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Article

Correlation of Urinary Glyphosate Levels with Whole Blood Selenium Levels among a Representative Sample of US Adults: NHANES 2013-2018

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Equal contribution.

Short running head: Glyphosate and selenium in Americans

Abstract: Purpose: Glyphosate and glyphosate-based herbicides (GBH), extensively utilized as herbicides worldwide, have been associated with numerous health issues. Previous experimental studies have indicated their potential to disrupt selenium homeostasis by either interfering with uptake or increasing oxidative stress. However, there is a significant research gap concerning the connection between glyphosate exposure and selenium status in epidemiological studies, particularly within nationally representative samples. **Methods:** In this study, we examined data from the 2013-2018 National Health and Nutrition Examination Survey (NHANES), involving 3011 participants aged 3 and above. Our main objective was to examine the connection between urinary glyphosate levels, whole blood selenium, and selenium intake. **Results:** Our analysis did not uncover an association between urinary glyphosate and selenium intake. Nevertheless, we observed a negative correlation between urinary glyphosate levels and whole blood selenium, with a β coefficient of -1.984, S.E. = 0.639, and $P = 0.003$ in the final model. We also reported a notable decrease in the average concentrations of whole blood selenium as glyphosate tertiles increased, with P -values for trend of 0.033. Furthermore, the association was particularly prominent among females, non-Hispanic whites, and individuals with lower selenium intake. **Conclusions:** In this thorough examination of NHANES data, our study uncovers a possible detrimental connection between glyphosate exposure and whole blood selenium levels. These findings underscore the importance of further investigation into the health consequences of glyphosate exposure and its potential influence on selenium status, thereby raising awareness of potential implications for public health.

Keywords: Glyphosate; Oxidative stress; National Health and Nutrition Examination Survey (NHANES); Selenium

1. Introduction

Selenium, a vital trace mineral for human health, shares properties that place it between sulfur and tellurium on the periodic table [1]. The human body primarily acquires selenium through dietary sources, with foods like nuts, fish, meat, eggs, and select grains being significant contributors to selenium intake [2]. Selenium impacts human physiology through multiple vital mechanisms. It enhances antioxidant defenses, regulates thyroid hormones, and modulates immune responses [1]. In the United States, the risk of selenium deficiency is minimal due to the high selenium content in

certain areas' soil, which eventually enters the food chain [3]. Nevertheless, selenium deficiency remains a significant global health concern, affecting approximately fifteen percent of the world's population [1].

Glyphosate and glyphosate-based herbicides (GBH) function by interrupting a critical metabolic process crucial for plants to produce key amino acids. These herbicides have been widely utilized due to their outstanding effectiveness in controlling weed growth [4]. However, their widespread use has led to a significant rise in both glyphosate levels and detection rates among Americans over time [5,6]. Because their cytotoxic and genotoxic effects on experimental studies, the International Agency for Research on Cancer categorized glyphosate as a probable carcinogen for human [7]. Recent studies in the general population also link glyphosate exposure to several health issues, including anemia, reduced hand grip strength, diabetes mellitus, metabolic syndrome, and cognitive decline [6,8–10].

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 [11,12]. Additionally, glyphosate may chelate selenium in the gastrointestinal tract, similar to its observed effects on plants [13,14]. Moreover, glyphosate could impact the gut microbiome and suppress *Lactobacillus* activity, which is involved in converting inorganic selenium into more readily absorbed organic forms [15,16]. 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 [17,18], several studies have suggested that GBH may disrupt homeostasis and increase oxidative damage [19–21], potentially leading to selenium depletion. However, there's still a lack of research delving into the connection among glyphosate exposure, selenium intake, and whole blood selenium levels in epidemiological studies, particularly within nationally representative samples of the general populace.

In order to address this gap in understanding, we examined information from the National Health and Nutrition Examination Survey (NHANES) spanning 2013 to 2018. This dataset provides details on urinary glyphosate levels, selenium intake, and whole blood selenium levels. Our study sought to deepen our understanding of the connection between glyphosate levels and selenium status in the 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 [22]. In this study, we utilized the NHANES 2013–2018 dataset, specifically targeting individuals with documented glyphosate exposure, whole blood selenium levels, selenium intake, and pertinent demographic details in model 1. Our analysis encompassed 3011 subjects, and Figure 1 illustrates the selection process visually.

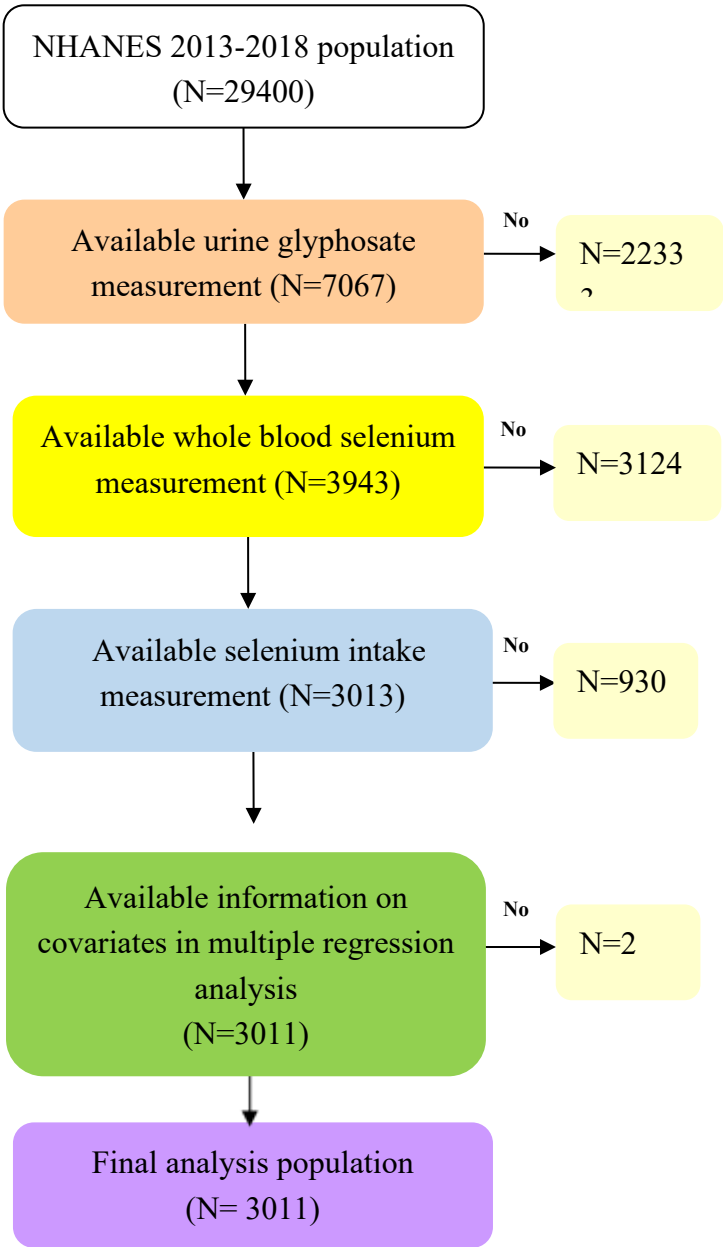


Figure 1. Flow chart algorithm.

2.2. Measurement of Urinary Glyphosate Levels

In the NHANES 2013–2018 survey, urinary glyphosate concentrations were assessed in all participants aged 3 to 5 years and a one-third subsample of those aged 6 years and older. The

methodologies for evaluating glyphosate levels have been detailed in prior publications [23], and the analytical techniques used in the study are available on the NHANES website [24].

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 [25].

2.4. Covariates

Data regarding sociodemographic factors such as age, gender, 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 [26]. 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 [27]. Total 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.

2.3. Statistics

Glyphosate, whole blood selenium, and total 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. Sampling weights, designed to adjust for varying probabilities of selection, were applied following the protocols outlined on the NHANES website [28]. Similarly, to investigate the relationship between urinary glyphosate and whole blood selenium, a linear regression analysis with complex sampling was conducted. Two separate models were utilized for covariate adjustment. In Model 1, adjustments were made for age, gender, ethnicity, smoking status, and urinary creatinine. Model 2, in addition to the adjustments in Model 1, incorporated selenium intake. A result was deemed statistically significant only if it demonstrated significance in both models [29,30]. Due to its non-Gaussian distribution, the natural logarithm (ln) of glyphosate was employed in the analysis. 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 (SD) of 33.32 (24.54) years, ranging from 3 to 80 years old. Approximately 90.1% of individuals showed detectable levels of glyphosate, with a mean glyphosate concentration (SD) of 0.51 (0.63) $\mu\text{g/L}$. The average (SD) total selenium intake was 108.27 (53.86) mcg/day, ranging from 1.85 to 447.30 mcg/day. Only 6.4% of participants had selenium intake below the recommended dietary allowance (RDA) [31,32]. The mean (SD) whole blood selenium level was 187.35 (26.62) $\mu\text{g/L}$, with values ranging from 139.73 to 275.49 $\mu\text{g/L}$. Dietary selenium intake and whole blood selenium levels were significantly correlated, with a Spearman's correlation coefficient of 0.160; $P < 0.001$.

Table 1 presents the means of glyphosate, whole blood selenium, and selenium intake among different subgroups. It indicates that urinary glyphosate levels (adjusted for urinary creatinine) were higher in females, individuals aged 3-19 years, and non-smokers. Furthermore, whole blood selenium levels were elevated among individuals aged 20-59 years, non-Hispanic Asians, and current smokers. Additionally, the table shows that males, individuals aged 20-59 years, non-Hispanic Asians, and active smokers had higher selenium intake.

In the multiple regression analyses outlined in Table 2, a one-unit increase in ln-glyphosate levels did not show an association with food or total selenium intake (β coefficient = -2.567; S.E. = 1.973; P = 0.200 for total selenium intake). Conversely, Table 3 illustrates that a one-unit rise in ln-glyphosate levels was inversely correlated with whole blood selenium levels (β coefficient = -1.984; S.E. = 0.639; P = 0.003 in model 2). Figure 2 presents a summary of the mean (S.E.) of whole blood selenium across tertiles 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 = 0.033).

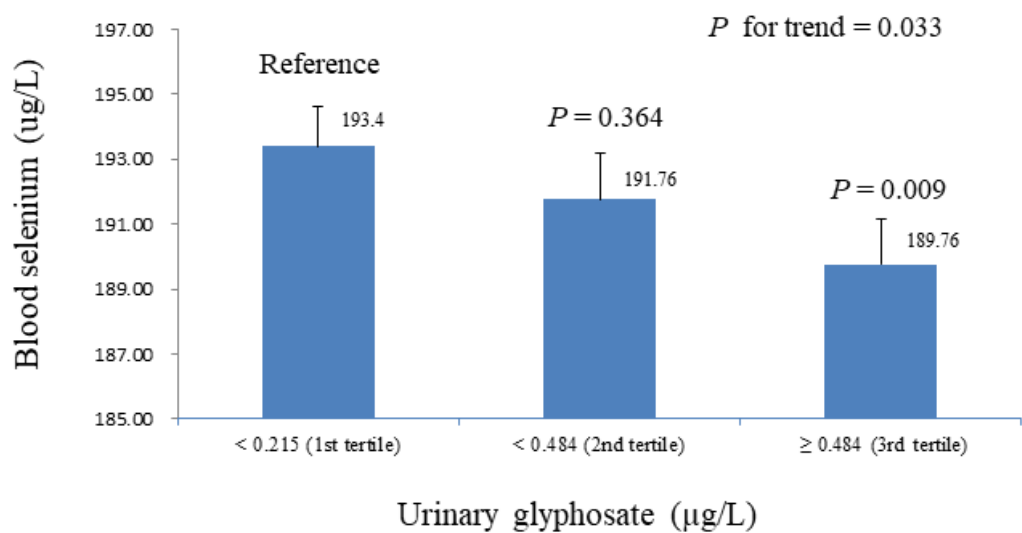


Figure 2. Mean (SE) of serum selenium across tertiles of urine glyphosate in multiple linear regression models (adjusted for model 2), with results weighted for sampling strategy (N=3011).

Table 4 presents the regression coefficients (S.E.) 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.

Table 1. The means (S.E.) of urinary glyphosate levels in different subgroups.

	N.	Glyphosate (μg/g creatinine).	P value.	Whole blood selenium m. (ug/L).	P value.	Total selenium intake. (mcg/day).	P value.
Total.	301	0.56 (0.01)..		187.35 (0.49)..		108.27 (0.98)..	
Sex..			0.034..		0.290..		<0.001..
Males.	150	0.54 (0.02)..		187.87 (0.64)..		123.01 (60.26)..	
Females.	150	0.59 (0.02)..		186.84 (0.73)..		93.54 (41.72)..	
Age (years)..			<0.001..		<0.001..		<0.001..

3-19.	126	0.72 (0.02)..				
	{		178.94 (0.56)..	93.94 (1.23)..	.	
20-59.	111	0.39 (0.02)..	193.39 (0.72)	122.18 (1.74) ..	.	
	(		..			
≥ 60.	633.	0.55 (0.02)..	187.35 (1.45)	112.56 (2.28) ..	.	
			..			
Ethnicity..	.		0.056..	<0.001..	0.003..	
Mexican-	511.	0.57(0.03)..	186.42 (1.06)	106.33 (2.19)..	.	
America			..			
n.						
Other	301.	0.54 (0.03)..		106.22 (3.11)..	.	
Hispani			186.57 (1.47)..			
c.						
Non-	107	0.61 (0.02)..	190.04 (0.94)	111.67 (1.67)..	.	
Hispani	(		..			
c white.	.					
Non-	678.	0.51 (0.02)..	182.51 (0.85)	102.45 (2.09)..	.	
Hispani			..			
c black.						
Non-	285.	0.53 (0.04)..	191.89 (1.47)..	115.21 (3.33)..	.	
Hispani						
c Asian.						
Other	166.	0.60 (0.05)..	186.36 (1.83)	107.85 (4.16)..	.	
ethnicit			..			
y.						
Smoking	.		<0.001..	0.011..	<0.001..	
status..						
Non-smoker.	205	0.61 (0.12)..		106.45 (1.15)..	.	
	1		186.39 (0.57)..			
	.					
ETS.	547.	0.50 (0.03)..	188.90 (1.36)..	107.26 (2.26)..	.	
Current	413.	0.40 (0.02)..	190.11 (1.14)..	118.63 (3.04)..	.	
smoker.						

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

Table 2. Linear regression coefficients (standard error) of selenium intake with a unit increase in ln-urinary glyphosate and continuous covariates in multiple linear regression models, with results weighted for sampling strategy (N=3011).

	Selenium intake (mcg/day) ..			
	Food intake		Total intake	
Continuous variables	Adjusted β (SE)	P value	Adjusted β (SE)	P value
Ln-glyphosate ($\mu\text{g/L}$)	-1.626 (1.609)	0.318	-2.567 (1.973)	0.200
Age (years)	0.171 (0.054)	0.003	0.366 (0.063)	<0.001
Urinary creatinine (g/L)	-0.545 (1.584)	0.732	-1.651 (2.006)	0.415

Model adjusted for model 1: Age, gender, ethnicity, smoking, and urinary creatinine.

Table 3. Linear regression coefficients (standard error) of blood selenium with a unit increase in ln-urinary glyphosate and continuous covariates in multiple linear regression models, with results weighted for sampling strategy (N=3011).

	Whole blood selenium (ug/L)			
	Model 1		Model 2	
Continuous variables	Adjusted β (SE)	P value	Adjusted β (SE)	P value
Ln-glyphosate ($\mu\text{g/L}$)	-2.163 (0.618)	0.001	-1.984 (0.639)	0.003
Age (years)	0.221(0.043)	<0.001	0.196 (0.045)	<0.001
Urinary creatinine (g/L)	0.605 (1.077)	0.577	0.721 (1.046)	0.494
Total selenium intake (mcg/day)			0.070 (0.025)	0.008

Model 1 adjusted for age, gender, ethnicity, smoking, and urinary creatinine. Model 2 adjusted for model 1 plus selenium intake.

Table 4. Linear regression coefficients (SE) of whole blood selenium per unit increase in ln glyphosate in subpopulation, with results weighted for sampling strategy (N=3011).

	Number	Adjusted β (SE)	P value
Gender			
Male	1504	-0.824 (1.022)	0.424
Female	1507	-3.072 (0.946)	0.002
Age, years			
3-19	1268	-0.260 (0.980)	0.792
20-59	1110	-0.871 (1.030)	0.402
≥ 60	633	0.142 (3.090)	0.964
Ethnicity			
Non-Hispanic white	1070	-3.113 (0.960)	0.002
Other	1941	-0.188 (0.608)	0.759
Total selenium intake (mcg/day)			
< 97.5	1506	-3.069 (1.486)	0.045
≥ 97.5	1505	-0.776 (1.195)	0.519

Adjusted for model 2.

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. However, due to the relatively small magnitude of the impact, uncertainties persist regarding the extent to which the decrease in selenium resulting from glyphosate exposure contributes to clinically relevant health conditions. The importance 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.

In our study, we found a mean urinary glyphosate level of 0.56 µg/L, consistent with a review suggesting that levels in the general population are typically below 4 µg/L [33]. 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 to 0.314 µg/L during 2014-2016 [5]. 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 [34]. Recent cross-sectional studies have associated glyphosate exposure with biomarkers of kidney injury in infants and children [35]. Longitudinal investigations further link childhood glyphosate exposure to liver injury and metabolic syndrome in early stages of maturity. [36]. With 90.1% of participants exhibiting detectable glyphosate levels in our study, minimizing exposure among the younger population is crucial from various perspectives.

Suitable biomarkers for selenium status are still debated. Dietary intake assessed via questionnaires is commonly used, but discrepancies exist, especially given the limited coverage of typical questionnaires and the variability in selenium content across foods [37]. Additionally, blood selenium levels correlate directly with intake in deficient individuals, but the association varies based on the type ingested in non-deficient subjects, with inorganic selenium resulting in minimal increases and selenium-containing amino acids leading to higher levels [38]. Therefore, dietary questionnaires may misestimate selenium intake. In this study, selenium intake is positively correlated with whole blood selenium. However, the Spearman's correlation coefficient is only 0.160. This could be attributed to the fact that only 6.4% of subjects had selenium intake below the RDA, and the different forms of selenium in foods may contribute to this result.

Whole-blood selenium, encompassing selenium levels in both red blood cells and plasma, has been validated as a reliable biomarker of selenium status [39,40]. Apart from being influenced by selenium intake, previous studies have also associated whole-blood selenium levels with gender, age, and human inflammatory responses [41,42]. 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 [17,18]. Numerous research findings suggest that selenium supplementation significantly reduces malondialdehyde levels while enhancing glutathione levels and overall antioxidant capacity [43].

Several experimental studies have demonstrated that exposure to glyphosate and GBH induces oxidative stress in different types of cells [19–21]. Occupational research in humans also suggests that individuals exposed to glyphosate may also experience increased oxidative stress and inflammation levels [44,45]. 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 [46]. In another study involving 128 infertile French men, glyphosate and AMPA levels were analyzed in both seminal and plasma samples. The results revealed that glyphosate levels in seminal plasma were four times higher than those in plasma. Correlations were observed between glyphosate concentrations and oxidative stress biomarkers, especially 8-hydroxy-2'-deoxyguanosine [47]. Although studies conducted in both occupational settings and the general population have demonstrated a direct correlation between glyphosate exposure and markers of oxidative stress, such as lipid and DNA oxidation, these studies have primarily targeted specific occupational groups, pregnant women, or infertile men, with relatively small sample sizes. Furthermore, it's crucial to acknowledge the limited number of studies exploring the link between glyphosate exposure and serum antioxidant levels in a nationally representative sample of the general human population. 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. If our findings are confirmed, it suggests that exposure to glyphosate-induced oxidative stress likely contributes to a decline in whole blood selenium levels. These results echo previous research and carry implications for a broader population.

According to our study findings, we noted a stronger negative correlation between glyphosate exposure and whole blood selenium levels in females. It's plausible that sex hormones may influence this association. Previous research suggests that estrogen could act as an antioxidant, providing protection against oxidative stress [48]. Additionally, studies propose that glyphosate may interfere with estrogen signaling pathways [49]. It's conceivable that glyphosate could deplete blood selenium directly through alternative mechanisms while also indirectly increasing oxidative stress by impacting estrogen expression in females. This observation is consistent with our discovery that women are more vulnerable to glyphosate-induced oxidative stress. Our study also revealed an interaction between ethnicity and glyphosate concerning their impacts on whole blood selenium levels. This interaction could stem from disparities among different ethnicities in lifestyle, dietary habits, genetic makeup, and other factors, influencing their response to glyphosate exposure and consequently impacting selenium levels in the blood.

For optimal activity of selenium-dependent proteins like glutathione peroxidases, whole blood selenium levels should ideally range between 125-163 µg/L (Muecke et al. 2018). Beyond this range, increasing selenium levels do not enhance glutathione peroxidase synthesis further (Ayling 2014). In our study, the mean whole blood selenium level among subjects was 187.35 µg/L, with all participants exceeding 125 µg/L. Additionally, only 6.4% of participants had selenium intake below the RDA, suggesting that our study population should theoretically have sufficient antioxidant capacity. However, we observed a more pronounced negative correlation between glyphosate and whole blood selenium levels among individuals with below-average selenium intake. If this negative correlation is due to increased oxidative stress caused by glyphosate, increasing selenium intake may still offer beneficial effects in protecting against glyphosate toxicity for individuals in the United States who already have adequate selenium levels. Recent research suggests that selenoprotein P, a protein essential for transporting selenium to tissues, requires increased selenium levels for maximal expression (Burk & Hill 2005, Hurst et al. 2010). Furthermore, clinical trials administering therapeutic doses of selenite to cancer and end-stage heart failure patients have found that maximal plasma levels of selenoprotein P plateau at or around 400 mcg/day, surpassing the RDA (Brodin et al. 2020). These findings suggest that tissue selenoprotein expression may demand higher selenium intake, especially in response to oxidative stress threats, potentially necessitating additional selenium supplementation.

It's 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.

4. Conclusions

Following an examination of a representative sample of U.S. adults, our study has revealed compelling evidence indicating a negative association between urinary glyphosate levels and whole blood selenium levels. The impact of our findings on clinically significant health disorders remains unknown. Further investigation is warranted to clarify the intricate interactions between glyphosate exposure and selenium status. Such research endeavors can inform health policies regarding glyphosate usage, thus ensuring the protection of human health.

Author's contributions: Pei-Lun Chu and Ching Chung Hsiao conducted the literature review and paper writing. Chi-Kang Wang handled statistical analysis. Chien-Yu Lin contributed significantly to hypothesis development and approved the paper's final revision.

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Institutional Review Board Statement: This study was approved by the Ethics Committee of the En Chu Kong hospital (ECKH_W11403).

Informed Consent Statement: Informed consent was obtained from all individual participants included in the study.

Availability of data and materials: The datasets analyzed in this study can be accessed on the NHANES website (<https://www.cdc.gov/nchs/nhanes/index.htm>) (accessed on May 28, 2024).

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Competing interests: The authors confirm no competing financial interests

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