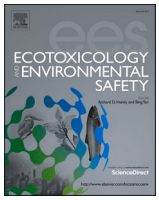
Ecotoxicology and Environmental Safety 292 (2025) 117989

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv



Urinary glyphosate, selenium status, and their impact on mortality: Evidence from NHANES 2013–2018

Pei-Lun Chu [a,b,1], Ching-Chung Hsiao [c,d,1], Ta-Chen Su [e,f,g,h], Chikang Wang [i], Chien-Yu Lin [a,i,j,*]

[a] School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei 242, Taiwan
[b] Department of Internal Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei 242, Taiwan
[c] Department of Nephrology, New Taipei Municipal Tucheng Hospital, New Taipei City, Taiwan
[d] College of Medicine, Chang Gung University, Taoyuan, Taiwan
[e] Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei 100, Taiwan
[f] Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan
[g] Institute of Environmental and Occupational Health Sciences, College of Public Health, National Taiwan University, Taipei 100, Taiwan
[h] School of Medicine, College of Medicine, National Cheng-Kung University, Tainan 700, Taiwan
[i] Department of Environmental Engineering and Health, Yuanpei University of Medical Technology, Hsinchu 300, Taiwan
[j] Department of Internal Medicine, En Chu Kong Hospital, New Taipei City 237, Taiwan

ARTICLE INFO

Edited by Dr. Renjie Chen

Keywords:
Glyphosate
Glyphosate-based herbicides (GBH)
Mortality
National Health and Nutrition Examination Survey (NHANES)
Selenium intake
Whole blood selenium

ABSTRACT

Purpose: Glyphosate and glyphosate-based herbicides (GBHs), extensively used worldwide, have been associated with various health concerns, including an elevated risk of mortality. Experimental studies suggest that these herbicides may disrupt selenium homeostasis by hindering its uptake or promoting oxidative stress. However, the interplay between glyphosate exposure and selenium status remains poorly understood in epidemiological studies, particularly regarding selenium's role in modulating the mortality risk associated with glyphosate exposure in nationally representative populations.

Approach and results: In this study, we analyzed data from the 2013–2018 National Health and Nutrition Examination Survey (NHANES), which included 6410 participants aged 3 years and older. This dataset was linked to mortality information from the National Center for Health Statistics (NCHS) for individuals aged 18 and older, with follow-up through 2019. The primary aim was to investigate the relationships between urinary glyphosate levels, whole blood selenium, selenium intake, and the influence of selenium status on glyphosate-related all-cause mortality risk. A significant negative correlation was observed between the natural logarithm (ln) of urinary glyphosate levels and the ln of whole blood selenium in the complex multiple linear regression models, with a ß coefficient of −0.010 (SE = 0.003, P = 0.003). However, no association was found between urinary glyphosate levels and selenium intake. Furthermore, the association was particularly prominent among females, non-Hispanic whites, and individuals with lower selenium intake. When examining the relationship between glyphosate exposure, whole blood selenium levels, and all-cause mortality, higher ln-urinary glyphosate levels were significantly associated with an increased risk of mortality (Hazard Ratio [HR] = 1.43; 95 % CI: 1.00–2.09). This elevated risk was especially pronounced in individuals with whole blood selenium concentrations at or above the 50th percentile. Additionally, ln-whole blood selenium was associated with a protective effect against all-cause mortality (HR = 0.01; 95 % CI: 0.00–0.18), with the strongest protective effect observed in individuals with selenium levels below the 50th percentile.

Conclusions: In this comprehensive analysis of NHANES data, our study identifies a potentially harmful relationship between glyphosate exposure and whole blood selenium levels. Notably, excessively high whole blood selenium levels may not only reduce the protective effects against all-cause mortality but could also increase the

Abbreviations: AMPA, Aminomethylphosphonic acid; BMI, Body mass index; ETS, Environmental tobacco smoke; GBH, Glyphosate-based herbicides; HR, Hazard Ratio; IC-MS/MS, Ion chromatography coupled with tandem mass spectrometry; Ln, Natural logarithm; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; RDA, Recommended dietary allowance.

* Correspondence to: Department of Internal Medicine, En Chu Kong Hospital, No. 399, Fuxing Rd., Sanxia Dist., New Taipei City 237, Taiwan.
E-mail address: lin7010@mail2000.com.tw (C.-Y. Lin).

[1] These authors contributed equally.

https://doi.org/10.1016/j.ecoenv.2025.117989
Received 1 January 2025; Received in revised form 25 February 2025; Accepted 25 February 2025
Available online 1 March 2025

risk of glyphosate-related mortality, suggesting a U-shaped relationship between selenium levels and mortality risk. These findings highlight the need for further research into the health effects of glyphosate exposure and its interaction with selenium status, emphasizing the potential public health implications.

1. Introduction

Selenium, an essential trace element, plays a vital role in maintaining the health of humans and animals. It supports human physiology by enhancing antioxidant defenses, regulating thyroid hormone metabolism, and modulating immune system function (Zakeri et al., 2021). The primary source of selenium for the human body is diet, with selenium-rich foods such as nuts, fish, meat, eggs, and certain grains serving as key contributors (Rayman, 2008). While selenium deficiency can lead to various health problems, it is also important to recognize that excessive selenium intake may be toxic, exhibiting pro-oxidant and immunotoxic properties (Filippini et al., 2023; Vinceti et al., 2022). Recent epidemiological studies have linked elevated selenium status to adverse health outcomes (Soares et al., 2024; Vinceti et al., 2018; Williams et al., 2025). As concerns over selenium toxicity at high levels grow, there is an increased emphasis on avoiding excessive selenium intake, especially from supplements, to mitigate potential harmful effects (CDC, 2014; Rayman et al., 2018). In the United States, the risk of selenium deficiency is low due to the high selenium content in certain regions' soils, which is transferred into the food chain (Rayman, 2008).

Since their introduction in 1974, glyphosate and glyphosate-based herbicides (GBHs), which target the shikimate pathway in plants and microorganisms, have become some of the most widely used broad-spectrum herbicides worldwide (Lacroix and Kurrasch, 2023). Their widespread adoption is largely attributed to their high effectiveness, perceived low toxicity, environmental safety, and the development of glyphosate-resistant crop varieties (Lacroix and Kurrasch, 2023). Long regarded as harmless to animals, recent research has raised concerns about potential health risks associated with glyphosate, including cytotoxicity, genotoxicity, and effects on the immune system. In 2017, the International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" (Barnor et al., 2023). Recent studies in the general population have associated glyphosate exposure with various health issues, including altered iron metabolism, diabetes mellitus, metabolic syndrome, and cognitive decline (Chu et al., 2024; Eskenazi et al., 2023; Hsiao et al., 2023; Qi et al., 2023). Additionally, a nationally representative study reported an association between urinary glyphosate levels and an increased risk of mortality (Untalan et al., 2024).

There are several ways in which glyphosate could potentially interfere with the supply of selenium to humans. Glyphosate's strong ability to form complexes with cationic nutrients may disrupt selenium uptake in plants (Mertens et al., 2018). Additionally, glyphosate may chelate selenium in the gastrointestinal tract, similar to its observed effects on plants (Romano et al., 2021). Moreover, glyphosate could impact the gut microbiome and suppress Lactobacillus activity, which is involved in converting inorganic selenium into more readily absorbed organic forms (Shehata et al., 2013). In addition to affecting the body's selenium uptake, exposure to glyphosate may also deplete the body's selenium reserves. While selenium has shown its ability to protect human tissues from oxidative stress (Zeng et al., 2013), several studies have suggested that GBH may disrupt homeostasis and increase oxidative damage (Bali et al., 2019), potentially leading to selenium depletion. However, there remains a lack of research exploring the relationship between glyphosate exposure, selenium intake, and whole blood selenium levels, as well as the role of selenium status in modulating the mortality risk associated with glyphosate exposure in epidemiological studies, particularly within nationally representative samples of the general population.

To bridge this gap in understanding, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) for the years 2013–2018, linked to mortality outcomes recorded by the National Center for Health Statistics (NCHS) through 2019. This comprehensive dataset includes information on urinary glyphosate levels, selenium intake, whole blood selenium concentrations, and mortality outcomes. Our study aimed to enhance understanding of the relationship between glyphosate exposure and selenium status within the general population.

2. Materials and methods

2.1. Study population

The NHANES, conducted biennially, collects data from a broad spectrum of the U.S. population. Detailed information about survey methods and consent forms can be found on the NHANES website (CDC, 2020d). This study utilized data from the NHANES 2013–2018 dataset, initially comprising 29,400 participants. After excluding individuals without urinary glyphosate measurements, the sample size was reduced to 7067 participants. An additional 655 participants were excluded due to missing data on oral selenium intake or whole blood selenium levels. From the remaining 6412 participants, 2 were further excluded due to incomplete covariate data. Ultimately, our analysis included 6410 participants. The selection process is visually summarized in Fig. 1.

2.2. Measurement of urinary glyphosate levels

In the NHANES 2013–2018 survey, urinary glyphosate

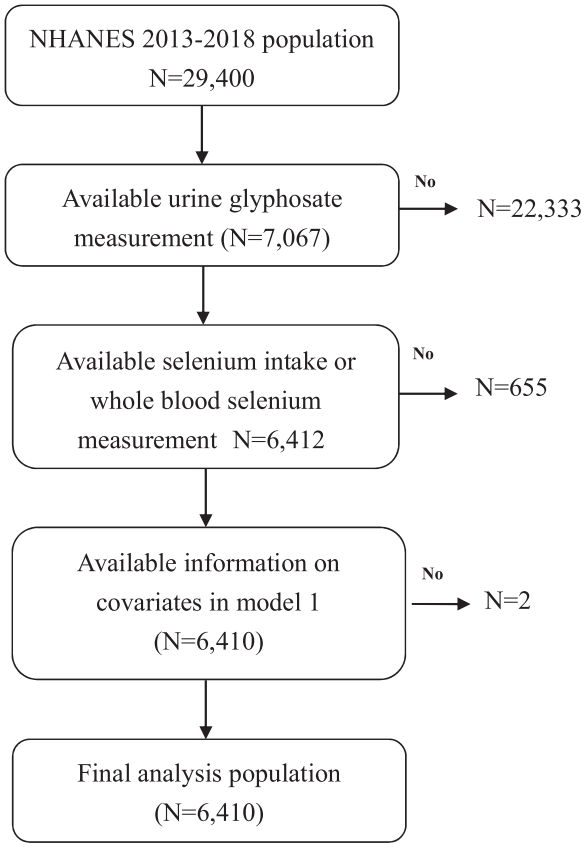


Fig. 1. Flow chart algorithm.

concentrations were assessed in all participants aged 3–5 years and a one-third subsample of those aged 6 years and older. The urinary samples were analyzed using a highly sensitive and specific two-dimensional on-line ion chromatography coupled with tandem mass spectrometry method with isotope dilution for quantification. For concentrations below the limits of detection (LOD), a value was imputed using the square root of 2 times the LOD value, according to NHANES protocol. The methodologies for evaluating glyphosate levels have been detailed in the NHANES website (CDC, 2023).

2.3. Measurement of whole blood selenium

In NHANES 2013–2018, whole blood selenium levels were assessed in all participants aged 1 year and older. Our focus was on data collected from individuals aged 3 years and above. Following a straightforward dilution and sample preparation process, the method directly measured selenium levels in whole-blood samples using mass spectrometry. The comprehensive method is accessible on the NHANES website (CDC, 2020c).

2.4. Covariates

Data regarding sociodemographic factors such as age, sex, and ethnicity were gathered was collected from the NHANES database. Smoking status was categorizing subjects as active smokers, those exposed to environmental tobacco smoke (ETS), or non-smokers (CDC, 2020a). Alcohol consumption was assessed via a questionnaire asking whether the participant had consumed at least 12 alcoholic drinks in the past year. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Physical activity was quantified by metabolic equivalent scores suggested in NHANES website (Wang et al., 2017). Hypertension was identified either by self-reported use of antihypertensive medications or an average blood pressure of $\geq$ 140/90 mmHg. Diabetes mellitus was defined as a fasting serum glucose level of $\geq$ 126 mg/dL, a glycated hemoglobin level of $\geq$ 6.5 %, or the self-reported use of anti-diabetic medications. Hypercholesterolemia was characterized by a fasting low-density lipoprotein cholesterol level of $\geq$ 130 mg/dL or current treatment for hypercholesterolemia. Chronic kidney disease was defined as an estimated glomerular filtration rate below 60 mL/min/1.73 m^2. The average food selenium intake was calculated from responses to the two-day selenium intake questionnaire, while selenium supplement intake was evaluated by averaging data from two days of supplement intake and information gathered from the 30-day supplement questionnaire (CDC, 2020b). Oral selenium intake was calculated by combining selenium intake from food and supplements. Urinary creatinine was included as an individual independent variable in this analysis, rather than being adjusted for hydration status.

2.5. Outcomes

The NCHS has linked the 2013–2018 NHANES data to mortality records, enabling researchers to track participants' long-term health outcomes. This linkage provides detailed information on both overall and cause-specific mortality, with follow-up extending through 2019 for participants aged 18 and older. For this study, we collected data on participants' survival status and follow-up duration. Due to the relatively short follow-up period and limited number of deaths observed, we focused exclusively on all-cause mortality in our analysis. A comprehensive description of the analytical methods used is available on the NCHS website (NCHS, 2022).

2.6. Statistics

Glyphosate, whole blood selenium, and oral selenium intake were utilized to compute the exponential mean (SD) for different subgroups. To assess differences between subgroups, both a two-tailed Student's *t*-test and one-way analysis of variance were utilized. Due to its non-Gaussian distribution, the natural logarithm (ln) of glyphosate, urinary creatinine, Oral selenium intake, and whole blood selenium was employed in the analysis. Sampling weights, designed to adjust for varying probabilities of selection, were applied following the protocols outlined on the NHANES website (CDC, 2005). To investigate the relationship between oral selenium intake and whole blood selenium levels, we performed complex multiple regression analysis within a complex linear model framework. Covariates were adjusted for using Model 1, which accounted for age, sex, ethnicity, smoking status, and urinary creatinine. Similarly, to examine the relationship between urinary glyphosate and whole blood selenium, we applied two models with covariates: Model 1 and Model 2. Model 2 included all covariates in Model 1, plus selenium intake. A result was considered statistically significant only if it was significant in both models. To assess potential non-linear relationships, we also performed additional analyses incorporating polynomial terms, such as squared and cubic terms. To visualize this relationship, a scatter plot was generated with exposure on the x-axis and the predicted outcome levels on the y-axis.

The hazard ratio (HR) for all-cause mortality were evaluated per one-unit increase in the ln of urinary glyphosate, whole blood selenium, and oral selenium intake. A weighted Cox regression model was utilized for the analysis, adjusting for covariates included in Model 3. These covariates encompassed age, sex, ethnicity, family poverty-to-income ratio, smoking, alcohol consumption, BMI, physical activity, hypertension, hypercholesterolemia, diabetes mellitus, chronic kidney disease, and urinary creatinine. Additionally, we conducted stratified analyses by age and sex. We also evaluated the effects of selenium status on glyphosate-related all-cause mortality. Given the collinearity between whole blood selenium and oral selenium intake, they were included separately in the model 3. Additionally, we estimated HR for all-cause mortality associated with a one-unit increase in oral selenium intake and within blood selenium subgroups stratified by the 50th percentile. Interaction effects were examined by incorporating cross-product terms into the regression models. The statistical analysis was conducted using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA), with a significance level set at $P < 0.05$ to establish statistical significance.

3. Results

The study participants had a mean age of 35.64 $\pm$ 24.14 years, ranging from 3 to 80 years. Detectable levels of glyphosate were observed in 93.7 % of individuals, with an average concentration of 0.57 $\pm$ 0.73 μg/L, ranging from 0.02 to 30.45 μg/L. The average daily oral selenium intake was 113.57 $\pm$ 58.09 mcg, primarily derived from food sources (107.59 $\pm$ 51.33 mcg/day), while selenium from supplements contributed only 5.11 $\pm$ 22.27 mcg/day. Notably, only 9.5 % of participants reported using selenium supplements. Only 6.9 % of participants had selenium intake below the recommended dietary allowance (RDA) (NIH, 2021). The mean whole blood selenium level was 186.54 $\pm$ 26.30 μg/L, with values ranging from 95.65 to 734.80 μg/L. Table 1 presents the geometric means of glyphosate, whole blood selenium, and selenium intake among different subgroups. To compare the distribution of urinary glyphosate, oral selenium intake, and whole blood selenium within the same group across different demographics, it indicates that urinary glyphosate levels (adjusted for urinary creatinine) were higher in females, individuals aged 3–17 years, non-Hispanic white, and non-smokers. Furthermore, whole blood selenium levels and oral selenium intake were elevated among males, individuals aged 20–59 years, and non-Hispanic Asians. Additionally, the table shows that active smokers had higher whole blood selenium levels.

In a complex polynomial regression model evaluating the relationship between oral selenium intake and whole blood selenium levels, a one-unit increase in ln-oral selenium intake and its squared term was associated with ln-whole blood selenium levels. Specifically, the linear term for oral selenium intake showed a negative association (β =

Table 1
The geometric means (geometric SE) of urinary glyphosate and selenium status in different subgroups.

	Number	Glyphosate (μg/g creatinine)	*P* value	Number	Whole blood selenium (ug/L)	*P* value	Number	Oral selenium intake (mcg/day)	*P* value
		Geometric means (SE)			Geometric means (SE)			Geometric means (SE)	
Total	6410	0.39 (1.01)		3941	184.90 (1.00)		5480	100.82 (1.01)	
Sex			<0.001			0.044			<0.001
Males	3168	0.35 (1.02)		1982	185.67 (1.00)		2690	115.45 (1.01)	
Females	3242	0.42 (1.02)		1959	184.12 (1.00)		2790	88.48 (1.01)	
Age (years)			<0.001			<0.001			<0.001
3–17	2134	0.53 (1.02)		1672	176.25 (1.00)		1646	85.40 (1.01)	
18–59	2844	0.29 (1.02)		1487	191.65 (1.00)		2551	111.13 (1.01)	
≥ 60	1432	0.42 (1.02)		782	191.33 (1.01)		1283	102.81 (1.01)	
Ethnicity			<0.001			<0.001			<0.001
Mexican-American	1120	0.38(1.03)		719	183.87 (1.00)		912	99.61 (1.02)	
Other Hispanic	646	0.38 (1.03)		398	183.18 (1.01)		549	102.50 (1.02)	
Non-Hispanic white	2332	0.43 (1.02)		1355	187.65 (1.00)		2047	104.07 (1.01)	
Non-Hispanic black	1350	0.34 (1.02)		849	181.01 (1.00)		1179	93.13 (1.02)	
Non-Hispanic Asian	628	0.35 (1.03)		400	188.85 (1.01)		513	109.18 (1.02)	
Other ethnicity	334	0.39 (1.05)		220	182.63 (1.01)		280	97.22 (1.03)	
Smoking status			<0.001			<0.001			0.214
Non-smoker	4298	0.41 (1.01)		2706	183.76 (1.00)		3643	100.13 (1.01)	
ETS	1093	0.36 (1.03)		714	186.46 (1.00)		926	101.09 (1.02)	
Current smoker	1019	0.31 (1.03)		521	188.72 (1.01)		911	103.39 (1.02)	

Tested by Student's 2-tailed *t*-test or by one-way analysis of variance
Abbreviations: ETS, environmental tobacco smoke.

−0.236; SE = 0.108; P = 0.034), while the squared term demonstrated a positive association (β = 0.029; SE = 0.012; P = 0.020), suggesting a U-shaped relationship. As shown in Supplemental Figure 1, the scatter plot of the predicted values clearly depicts a U-shaped curve, demonstrating that both low and high levels of oral selenium intake are associated with higher whole blood selenium levels, while moderate intake levels are linked to lower whole blood selenium levels. In the multiple regression analyses presented in Table 2, a one-unit increase in ln-glyphosate levels was not associated with food or oral selenium intake (β = −2.567; SE = 1.973; P = 0.200 for oral selenium intake). However, ln-glyphosate levels showed an inverse correlation with whole blood selenium levels (β = −1.984; SE = 0.639; P = 0.003 in Model 2). In the complex polynomial regression model, the relationship between glyphosate exposure and whole blood selenium was found to be insignificant for both the linear and squared terms, suggesting that the association may be purely linear. Fig. 2 presents a summary of the mean (SE) of whole blood selenium across quartiles of urinary glyphosate in multiple linear regression models. The study revealed a significant decrease in mean whole blood selenium levels with increasing tertiles of glyphosate in model 2 (*P* for trend = 0.021). Table 3 presents the regression coefficients (SE) for the relationship between whole blood selenium and ln-glyphosate per unit increase within the specified subpopulation. The findings indicate a significant decrease in mean whole blood selenium with rising glyphosate levels among females, non-Hispanic whites, and individuals with lower selenium intake. The interaction between ln-glyphosate and ethnicity was statistically significant (P = 0.004). However, no significant interactions were observed for sex, age, or oral selenium intake.

Among the 3847 participants with available outcome data and no missing covariates in model 3, a total of 185 deaths were recorded during a median follow-up period of 47.08 months. Supplemental table 1 presents the HR for all-cause mortality associated with a unit increase in ln-urinary glyphosate and ln-selenium status across different subgroups, adjusted for Model 3 covariates. For urinary glyphosate, the overall hazard ratio (HR) was 1.34 (95 % CI: 1.06–1.70), with females exhibiting a higher HR compared to males. The HR was also higher in individuals aged 18–49 than in those aged 50 and older. The interaction between sex and glyphosate exposure was marginally significant (P = 0.053). For oral selenium intake, the overall HR was 0.86 (95 % CI: 0.58–1.27). However, the HR was higher among individuals aged 18–49 compared to those aged 50 and above, with a significant age interaction (P = 0.035). For whole blood selenium, the overall HR was 0.01 (95 % CI: 0.00–0.12), with a more pronounced effect in males than females. The protective effect of whole blood selenium was stronger in individuals aged 50 and above. No significant interactions with age or sex were observed.

Table 4 presents HR for all-cause mortality associated with a one-unit

Table 2
Linear regression coefficients (SE) of ln-selenium status with a unit increase in ln-urinary glyphosate in multiple linear regression models, with results weighted for sampling strategy.

	Glyphosate (μg/L)					
	Unweighted no./ Population size	Model 1 Adjusted *β* (SE)	*P* value	Unweighted no. / Population size	Model 2 Adjusted *β* (SE)	*P* value
Whole blood selenium (ug/L)	3941/478,202,567	−0.014 (0.003)	<0.001	3011/384,743,993	−0.010 (0.003)	0.003
Oral selenium intake (mcg/day)						
Food intake	5480/732,989,553	−0.010 (0.011)	0.354			
Total intake	5480/732,989,553	−0.015 (0.012)	0.222			

Abbreviations: Ln, natural logarithm.
Model 1 adjusted for age, sex, ethnicity, smoking, and urinary creatinine.
Model 2 adjusted for model 1 plus oral selenium intake.

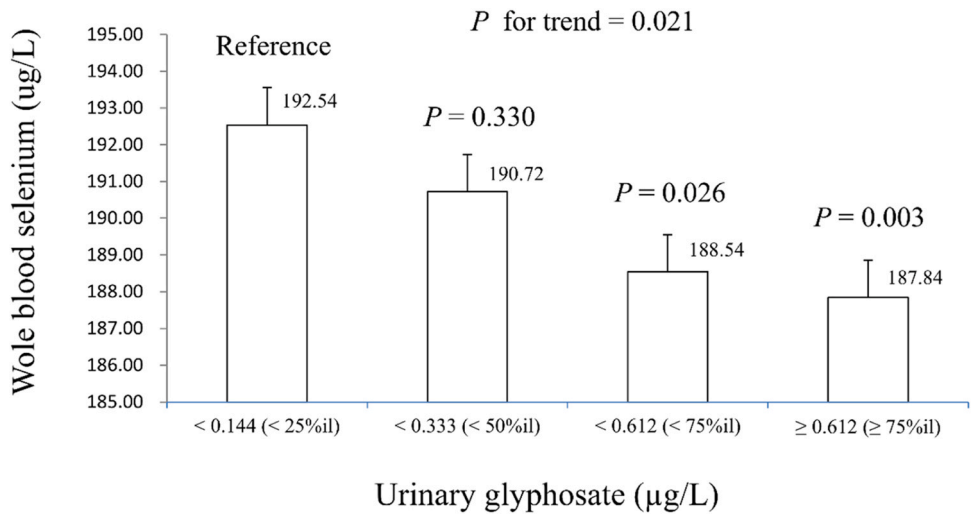


Fig. 2. Geometric mean (geometric SE) of serum selenium across quartiles of urine glyphosate in multiple linear regression models (Adjusted for age, sex, ethnicity, smoking, urinary creatinine, and oral selenium intake (model 2)), with results weighted for sampling strategy (N = 3011).

Table 3
Linear regression coefficients (SE) of ln-whole blood selenium per unit increase in ln-glyphosate in subpopulation, with results weighted for sampling strategy. Ln-glyphosate (μg/L).

	Glyphosate (μg/L)			
Whole blood selenium (ug/L)	Number	Adjusted β (SE)	*P* value	*P* for interaction
Sex				0.240
Male	1504/ 183,968,732	−0.005 (0.005)	0.342	
Female	1507/ 200,775,261	−0.016 (0.004)	0.001	
Age, years				0.574
3–17	1184/ 86,625,606	0.002 (0.007)	0.810	
18–59	1194/ 212,351,576	−0.004 (0.006)	0.461	
≥ 60	633/ 85,766,812	0.001 (0.013)	0.960	
Ethnicity				0.004
Non-Hispanic white	1070/ 236,442,281	−0.016 (0.005)	0.003	
Other	1941/ 148,301,713	−0.002 (0.003)	0.581	
Oral selenium intake (mcg/day)				0.731
< 97.5 (50 % ile)	1504/ 167149496	−0.017 (0.007)	0.023	
≥ 97.5 (50 % ile)	1507/ 217594498	−0.004 (0.006)	0.516	

Adjusted for model 2: Age, sex, ethnicity, smoking, and urinary creatinine, and oral selenium intake

increase in ln-urinary glyphosate and ln-selenium status (oral selenium intake or whole blood selenium), stratified by selenium subgroups. In the overall population, glyphosate exposure was significantly associated with an increased risk of all-cause mortality. This association remained significant after adjusting for oral selenium intake in Model 3 (HR = 1.30; 95 % CI: 1.01–1.66) and for whole blood selenium levels in Model 3 (HR = 1.43; 95 % CI: 1.00–2.09). In the subgroup with higher whole blood selenium levels (≥191.30 μg/L, 50th percentile), glyphosate exposure was associated with a significantly increased risk of mortality (HR = 2.49; 95 % CI: 1.28–4.86). However, this association was not observed in individuals with selenium levels below the 50th percentile. For selenium status and all-cause mortality, higher oral selenium intake

Table 4
HR (95 % CI) for all-cause mortality associated with a unit increase in ln-urinary glyphosate and ln-selenium status in different selenium status subgroups. Results are derived from a weighted Cox regression model accounting for complex sampling design.

	All-cause mortality		
	Number/ Population size	HR (95 % CI)	*P* for interaction
Glyphosate and all-cause mortality			
Oral selenium intake (mcg/day)			0.748
Total	3488/ 561,123,356	1.30 (1.01—1.66)	
< 110.90 (50 %ile)	1745/ 269,656,925	1.47 (0.95—2.27)	
≥ 110.90 (50 %ile)	1743/ 291,466,432	1.11 (0.81—1.52)	
Whole blood selenium (ug/L)			0.494
Total	1995/ 324,776,643	1.4 (1.00—2.09)	
< 191.30 (50 %ile)	997/ 154,886,780	1.2 (0.80—1.98)	
≥ 191.30 (50 %ile)	998/ 168,374,879	2.49 (1.28—4.86)	
Oral selenium intake and all-cause mortality			
Oral selenium intake (mcg/day)			
Total	3488/ 561,123,356	0.86 (0.58—1.28)	
< 110.90 (50 %ile)	1745/ 269,656,925	0.42 (0.22—0.82)	
≥ 110.90 (50 %ile)	1743/ 291,466,432	0.93 (0.33—2.68)	
Whole blood selenium and all-cause mortality			
Whole blood selenium (ug/L)			
Total	1995/ 324,776,643	0.01 (0.00—0.18)	
< 191.30 (50 %ile)	997/ 154,886,780	0.01 (0.00—0.37)	
≥ 191.30 (50 %ile)	998/ 168,374,879	2.54 (0.19—33.33)	

Adjusted for Model 3, with either oral selenium intake or whole blood selenium levels, depending on the subgroup's selenium status.

was not linked to mortality risk in the overall population. Nevertheless, a reduced mortality risk was observed among participants with lower oral selenium intake (<110.90 μg/day, 50th percentile) (HR = 0.42; 95 % CI: 0.22–0.82). In contrast, higher whole blood selenium levels demonstrated a strong protective effect against all-cause mortality (HR = 0.01; 95 % CI: 0.00–0.18), particularly at lower selenium levels (<191.30 μg/L, 50th percentile) (HR = 0.02; 95 % CI: 0.00–0.37). This protective effect was not evident at higher selenium levels (≥191.30 μg/L). Interaction tests did not indicate any statistically significant modification of these associations by selenium status.

4. Discussion

Our study utilized a nationally representative sample from the United States, marking the first report of the inverse correlation between urinary glyphosate levels and whole blood selenium. If the observed correlation suggests causation, it prompts concerns regarding the possible influence of glyphosate exposure on reduced selenium storage. In addition, our results suggest a complex relationship between glyphosate exposure, selenium status, and mortality risk. Glyphosate exposure is significantly associated with increased all-cause mortality, particularly in individuals with higher whole blood selenium levels, indicating a potential modifying effect of selenium. While selenium at lower levels shows protective effects, higher selenium levels appear to diminish this protection or even exacerbate glyphosate's harmful effects. This dual role of selenium aligns with its known biphasic nature, where it is beneficial at adequate levels but potentially harmful when excessive. These findings highlight the need for balanced selenium intake and raise concerns about the health risks of glyphosate exposure in the general US population, emphasizing the importance of further research to explore the mechanisms underlying these interactions and their implications for public health.

In our study, we found a mean urinary glyphosate level of 0.57 μg/L, consistent with a review suggesting that levels in the general population are typically below 4 μg/L (Gillezeau et al., 2019). Glyphosate levels in Americans have risen notably over time. A 23-year trend study observed increasing glyphosate concentrations in the urine of 100 Californian residents, from an average of 0.0204 μg/L during 1993–1996–0.314 μg/L during 2014–2016 (Mills et al., 2017). Our study findings indicate that individuals aged 3–19 exhibit higher urinary glyphosate levels compared to other age groups, underscoring children as a vulnerable demographic to glyphosate exposure. This insight is significant as previous research on glyphosate in non-occupationally exposed children is limited (Ferreira et al., 2021). Recent cross-sectional studies have associated glyphosate exposure with biomarkers of kidney injury in infants and children (Trasande et al., 2020). Longitudinal investigations further link childhood glyphosate exposure to liver injury and metabolic syndrome in early stages of maturity (Eskenazi et al., 2023). With 93.7 % of participants exhibiting detectable glyphosate levels in our study, minimizing exposure among the younger population is crucial from various perspectives.

The selection of suitable biomarkers for selenium intake remains contentious. While dietary intake assessments via questionnaires are common, they often lack accuracy due to limited food coverage and variability in selenium content (Combs et al., 2011). Whole blood selenium levels are considered a reliable biomarker, especially in deficient individuals, where intake and levels correlate strongly. However, in non-deficient populations, the correlation varies depending on the form of selenium consumed, with inorganic selenium causing minimal increases and selenium-containing amino acids producing higher levels (Burk et al., 2006). Our study found a U-shaped relationship between oral selenium intake and whole blood selenium levels, which aligns with findings from another NHANES study that also identified a significant nonlinear association between these variables (Bai et al., 2024). At low intake levels, the body may increase selenium absorption to compensate for deficiency, leading to higher blood concentrations. In our study, only 6.9 % of participants had selenium intake below the RDA, which explains why fewer cases were observed on the lower end of the U-shape. Conversely, at very high intake levels, excessive selenium is detoxified through the methylation of various selenium compounds. However, the body may struggle to eliminate excess selenium, resulting in its accumulation in the blood (Bai et al., 2024). The results emphasize the need for optimal selenium levels and highlight the importance of further research to determine the ideal intake range for health.

Selenium plays a vital role in maintaining health, primarily due to its antioxidant properties. Laboratory studies have demonstrated that selenoproteins—proteins incorporating selenium as selenocysteine—can safeguard human tissues from oxidative stress (Zeng et al., 2013). Numerous research findings suggest that selenium supplementation significantly reduces malondialdehyde levels while enhancing glutathione levels and overall antioxidant capacity (Zakeri et al., 2021). However, the role of selenium in human health remains a topic of debate. Epidemiological studies using NHANES data have explored the relationship between selenium status and mortality in U.S. adults. Higher serum selenium levels were associated with reduced all-cause and cardiovascular mortality in patients with chronic kidney disease (Zhu et al., 2023). Additionally, higher selenium intake was linked to lower all-cause mortality in adults aged 50 and older (Zhang et al., 2024). In contrast, randomized controlled trials do not provide evidence supporting a beneficial effect of selenium supplementation on cardiovascular or overall mortality (Clark et al., 1996; Lippman et al., 2009). In fact, some trials suggest the opposite, particularly concerning overall mortality (Rayman et al., 2018). The current study found that increased oral selenium intake was not associated with all-cause mortality in the general population. However, it was linked to a reduced risk of mortality among individuals with lower selenium intake (<110.9 μg/day). Additionally, although elevated whole blood selenium levels showed a protective effect against mortality, this effect was only observed in individuals with lower selenium levels (<191.3 μg/L) in the stratified analysis. The protective effect diminished at higher selenium levels, suggesting a threshold beyond which no further benefits were observed. These findings support the notion of a U-shaped relationship between selenium levels and mortality risk, where selenium appears beneficial at moderate levels but may become detrimental at high levels. This is consistent with randomized controlled trials that suggest excessive selenium may have detrimental effects. This highlights the critical importance of maintaining an optimal selenium status, as both deficiency and excess may influence mortality outcomes, underscoring the complexity of selenium's role in health.

Experimental study has demonstrated that exposure to glyphosate and GBH induces oxidative stress (Bali et al., 2019). Occupational research also suggests that individuals exposed to glyphosate may also experience increased oxidative stress and inflammation levels (Chang et al., 2023). However, research within the general population is scarce. A study examining 227 pregnant women in the United States evaluated urinary levels of oxidative stress biomarkers, glyphosate, and aminomethylphosphonic acid (AMPA), a prominent environmental glyphosate metabolite. The results unveiled an association between heightened AMPA levels and elevated concentrations of oxidative stress biomarkers, notably 8-iso-prostaglandin-F2α (Eaton et al., 2022). In another study involving 128 infertile French men, correlations were observed between glyphosate concentrations and oxidative stress biomarkers, especially 8-hydroxy-2′-deoxyguanosine (Vasseur et al., 2024). However, these studies have primarily targeted specific occupational groups, pregnant women, or infertile men, with relatively small sample sizes. In our recent study, we discovered a negative correlation between urinary glyphosate levels and whole blood selenium in a representative sample of American adults. Although multiple factors affect how glyphosate influences selenium status, including its impact on selenium uptake, our research carefully accounted for dietary selenium intake using NHANES data. It is possible that exposure to glyphosate-induced oxidative stress likely contributes to a decline in whole blood selenium levels.

Our study identified an interaction between ethnicity and glyphosate exposure in relation to whole blood selenium levels, with the negative association between glyphosate and selenium being more pronounced in non-Hispanic whites. Ethnicity may act as a modifier, influencing how different groups respond to glyphosate exposure and, consequently, affecting selenium concentrations in the blood. This variation may be due to factors such as lifestyle, dietary habits, genetics, and environmental influences unique to each ethnic group. Therefore, it is important to interpret these findings with caution, as the relationship between glyphosate exposure and selenium levels is not consistent across all ethnic groups. Further research is needed to explore the underlying factors contributing to these differences.

We also observed a significant decrease in whole blood selenium levels with increasing glyphosate exposure among females and individuals with lower selenium intake, although no significant interaction effect was found. Several factors should be considered when interpreting these findings. First, heterogeneity between subgroups may still exist due to unmeasured variables or residual confounding, which could affect the results. Additionally, statistical power may vary across subgroups, with those exhibiting greater variability potentially having lower power to detect significant associations. Furthermore, while sex and selenium intake may influence the strength of the association, they do not modify the relationship between glyphosate and selenium, suggesting an additive effect rather than a synergistic one. Previous research indicates that estrogen may act as an antioxidant, offering protection against oxidative stress (Mohamad et al., 2020), and other studies suggest that glyphosate may interfere with estrogen signaling pathways (Geier and Geier, 2023; Kaboli Kafshgiri et al., 2022). It is plausible that glyphosate depletes blood selenium by directly increasing oxidative stress, as well as indirectly by influencing estrogen expression in females. This is consistent with our finding that women may be more susceptible to glyphosate-induced oxidative stress, which contributes to the observed differences in the relationship between glyphosate and whole blood selenium across genders.

For optimal function of selenium-dependent enzymes, such as glutathione peroxidases, whole blood selenium levels are typically recommended to be between 125 and 163 μg/L (Muecke et al., 2018). In our study, the average whole blood selenium level was 186.54 (SD = 26.30), indicating adequate antioxidant capacity. However, a stronger negative correlation between glyphosate and whole blood selenium was observed in individuals with below-average selenium intake. This suggests that glyphosate may interfere with selenium metabolism or bioavailability, particularly in those with insufficient dietary selenium. Despite this, the lack of a significant interaction implies that the effect of glyphosate on selenium levels is consistent across individuals, regardless of selenium intake, suggesting an additive rather than a modifying effect. These findings underscore the importance of considering both dietary selenium and environmental exposures when evaluating antioxidant capacity and health outcomes.

Recent studies suggest a potential link between glyphosate exposure and increased mortality. In Washington State, individuals exposed to glyphosate-associated land use had 33 % higher odds of premature mortality from Parkinson's disease (Caballero et al., 2018). An ecological study in an Argentine agricultural town detected high glyphosate pollution and observed cancer incidence, prevalence, and mortality rates two to three times higher than national reference values (Vazquez et al., 2017). A previous study using the NHANES 2013–2016 database reported that glyphosate exposure is significantly associated with an increased risk of all-cause mortality (Untalan et al., 2024). Our study, utilizing the NHANES 2013–2018 data, found similar results but with a more rigorous adjustment for covariates, including consideration of selenium status and chronic diseases such as diabetes, chronic kidney disease, hypertension, and hypercholesterolemia. Additionally, we observed that elevated urinary glyphosate levels were associated with an increased mortality risk, particularly in females and younger individuals. The stronger association seen in females and younger adults underscores the potential vulnerability of these groups to glyphosate exposure.

Interestingly, the association between glyphosate exposure and mortality risk was particularly pronounced in individuals with above-average whole blood selenium levels. In contrast, no significant association was observed among individuals with below-average selenium levels. From a biological and toxicological perspective, selenium is a vital trace element involved in numerous enzymatic reactions, primarily through its role as a cofactor in selenoproteins that mediate antioxidant defense and redox balance (Zeng et al., 2013). However, excessive selenium intake can lead to toxicity, a condition known as selenosis (Filippini et al., 2023; Vinceti et al., 2022). In this context, elevated selenium levels could enhance the toxicological effects of environmental stressors like glyphosate. Since glyphosate has been suggested to disrupt mitochondrial function, cause oxidative stress, and interfere with cell signaling (Bali et al., 2019), high selenium levels may amplify these effects by further promoting oxidative damage, leading to increased inflammation, mitochondrial dysfunction, and cellular apoptosis. The interaction between selenium and glyphosate could thus be understood as a complex interplay where, under normal physiological conditions, selenium acts as a protective antioxidant, mitigating oxidative stress and reducing mortality risk. However, in the presence of high selenium levels, the balance may shift, and selenium may transition from being protective to potentially exacerbating glyphosate's toxic effects. Further research is needed to elucidate the precise molecular mechanisms underlying the interaction between selenium and glyphosate, including their combined effects on oxidative stress, inflammation, and cellular integrity.

The advantage of our study stems from the extensive variables accessible via the NHANES database, encompassing the most challenging aspect of collecting detailed dietary information. This factor is pivotal as oral selenium intake notably influences whole blood selenium levels. Additionally, the analysis outcomes offer insights into the wider American population. It's also essential to acknowledge the constraints of this investigation. Firstly, while NHANES provides valuable glimpses into the health status of the U.S. population, its cross-sectional format inherently harbors limitations. Moreover, the research neglected to account for the possible impact of other pollutants that might have been simultaneously encountered alongside glyphosate or could have affected the results. Lastly, the sole concentration on individuals within the United States confines the relevance of the findings to other geographical regions.

5. Conclusions

Following an examination of a representative sample of U.S. adults, our study provides novel insights into the relationship between urinary glyphosate levels and whole blood selenium, suggesting a potential inverse correlation. When whole blood selenium levels are below the 50th percentile, higher selenium concentrations appear to provide protective effects against all-cause mortality. However, this protection is not observed at higher selenium levels. Furthermore, glyphosate exposure is significantly associated with increased all-cause mortality, particularly in individuals with higher whole blood selenium levels, suggesting a potential modifying role of selenium. These results underscore the importance of further research to elucidate the underlying mechanisms of glyphosate and selenium interactions and their broader implications for public health, particularly in the context of environmental exposures.

CRediT authorship contribution statement

Su Ta-Chen: Supervision, Conceptualization. **Chu Pei-Lun:** Writing – original draft, Formal analysis. **Hsiao Ching-Chung:** Writing – original draft, Formal analysis, Data curation. **Wang Chikang:** Supervision, Software, Methodology. **Lin Chien-Yu:** Writing – review & editing,

Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research received no external funding. We extend our heartfelt gratitude to all those who have played a role in advancing NHANES. We express our deepest appreciation to the individuals whose participation, though anonymous, has been instrumental in making this study a reality.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.117989.

Data availability

Data will be made available on request.

References

Bai, Y.Z., et al., 2024. A nonlinear association between total selenium intake and blood selenium concentration: an analysis based on the National Health and Nutrition Examination Survey 2011-2018. J. Food Sci. 89, 9955–9967.
Bali, Y.A., et al., 2019. Learning and memory impairments associated to acetylcholinesterase inhibition and oxidative stress following glyphosate based-herbicide exposure in mice. Toxicology 415, 18–25.
Barnor, K., et al., 2023. The role of funding on research and science: the impact of glyphosate herbicides on health and the environment. J. Policy Model. 45, 103–120.
Burk, R.F., et al., 2006. Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial. Cancer Epidemiol. Biomark. Prev. 15, 804–810.
Caballero, M., et al., 2018. Estimated residential exposure to agricultural chemicals and premature mortality by Parkinson's disease in Washington state. Int. J. Environ. Res. Public Health 15, 2885.
CDC, 2005. Analytic and reporting guidelines: The National Health and Nutrition Examination Survey (NHANES). National Center for Health Statistics.
CDC, 2014. Public Health Statement for Selenium. https://wwwn.cdc.gov/TSP/PHS/PHS.aspx?phsid=151&toxid=28 (accessed 2027 February 2025).
CDC, 2020a. 2017-2018 Data Documentation, Codebook, and Frequencies Smoking - Cigarette Use. https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2017/DataFiles/SMQ_J.htm (accessed 27 February 2025).
CDC, 2020b. 2017-2018 Dietary Data - Continuous NHANES. https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Dietary&CycleBeginYear=2017 (accessed 27 February 2025).
CDC, 2020c. Lead, Cadmium, Total Mercury, Selenium, & Manganese - Blood. https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2017/DataFiles/PBCD_J.htm (accessed 27 February 2025).
CDC, 2020d. NHANES 2017-2018. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2017 (accessed 27 February 2025).
CDC, 2023. 2017-2018 Data Documentation, Codebook, and Frequencies: Glyphosate (GLYP). https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2017/DataFiles/SSGLYP_J.htm (accessed 27 February 2025).
Chang, V.C., et al., 2023. Glyphosate exposure and urinary oxidative stress biomarkers in the Agricultural Health Study. J. Natl. Cancer Inst. 115, 394–404.
Chu, P.L., et al., 2024. Association of urinary glyphosate levels with iron homeostasis among a representative sample of US adults: NHANES 2013-2018. Ecotoxicol. Environ. Saf. 284, 116962.
Clark, L.C., et al., 1996. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. JAMA 276, 1957–1963.
Combs Jr., G.F., et al., 2011. Determinants of selenium status in healthy adults. Nutr. J. 10, 75.
Eaton, J.L., et al., 2022. The association between urinary glyphosate and aminomethyl phosphonic acid with biomarkers of oxidative stress among pregnant women in the PROTECT birth cohort study. Ecotoxicol. Environ. Saf. 233, 113300.
Eskenazi, B., et al., 2023. Association of lifetime exposure to glyphosate and aminomethylphosphonic acid (AMPA) with liver inflammation and metabolic syndrome at young adulthood: findings from the CHAMACOS study. Environ. Health Perspect. 131, 37001.
Ferreira, C., et al., 2021. Urine biomonitoring of glyphosate in children: exposure and risk assessment. Environ. Res. 198, 111294.
Filippini, T., et al., 2023. Selenium and immune function: a systematic review and meta-analysis of experimental human studies. Am. J. Clin. Nutr. 117, 93–110.
Geier, D.A., Geier, M.R., 2023. Urine glyphosate exposure and serum sex hormone disruption within the 2013–2014 National Health and Nutrition Examination survey (NHANES). Chemosphere 316, 137796.
Gillezeau, C., et al., 2019. The evidence of human exposure to glyphosate: a review. Environ. Health 18, 2.
Hsiao, C.C., et al., 2023. Association between glyphosate exposure and cognitive function, depression, and neurological diseases in a representative sample of US adults: NHANES 2013-2014 analysis. Environ. Res 237, 116860.
Kaboli Kafshgiri, S., et al., 2022. Glyphosate effects on the female reproductive systems: a systematic review. Rev. Environ. Health 37, 487–500.
Lacroix, R., Kurrasch, D.M., 2023. Glyphosate toxicity: in vivo, in vitro, and epidemiological evidence. Toxicol. Sci. 192, 131–140.
Lippman, S.M., et al., 2009. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama 301, 39–51.
Mertens, M., et al., 2018. Glyphosate, a chelating agent—relevant for ecological risk assessment? Environ. Sci. Pollut. Res. 25, 5298–5317.
Mills, P.J., et al., 2017. Excretion of the herbicide glyphosate in older adults between 1993 and 2016. JAMA 318, 1610–1611.
Mohamad, N.V., et al., 2020. Are oxidative stress and inflammation mediators of bone loss due to estrogen deficiency? A review of current evidence. Endocr. Metab. Immune Disord. Drug Targets 20, 1478–1487.
Muecke, R., et al., 2018. Whole blood selenium levels and selenium supplementation in patients treated in a family doctor practice in Golßen (State of Brandenburg, Germany): a laboratory study. Integr. Cancer Ther. 17, 1132–1136.
NCHS, 2022. NCHS Data Linkage: 2019 Public-Use Linked Mortality Files. National Center for Health Statistics. https://www.cdc.gov/nchs/data-linkage/mortality-public.htm (accessed 27 February 2025).
NIH, 2021. Selenium: Fact Sheet for Consumers, National Institutes of Health. https://ods.od.nih.gov/factsheets/Selenium-Consumer/ (accessed 27 February 2025).
Qi, X., et al., 2023. Associations between urinary glyphosate and diabetes mellitus in the US general adult: a cross-sectional study from NHANES 2013-2016. Environ. Sci. Pollut. Res. Int. 30, 124195–124203.
Rayman, M.P., 2008. Food-chain selenium and human health: emphasis on intake. Br. J. Nutr. 100, 254–268.
Rayman, M.P., et al., 2018. Effect of long-term selenium supplementation on mortality: results from a multiple-dose, randomised controlled trial. Free Radic. Biol. Med. 127, 46–54.
Romano, R.M., et al., 2021. Could glyphosate and glyphosate-based herbicides be associated with increased thyroid diseases worldwide? Front. Endocrinol. (Lausanne) 12, 627167.
Shehata, A.A., et al., 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Curr. Microbiol. 66, 350–358.
Soares, T.D.C., et al., 2024. Association between selenium biomarkers and insulin resistance in women with obesity: a case-control study. Nutr. Health, 2601060241296004.
Trasande, L., et al., 2020. Glyphosate exposures and kidney injury biomarkers in infants and young children. Environ. Pollut. 256, 113334.
Untalan, M., et al., 2024. Urinary glyphosate levels and association with mortality in the 2013-16 National Health and Nutrition Examination Survey. Carcinogenesis 45, 163–169.
Vasseur, C., et al., 2024. Glyphosate presence in human sperm: first report and positive correlation with oxidative stress in an infertile French population. Ecotoxicol. Environ. Saf. 278, 116410.
Vazquez, M.A., et al., 2017. Association between cancer and environmental exposure to glyphosate. Int. J. Phys. Med. Rehabil. 08, 73–85.
Vinceti, M., et al., 2018. Environmental selenium and human health: an update. Curr. Environ. Health Rep. 5, 464–485.
Vinceti, M., et al., 2022. Safety of selenium exposure and limitations of selenoprotein maximization: molecular and epidemiologic perspectives. Environ. Res. 211, 113092.
Wang, J., et al., 2017. The association between leisure-time physical activity and risk of undetected prediabetes. J. Diabetes Res. 2017, 4845108.
Williams, S.C., et al., 2025. Urinary selenium, cranial MRI, and cognitive function in American Indians: the strong heart study. Environ. Res. 269, 120913.
Zakeri, N., et al., 2021. Selenium supplementation and oxidative stress: a review. PharmaNutrition 17, 100263.
Zeng, H., et al., 2013. Selenium in bone health: roles in antioxidant protection and cell proliferation. Nutrients 5, 97–110.
Zhang, Y., et al., 2024. Associations of dietary selenium intake with the risk of chronic diseases and mortality in US adults. Front. Nutr. 11, 1363299.
Zhu, D., et al., 2023. Higher serum selenium concentration is associated with lower risk of all-cause and cardiovascular mortality among individuals with chronic kidney disease: a population-based cohort study of NHANES. Front. Nutr. 10, 1127188.