence that smoking is a major contributor to EO exposure.

HbEO covalently binds with nucleophilic groups in DNA, forming reaction products that have the potential to induce genetic mutations and contribute to health issues. The carcinogenic effects of EO have been established mainly through animal experiments. In rodents, EO exposure can significantly increase the incidence of numerous tumors in a concentration-dependent manner, including adenocarcinomas, lung neoplasms, brain tumors, lymphomas, and peritoneal mesothelioma (Zhu et al. 2022). However, epidemiological studies involving 11 independent populations from 7 countries, comprising individuals in various occupations with EO exposure, did not find a significant correlation between cumulative EO exposure and an increased incidence of breast cancer and lymphohematopoietic tumors (Lynch et al. 2022). Dose differences may be the main reason for this discrepancy as dose levels employed in animal studies

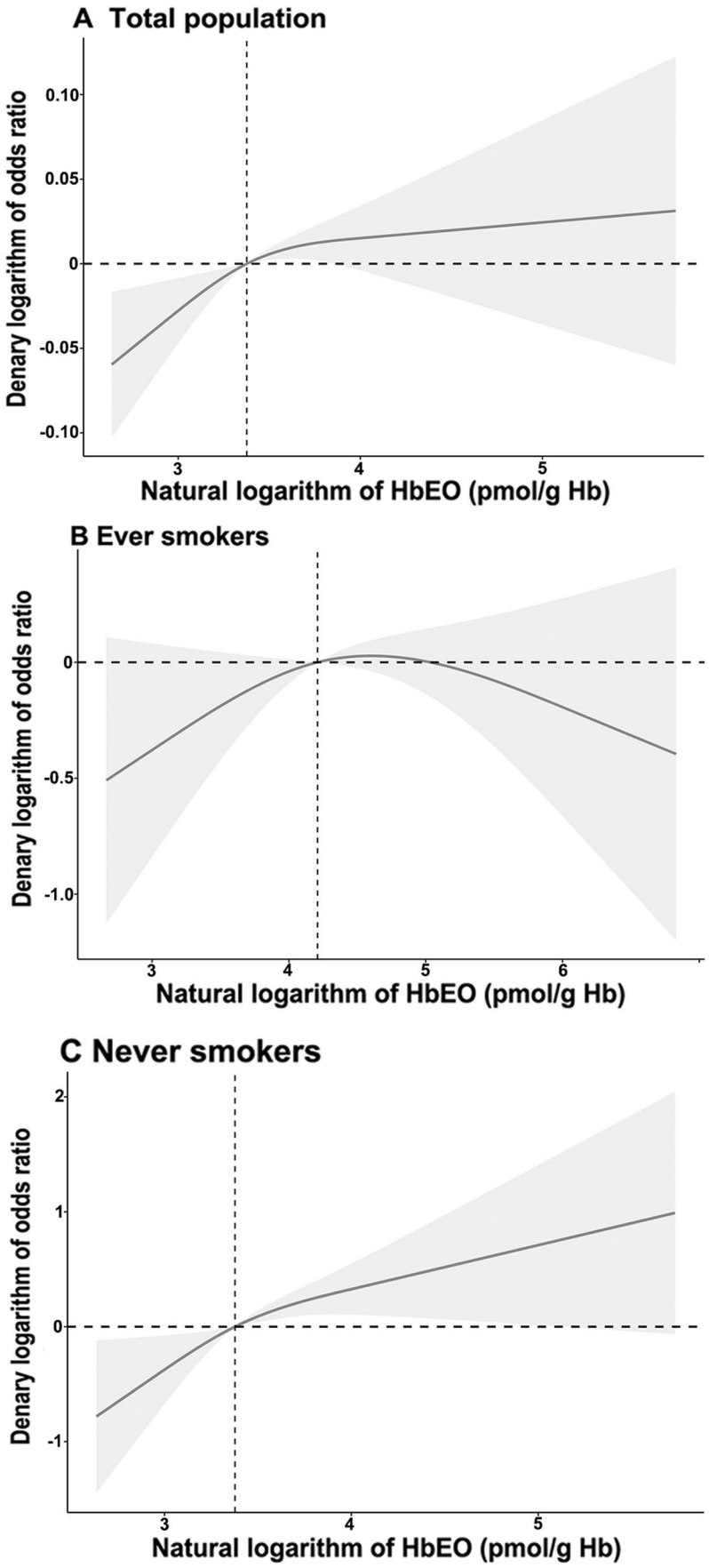

Fig. 2 Associations between natural logarithm of HbEO and CKD by restricted cubic spline regression models. **A** Total population; **B** ever smokers; **C** never smokers. HbEO, hemoglobin adducts of ethylene oxide

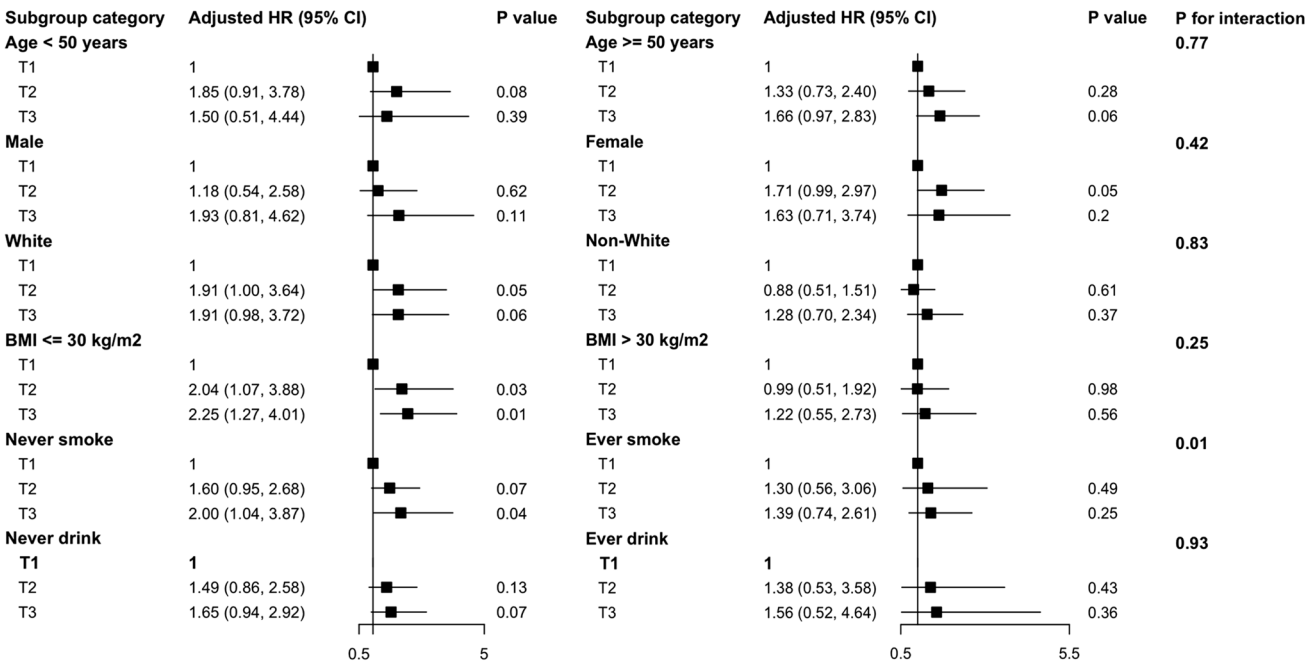

Fig. 3 Subgroup analysis of the association between HbEO and CKD. BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HbEO, hemoglobin adducts of ethylene oxide; HR, hazard ratio

were much higher than that in humans, even in individuals with occupational exposures. Apart from EO-induced carcinogenicity, animal experiments have provided evidence that high doses of EO exposure can cause damages in multiple systems, including respiratory, hematological, neurological, and reproductive systems. Regarding the renal system, in the study conducted by Hollingsworth et al. (1956), rats and guinea pigs exposed to EO vapor at 841 ppm exhibited kidney abnormalities such as enlargement, slight congestion, and cloudy swelling of convoluted tubules. Similarly, a study involving mice exposed to EO vapor for 14 weeks showed that renal tubular degeneration occurred in a dose-dependent manner, with higher concentrations of EO exposure (400 and 600 ppm) leading to increased incidence of renal necrosis (Toxicological Profile for Ethylene Oxide. 2022). The impact of HbEO on the prevalence and prognosis of CKD rarely has been evaluated. The present study is the first comprehensive analysis to explore the impact of HbEO on the prevalence and prognosis of CKD in US adults. Our analysis, which included 2900 participants from NHANES 2013–2016, revealed that high HbEO levels were significantly associated with the prevalence of CKD and worse prognosis in terms of CKD progression. Our study provides valuable insights into the potential role of EO in the pathogenesis and progression of CKD in the US population.

Our subgroup analysis revealed that the association between HbEO levels and the prevalence of CKD was significantly influenced by smoking status. Among individuals who had never smoked, we observed a linear positive correlation between HbEO levels and CKD prevalence. However, this correlation was not observed among individuals who had ever smoked or were current smokers, despite that they had higher HbEO levels compared to never smokers. These findings are consistent with a previous study that investigated the impact of EO exposure on the risk of DM. In that study, elevated HbEO levels were associated with a higher prevalence of DM, and this correlation was more pronounced in nonsmokers than in smokers (Guo et al. 2021). This finding may be explained by the followings. Firstly, smokers are exposed to a wide range of pollutants released during tobacco combustion, which may also have significant implications for the development of CKD. Hu et al. (2023) explored the impact of exposure to multiple serum metals on the risk of CKD in the elderly and found that concentrations of lead, cadmium, cobalt, and manganese were significantly associated with the risk of CKD. A recent study using data from the NHANES database revealed that elevated cadmium levels are associated with increased all-cause mortality among US adults with CKD, and smoking was the mainly source of cadmium exposure (Zhang et al. 2023). In the present study, urinary cadmium was included in the regression models, and the results showed that the association of HbEO and CKD was not affected. Nevertheless, the potential influence of other pollutants on the association cannot be completely removed due to a lack of relevant data collection. Additionally, co-exposure to other chemicals, both from smoking and other sources, can interact with EO exposure and potentially modify the risk of CKD. Besides, many behavioral or

environmental factors that may be associated with increased risk of CKD were not fully adjusted and may contribute to the association between HBEO and CKD observed in never smokers. Furthermore, individual susceptibility may also play a vital role in determining the health effects of EO exposure. As a cross-sectional designed study, we cannot establish a cause-and-effect relationship between HbEO and CKD, and to verify this hypothesis, prospective studies investigating the influence of EO exposure on the incidence of CKD in both smokers and nonsmokers are warranted.

The exact mechanism by which elevated EO exposure increases the risk of CKD is not yet sufficiently understood. Apart from the tumor-promoting effects, data from animal studies have revealed that high-dose EO exposure can cause multi-system damages. However, there is currently no further in-depth mechanism research. Recent analyses based on NHANES data have shown that high levels of EO exposure are significantly associated with various metabolic and chronic diseases including dyslipidemia (Zhu et al. 2022), DM (Guo et al. 2021), hypertension (Wu et al. 2022), CVD (Zeng et al. 2021), and asthma (Li et al. 2023), and it is speculated that inflammatory activation caused by EO might be a common mechanism in mediating these associations. Inflammation is recognized as an important contributor to the incidence of CKD, and oxidative stress, proinflammatory cytokines, acidosis, chronic infections, and altered metabolism of adipose tissue play important roles in the development of CKD (Mihai et al. 2018). The correlation of high HbEO levels with increased prevalence and worse prognosis of CKD might be partially explained by activated inflammation and oxidative stress. Our present study only provides evidence of an association of HbEO and CKD, but cannot establish a causal relationship, besides, we also cannot provide further information on the underlying mechanisms behind this association. Further prospective cohort studies are still needed to clarify the relationship between EO exposure and the occurrence and prognosis of CKD, and in-depth research is required to unravel the specific mechanisms through which EO exposure may lead to renal injury and development of CKD.

One notable strength of this study is that it is the first prospective evaluation of the impact of EO exposure on CKD in a large US adult population. The data collected in the NHANES program was meticulously gathered by trained researchers, adding to the credibility and reliability of the results. The utilization of the well-established modified Edman reaction method for HbEO level testing by HPLC-MS/MS further enhances the reliability of the test results. Several limitations of the study should be acknowledged. Firstly, the cross-sectional design hinders the establishment of a causal association between high HbEO levels and increased CKD risk. To obtain conclusive results, it is crucial to conduct well-designed prospective cohort studies. Secondly, individuals are commonly exposed to various pollutants that may also be linked to the development of CKD (Liu et al. 2023). However, due to the lack of data on these specific substances, it is unavailable to adjust them in the regression models, which may cause significant impacts on current findings. Besides, we did not adjust for all other pollutants released during tobacco combustion, which may introduce confounding effects in subgroup analysis for individuals who were current or former smokers. Further research is needed to examine mixture exposure and determine the specific contribution of EO exposure to the risk of CKD. Thirdly, in our sensitivity analysis, although cotinine was used as a marker of smoking and included in regression models for adjustment, it is important to note that a significant number of individuals with high cotinine levels may be vapers rather than smokers. This distinction could blur the influence of toxicological exposures relevant to CKD. Fourthly, as the RCS model has high degrees of freedom when dealing with binary dependent variables, estimates near the boundary values may not be very reliable. Furthermore, measurement errors may exist in the process of data collection and were not accounted for in our analysis, which may also affect the accuracy of our results to some extent. Lastly, as the study was conducted based on the US population, caution should be exercised when generalizing the conclusions to other populations.

Conclusions

In conclusion, the present study reveals a significant association between high HbEO levels and increased risk of CKD, as well as a worse prognosis of CKD. The impact of smoking status on this correlation was significant, which remained significant in never smokers, but lost significance in smokers. Further studies are needed to confirm the impact of EO exposure on CKD and clarify the underlying mechanisms.

Abbreviations *BMI*: Body mass index; *CKD*: Chronic kidney disease; *CI*: Confidence interval; *eGFR*: Estimated glomerular filtration rate; *EO*: Ethylene oxide; *HbEO*: Hemoglobin adduct N-(2-hydroxyethyl) valine; *HPLC-MS/MS*: High-performance liquid chromatography coupled with tandem mass spectrometry; *hs-CRP*: High-sensitivity C-reactive protein; *KDIGO*: Kidney disease: improving global outcomes; *MET*: Metabolic equivalent; *MEC*: Mobile examination center; *NCEH*: National Center for Environmental Health; *NCHS*: National Center for Health Statistics; *OR*: Odds ratio; *POR*: Proportional odds ratio; *RCS*: Restricted cubic spline; *UACR*: Urine albumin to creatinine ratio

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-023-30712-4.

Acknowledgements We sincerely thank all staff for their industrious contributions and all participants in the NHANES program. We would like to express our gratitude to Prof. Zhang Jing from Shanghai Tongren Hospital for his invaluable contribution to our analysis of the

NHANES database. The nhanesR package and webpage that he developed have greatly facilitated our work with the database.

Author contribution YMY and JZ designed and supervised the study. SW carried out the statistical analysis and drafted the paper. SW, LLW, WX, SQL, JW, HZ, and XHS were responsible for data extraction and cleaning. YMY and JZ revised the manuscript and approved the final version for publication. All authors reviewed and approved the final version of the manuscript.

Funding This study received financial support from the Capital's Funds for Research and Application of Clinical Diagnosis and Treatment Technology with reference number Z191100006619121.

Data availability The NHANES data utilized in this paper is accessible to the public.

Declarations

Ethics and informed consent The Ethics Committee of the National Center for Health Statistics gave approval to the NHANES protocols, and participants were informed of the study and signed informed consent form.

Conflict of interest The authors declare no competing interests.

References

Armstrong T, Bull F (2006) Development of the World Health Organization Global Physical Activity Questionnaire (GPAQ). J Public Health 14:66–70

Bogen KT, Sheehan PJ, Valdez-Flores C, Li AA (2019) Reevaluation of historical exposures to ethylene oxide among US sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16:1738

Boogaard PJ, Rocchi PS, van Sittert NJ (1999) Biomonitoring of exposure to ethylene oxide and propylene oxide by determination of hemoglobin adducts: correlations between airborne exposure and adduct levels. Int Arch Occup Environ Health 72:142–150

CDC (2023) Centers for disease control and prevention: the National Health and Nutritional Examination Survey (NHANES) analytic and reporting guidelines. CDC, Atlanta https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx

Chavers BM, Simonson J, Michael AF (1984) A solid-phase fluorescent immunoassay for the measurement of human urinary albumin. Kidney Int 25:576–578

Filser JG, Klein D (2018) A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. Toxicol Lett 286:54–79

Fletcher BR, Damery S, Aiyegbusi OL et al (2022) Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis. PLoS Med 19:e1003954

GBD (2019) Diseases and Injuries Collaborators (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1204–1222

Guo J, Wan Z, Cui G, Pan A, Liu G (2021) Association of exposure to ethylene oxide with risk of diabetes mellitus: results from NHANES 2013-2016. Environ Sci Pollut Res Int 28:68551–68559

Hollingsworth RL, Rowe VK, Oyen F (1956) Toxicity of ethylene oxide determined on experimental animals. AMA Arch Ind Health 13:217–227

Hu W, Li G, He J, Zhao H, Zhang H, Lu H, Liu J, Huang F (2023) Association of exposure to multiple serum metals with the risk of chronic kidney disease in the elderly: a population-based case-control study. Environ Sci Pollut Res Int 30:17245–17256

Kirman CR, Hays SM (2017) Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: ethylene oxide. Regul Toxicol Pharmacol 91:165–172

Kirman CR, Li AA, Sheehan PJ, Bus JS, Lewis RC, Hays SM (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. J Toxicol Environ Health B Crit Rev 24:1–29

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (2009). A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604-612

Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco ALM, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ, Levey AS, Riella MC, Shlipak MG, Wang H, White CT, Winearls CG (2013) Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1–150

Li Z, Shi P, Chen Z, Zhang W, Lin S, Zheng T, Li M, Fan L (2023) The association between ethylene oxide exposure and asthma risk: a population-based study. Environ Sci Pollut Res Int 30:24154–24167

Liu W, Cao S, Ma J, Shi D, Yu L, Ye Z, Yang M, Wang B, Chen W (2023) Exposures to volatile organic compounds, serum vitamin D, and kidney function: association and interaction assessment in the US adult population. Environ Sci Pollut Res Int 30:7605–7616

Lumley T, Scott AJ (2015) AIC and BIC for modelling with complex survey data. J Surv Stat Methodol 3:1–18

Lynch HN, Kozal JS, Russell AJ, Thompson WJ, Divis HR, Freid RD, Calabrese EJ, Mundt KA (2022) Systematic review of the scientific evidence on ethylene oxide as a human carcinogen. Chem Biol Interact 364:110031

Matsushita K, Ballew SH, Wang AY, Kalyesubula R, Schaeffner E, Agarwal R (2022) Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol 18:696–707

Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, Mambet C, Anton G, Tanase C (2018) Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J Immunol Res 2018:2180373

Rao JNK, Scott AJ (1984) On chi-squared tests for multiway contingency tables with cell proportions estimated from survey data. Ann Statist 12:46–60

Schettgen T, Broding HC, Angerer J, Drexler H (2002) Hemoglobin adducts of ethylene oxide, propylene oxide, acrylonitrile and acrylamide-biomarkers in occupational and environmental medicine. Toxicol Lett 134:65–70

Stumbo P (2008) Considerations for selecting a dietary assessment system. J Food Compos Anal 21:S13–S19

Szwiec E, Friedman L, Buchanan S (2020) Levels of ethylene oxide biomarker in an exposed residential community. Int J Environ Res Public Health 17:8646

Toxicological Profile for Ethylene Oxide (2022). Agency for toxic substances and disease registry (US).

US Department of Health and Human Services and US Department of Agriculture (2015) 2015-2020 dietary guidelines for Americans, 8th edn https://health.gov/our-work/food-nutrition/previous-dietary-guidelines/2015

Webster AC, Nagler EV, Morton RL, Masson P (2017) Chronic kidney disease. Lancet 389:1238–1252

Wu N, Cao W, Wang Y, Liu X (2022) Association between blood ethylene oxide levels and the prevalence of hypertension. Environ Sci Pollut Res Int 29:76937–76943

Zhang J, Wang X, Ma Z, Dang Y, Yang Y, Cao S, Ouyang C, Shi X, Pan J, Hu X (2023) Associations of urinary and blood cadmium concentrations with all-cause mortality in US adults with chronic kidney disease: a prospective cohort study. Environ Sci Pollut Res Int 30:61659–61671

Zeng G, Zhang Q, Wang X, Wu KH (2021) Association between blood ethylene oxide levels and the risk of cardiovascular diseases in the general population. Environ Sci Pollut Res Int 28:64921–64928

Zhu X, Kong X, Chen M, Shi S, Cheang I, Zhu Q, Lu X, Yue X, Tang Y, Liao S, Zhou Y, Zhang H, Yao W, Li X (2022) Blood ethylene oxide, systemic inflammation, and serum lipid profiles: results from NHANES 2013-2016. Chemosphere 299:134336