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Associations of trace metal with depression: NHANES 2017-2018

By

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Abstract

In an analysis of NHANES 2017-2018 data, our study investigated the relationship between exposure to trace metals and depressive symptoms. We applied a quantile g-computation approach to assess the combined mixture effect of eleven trace metals, adjusting for age, gender, ethnicity, education, SES, and creatinine levels. The findings revealed a significant mixture effect, suggesting that an increase across quantile levels of metal exposures is correlated with an increment in depression scores. While individual metals like Cadmium initially presented a significant association, it turns insignificant after adjusting for covariates. Thiesignificant result of the mixture effect highlights the potential impact of simultaneous exposure to multiple metals on mental health. The cross-sectional design and small sample size are limitations. Further longitudinal research could provide deeper insights into these associations and inform preventative strategies for depression related to environmental factors.

Keywords: Depression, Trace Metal, Cadmium, Lead

Wordcounts: 3321

Introduction

Major Depressive Disorder (MDD) is not merely a temporary state of sadness, but a profound and persistent mood disorder impacting a significant portion of the global population. It extends beyond emotional disturbances, affecting physical well-being and cognitive functions, which can drastically diminish one's quality of life.

The causes of MDD are multifaceted. While genetic predisposition and environmental factors has been well-recognized, recent advancements in the field of psychiatry have shed light on the intriguing association between trace metals and the pathophysiology of MDD. Trace metals, though required only in minuscule amounts, are crucial for various bodily functions, particularly in brain metabolism (Bowen, 1966). Their imbalance could potentially derail neurological processes and has been linked to the manifestation of MDD symptoms.

With the advent of metallic research, we delve into exploring the concentrations of these trace metals within the human body, particularly through urine samples, which is less conventional than blood sample. The reason for this unique approach stems from the hypothesis that urine samples might yield a more dynamic and temporally relevant measure of metal levels in relation to depressive states (Fu et al., 2023).

This study stands apart in its focus on specific metals that have been underexplored in the context of MDD, coupled with a novel method of detection. It seeks to expand the existing knowledge on how these trace elements, through their physiological roles and interactions, may contribute to the development and severity of depression. Furthermore, we aim to account for various other factors—age, gender, ethnicity, education and socio-economic status—that could influence this relationship, providing a comprehensive view of the complex interactions and potential influence that various demographic and socio-economic factors have on the relationship between trace metal exposure and depressive symptoms.

Major Depressive Disorder

Major Depressive Disorder (MDD) is a prevalent, yet severe mood condition marked by experience of low mood and negative emotions for a long period of time(American Psychiatric Association, 2013a). In 2019, approximately 280 million individuals, which includes 5% of the adult population, were estimated to have experienced depression(*GBD Results*, n.d.). According to the statistics from the United States National Institute of Mental Health, around 21 million adults in the United States experienced at least one major depressive episode, accounting for 8.3% of all U.S. adults(*Major Depression - National Institute of Mental Health (NIMH)*, n.d.).

MDD is a multifaceted and intricate condition, which can result in impairment of psychosocial functioning and quality of life (Saragoussi et al., 2018). In addition to depressed feelings, patients with MDD may experience a wide range of physical and cognitive symptoms, including feelings of sadness, irritability, loss of interest or pleasure in activities, changes in appetite or weight, sleep disturbances, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and thoughts of death or suicide(American Psychiatric Association, 2013b). In our study, we evaluated depression symptoms across a continuum rather than as a discrete diagnosis, using PHQ-9. Unlike Major Depressive Disorder (MDD), which has specific criteria regarding duration and impact on daily functioning, depression symptoms can vary in their persistence and severity. Not all individuals who exhibit signs of depression will fulfill the diagnostic threshold for MDD. Additionally, while the presence of depressive symptoms may signal a potential risk for developing MDD, it does not confirm a diagnosis.

Trace Metal and MDD

Etiology of MDD includes biological, environmental, and personal vulnerabilities (England et al., 2009). Lately, there has been growing attention towards metallomic research in psychiatry, with a focus on examining the involvement of essential trace elements in both the development and progression of MDD symptoms. Metallomic is a research domain dedicated to unraveling the intricate ways metals influence biological processes at the molecular level (Mounicou et al., 2009), including trace metal study. An essential trace element refers to a mineral or dietary element necessary in small amounts for an organism's proper growth, development, and physiology(Bowen, 1966). These elements are vital for conducting essential metabolic activities in organisms. Examples of essential trace metals in human nutrition include Na, K, Mg, Ca, Fe, Mn, Co, Cu, Zn and Mo (Zoroddu et al., 2019). The trace metals play important catalytic and structural roles. These elements facilitate essential biochemical reactions by serving as cofactors for numerous enzymes and as stabilizing agents for the structures of enzymes and proteins (Prashanth et al., 2015). Alterations in the accumulation or absence of these components can trigger alternative metabolic pathways, potentially contributing to various neurodevelopmental diseases and conditions (Yui, 2016).

Tracing the complex interplay between mental health and trace elements, Baj et al. (2013) embarked on a narrative review exploring how varying serum levels of these elements could influence the emergence and progression of Major Depressive Disorder (MDD) (Baj et al., 2023). They find various ways in which bodily metal content aligns with MDD outcomes. Building on this, Li et al. (2020) found that heightened copper levels disrupt NMDA receptor function, a path that potentially leads to the cognitive impairments observed in MDD (Li et al., 2020). Furthermore, this copper escalation is linked to compromised AMPA receptor function, thereby interrupting glutamatergic transmission and lending support to the glutamate hypothesis of depression(Gerhard et al., 2016),(Peters et al., 2011),(Styczeń et al., 2017).

Our study utilized a cross-sectional design to examine the relationship between urinary trace element levels and depression symptoms within the general U.S. population. We implemented survey-weighted linear regression to evaluate the links between individual trace elements and depressive symptoms. Additionally, we employed quantile-based g-computation to analyze the combined impact of 11 trace metals and their respective contributions. The objective was to elucidate the associations of both singular and combined trace element exposures with depression, offering innovative perspectives and approaches to understanding the interplay between trace metal levels and depressive states.

Method

Dataset

This research employs a cross-sectional methodology, leveraging data from the National Health and Nutrition Examination Survey (NHANES) conducted by the US National Center for Health Statistics. Objectives of the survey encompass evaluating the health and nutritional conditions of individuals across the United States, as well as identifying the prevalence of significant diseases and their risk contributors. The NHANES database includes much information, such as demographic specifics, nutritional insights, results from physical exams, laboratory test results, participant questionnaire answers, and confidential data. We analyzed the data from NHANES 2017.

Study Population

For the trace metal dataset, participants aged 3 to 5 years, along with a one-third subset of those aged 6 and above, were considered eligible for this study. Due to privacy concerns, access to urine lead data for the 3 to 5 age group and urine strontium and uranium data for those aged 3 and above is restricted to the NCHS Research Data Center. However, the dataset does include urine lead data for participants aged 6 and older, as well as urine barium, cadmium, cesium, cobalt, manganese, molybdenum, antimony, thallium, tin, and tungsten for all eligible participants aged 3 and above. For the depression dataset, it only includes responses from individuals 18 years and older. Those under 18 and those who required a proxy respondent were excluded, with youth data accessible via the NCHS Research Data Center. This is due to the confidential nature of the survey content. The trace metal dataset initially includes 2979 participants, and the depression dataset includes 5536 participants. After merging the demographic dataset, depression dataset and metal dataset by sequence number, 1859 subject remains.

Description of Laboratory Methodology for Trace Metal

This technique accurately quantifies various metals in urine samples by utilizing mass spectrometry, preceded by a straightforward dilution preparation of the samples. The process begins with the introduction of liquid specimens into the mass spectrometer via an inductively coupled plasma (ICP) ionization source. Here, a nebulizer converts the sample into fine droplets within an argon gas stream. These droplets then proceed into the ICP, where they are ionized. The ions navigate through a focusing area, enter the dynamic reaction cell (DRC), pass through the quadrupole mass filter, and ultimately, the detector sequentially counts them in rapid succession. This method enables the precise identification of individual isotopes for each element analyzed.

Trace Metal

Within this study, we included 11 different trace metals from the dataset. They are Barium, Cadmium, Cobalt, Cesium, Molybdenum, Antimony, Manganese, Lead, Tin, Thallium and Tungsten.

Depression Assessment

The assessment of participants' depressive symptoms was conducted using the Patient Health Questionnaire-9 (PHQ-9), a nine-item instrument designed for depression screening. The PHQ-9 is recognized as a reliable and validated method for detecting common depression and related disorders, especially in primary care environments (Kim et al., 2016). This questionnaire includes nine prompts, with responses scored based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria as follows: 0 (“Never”), 1 (“A few days”), 2 (“More than a week”), and 3 (“Almost every day”), leading to a total possible score between 0 and 27. A score within the 0-9 range is considered indicative of a non-depressive state, whereas a score of 10 or higher suggests the presence of depression. In the study, participant’s depression index is shown as the total score of PHQ-9 and referred as DPQsum throughout the study. The PHQ-9 has demonstrated high sensitivity (0.88) and specificity (0.85) for identifying depression at a threshold score of 10 or above (Levis et al., 2019). The values 0.88 for sensitivity and 0.85 for specificity refer to the performance of the PHQ-9 in detecting depression. Sensitivity measures the proportion of actual positives correctly identified (true positives), meaning here it is 88% likely to correctly identify someone with depression. Specificity measures the proportion of actual negatives correctly identified (true negatives), meaning here it is 85% likely to correctly identify someone without depression. These values are important as they demonstrate the PHQ-9's effectiveness as a screening tool for depression, particularly its ability to accurately distinguish between individuals with and without the condition when a score of 10 or above is used as the cut-off.

Socioeconomic Status (SES)

We use family income to poverty ratio as an indicator of SES. This ratio is calculated by dividing the household income by the poverty threshold appropriate for the household size and composition. Value less than 1 indicate that the family's income is below the poverty threshold. Such families are often considered impoverished and may qualify for various government assistance programs. Value of 1 means they are exactly at the poverty line. Value from 1 to 2 means that the family has income above the poverty line but might still be considered near-poor or low-income, depending on other factors like cost of living and debt. Value of 2 or above indicate that the family income is at least twice the poverty threshold, suggesting a more stable financial situation. The higher the number, the more financially secure a family is relative to the poverty line.

Data Analysis

We first perform a descriptive analysis of the data and then we used "syvlm" function inside the "survey" package in r to perform linear regression on all 11 different trace metal. In these linear regression model, sum score of subject's depression assessment is the dependent variable and used concentration level of each trace metal is the independent variable. We then apply quantile-based g-computation to assess the relative contribution of each metal as well as association with MDD as metal mixture. In both models, we incorporate age, gender, ethnicity, education and SES as factors.

We used R (Version 4.3.3; R Core Team, 2024) and the R-packages coefplot (Version 1.2.8; Lander, 2022), dplyr (Version 1.1.4; Wickham, François, Henry, Müller, & Vaughan, 2023), forcats (Version 1.0.0; Wickham, 2023a), ggplot2 (Version 3.5.0; Wickham, 2016), gt (Version 0.10.1; Iannone et al., 2024), knitr (Version 1.45; Xie, 2015), lubridate (Version 1.9.3; Grolemund & Wickham, 2011), Matrix (Version 1.6.5; Bates, Maechler, & Jagan, 2024), nhanesA (Version 1.0; Endres, Ale, Gentleman, & Sarkar, 2024), papaja (Version 0.1.2; Aust & Barth, 2023), purrr (Version 1.0.2; Wickham & Henry, 2023), qgcomp (Version 2.15.2; Keil, 2023), readr (Version 2.1.5; Wickham, Hester, & Bryan, 2024), RNHANES (Version 1.1.0; Susmann, 2016), shiny (Version 1.8.1.1; Chang et al., 2024), stargazer (Version 5.2.3; Hlavac, 2022), stringr (Version 1.5.1; Wickham, 2023b), survey (Version 4.4.1; Lumley, 2004), survival (Version 3.5.8; Terry M. Therneau & Patricia M. Grambsch, 2000), tab (Rich, 2023; Version 5.1.1; Van Domelen, 2021; Yoshida & Bartel, 2022), table1 (Version 1.4.3; Rich, 2023), tableone (Version 0.13.2; Yoshida & Bartel, 2022), tibble (Version 3.2.1; Müller & Wickham, 2023), tidyr (Version 1.3.1; Wickham, Vaughan, & Girlich, 2024), tidyverse (Version 2.0.0; Wickham et al., 2019), tinylabels (Version 0.2.4; Barth, 2023), and tinytex (Version 0.50; Xie, 2019) for all our analyses.

Result

Table 1 shows the demographic and characteristics for participants included in the study and the table 2 will reflect the basic characteristic of each metal.

In exploring the relationship between trace metal exposure and health outcomes, our models revealed several significant findings. The regression model for Barium indicated that while the overall effect of Barium on the outcome was not significant (p

= 0.788), gender showed a significant effect, with females exhibiting an increased outcome measure by an average of 1.11 units (95% CI [0.18, 2.04], $p = 0.032$). Age and ethnic background did not significantly contribute to the model.

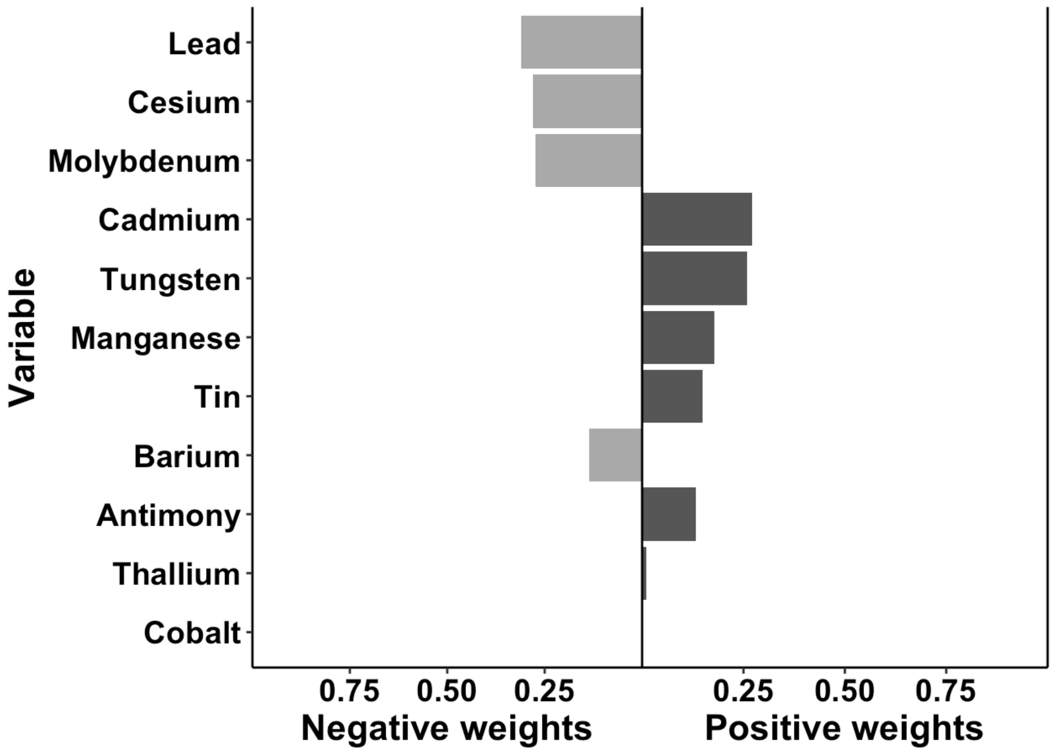
Initial analyses indicated a significant association between cadmium exposure and depression scores with a coefficient of 1.2474 ($p = 0.009$, SE = 0.414). However, after adjusting for age, gender, education and socioeconomic status, this relationship was no longer statistically significant ($p > 0.05$). This adjustment suggests that the initial association may be confounded by these demographic and socioeconomic factors.

The models for other metals such as Cobalt, Cesium, and Molybdenum did not show significant effects on the outcome. However, the analysis highlighted significant racial disparities in health outcomes, particularly among participants identified as 'Other Race - Including Multi-Racial', who consistently showed higher outcome measures across several models.

Income to Poverty Ratio (SES) was another significant predictor across most models, with a consistent negative association indicating that lower economic status is associated with poorer health outcomes, which is lower depression score (e.g., for Barium, $\beta = -0.298$, 95% CI [-0.513, -0.084], $p = 0.022$).

These findings are presented in Table 3, which summarizes the full regression results for each trace metal analyzed.

In the mixture analysis using quantile g-comp, the 11-metal combined mixture effect with 10 quantiles after taking into consideration of age, gender, ethnicity, education and SES as covariates shows promising result of psi1 = 0.232 (p = 0.033, SD = 0.109). This suggests that an increase in one quantile across all metal exposures is associated with an increase of 0.232 unit in DPQsum. The confidence interval ranges from 0.019 to 0.445. The mixture weight figure estimates the weight assigned to each metal in both directions.



Mixture Weight Figure

The mixture effect of Cadmium and Lead with same covariates also shows promising result. The coefficient psi1, which measures the overall effect of a one-quartile increase in the levels of both metals, is estimated at 0.0948 (p = 0.0219, SD = 0.04, 95%CI [0.014, 0.176]). This positive value indicates that as the exposure levels to these metals increase by one quantile, there is a corresponding increase in depression score by approximately 0.0948 units. The standard error of 0.0413 points to a moderate level of precision in this estimate, and the confidence interval from 0.0138 to 0.1758 further supports the existence of a positive association by not including zero. The statistical significance of this effect is confirmed by a p-value of 0.0219, substantiating the role of cadmium and lead exposure in depression.

Discussion

In crude analysis we observed significant association between Cadmium and depression score, but this association diminish after adjusting for key variates. Then, we found that urinary heavy metals co-exposure was significantly related to a higher score of depression, and cadmium were indicated as the most contributing metal to the mixture effects.

Our findings underscore the potent influence of Cadmium on mental health, beyond its well-documented effects on physical health conditions like kidney damage and bone density loss(Ma et al., 2022). Previous researches indicates that blood Cadmium level is positively correlated with many psychiatric disorders, including schizophrenia and bipolar disorder (Cybulska et al., 2021). Scinicariello's 2014 study of blood Cadmium level and depression for young adult(age 20-39) also discover the positive correlation between blood Cadmium level and depressive symptoms (Scinicariello et al., 2015). Another study reveal that low-level exposure to Cadmium, may increase the risk of depression and phenotypic age accounted for approximately 21.32% of the association between cadmium exposure and depression(Wu et al., 2023). However, not every study confirms the correlation between cadmium exposure and depression. Study of elderly Korean cannot conclude that blood cadmium have a positive correlation with the onset of its participants' depression symptoms(Han et al., 2016). Potential reason for this difference in finding might be due to different geographic location. Different geographic location (Korean and America) indicates different culture and different dietary habits. Since one of the main ways for people to have Cadmium intake is through diet, this difference in dietary habit can lead to different result. These results are particularly alarming given the widespread presence of Cadmium in various environmental media and consumer products, suggesting that a large segment of the population may be at risk for adverse mental health outcomes through exposure to this heavy metal.

Another finding of this study is the mixture effect of trace metal on depression. Previous study of Zinc, Chromium, Selenium, Iron, Cobalt, Iodine focused on the protective effect of those metal and pointing out the danger of certain trace metal deficiency, but our study finds a positive effect of mix trace metal on depression proving that having too much of these trace metal can be harmful for people(Janka, 2019). Within the 11 metals, Cadmium contributed the most. The significant association found using the quantile g-computation model highlights the complexity of environmental interactions and their impact on health. It underscores the necessity to consider combined exposures rather than focusing on a single pollutant. This holistic view can lead to more effective public health strategies and more accurate risk assessments.

What’s more, we found that Cadmium is often discussed with Lead, and both are a product of tobacco use. This association is particularly concerning because both metals are highly toxic and accumulate in the body over time, leading to long-term health consequences. Interestingly, in our mixture analysis, Lead was assigned a negative weight, suggesting that its role may differ in the context of combined exposures, indicating possible divergent or protective interactions compared to Cadmium. The co-exposure to Lead and Cadmium from smoking not only compounds their individual effects but also introduces synergistic toxicities that exacerbate cardiovascular, renal, and neurological conditions, further underscoring the critical need for public health interventions aimed at reducing exposure to these metals (Sujka et al., 2019). Additionally, their widespread presence in industrial emissions and consumer products demands tighter regulatory controls and enhanced public awareness to mitigate their impact on human health.

Limitation

The design of our study, inherently cross-sectional, does not allow us to infer causation. It's plausible that depressive symptoms could alter behaviors, potentially heightening exposure to heavy metals. Moreover, although we relied on spot urine samples to evaluate heavy metal exposure, this method is not impervious to measurement inaccuracies. While urine matrices suitably reflect chronic exposure for metals like Cadmium (Cd) and Mercury (Hg), for others, such as Lead (Pb), blood or bone would be the matrices of preference (Levin-Schwartz et al., 2022). Additionally, our analysis did not account for potentially influential health factors, such as family psychiatric history or childhood maltreatment. The relatively small sample size and the focus on NHANES data from only 2017, may further constrain the robustness of our conclusions. Considering these considerations, future research, both more comprehensive and longitudinal, is warranted to shed light on the subtleties of trace metal exposure and its psychiatric implications.

Conclusion

In this cross-sectional study, we examined associations between joint exposure to trace metal mixtures and depression. We found a significant, positive association, suggesting that trace metals exposure could link to the development of depression. It highlights a significant public health consideration of lowering exposure to heavy metals may have beneficial effects in preventing depression. Nevertheless, to corroborate these findings, further longitudinal research is needed to verify our study.

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	Overall (N=1859)
GENDER	
Male	909 (48.9%)
Female	950 (51.1%)
AGE	
Mean (SD)	50.1 (18.7)
Median [Min, Max]	52.0 [18.0, 80.0]
ETHNICITY	
Mexican American	263 (14.1%)
Other Hispanic	164 (8.8%)
Non-Hispanic White	636 (34.2%)
Non-Hispanic Black	430 (23.1%)
Other Race - Including Multi-Racial	366 (19.7%)
EDUCATION	
Less than 9th grade	146 (7.9%)
9-11th grade (Includes 12th grade with no diploma)	209 (11.2%)
High school graduate/GED or equivalent	445 (23.9%)
Some college or AA degree	548 (29.5%)
College graduate or above	406 (21.8%)
Refused	0 (0%)
Don't Know	3 (0.2%)
Missing	102 (5.5%)
SES	
Mean (SD)	2.53 (1.62)
Median [Min, Max]	2.09 [0, 5.00]
Missing	258 (13.9%)

Table 1

	Overall (N=1859)
Barium	
Mean (SD)	1.64 (2.39)
Median [Min, Max]	0.950 [0.0420, 45.1]
Missing	54 (2.9%)
Cadmium	
Mean (SD)	0.352 (0.444)
Median [Min, Max]	0.213 [0.0250, 7.58]
Missing	54 (2.9%)
Cobalt	
Mean (SD)	0.628 (1.38)
Median [Min, Max]	0.411 [0.0160, 32.4]
Missing	54 (2.9%)
Cesium	
Mean (SD)	5.22 (3.52)
Median [Min, Max]	4.60 [0.223, 33.3]
Missing	54 (2.9%)
Molybdenum	
Mean (SD)	48.6 (47.2)
Median [Min, Max]	36.1 [1.46, 588]
Missing	54 (2.9%)
Antimony	
Mean (SD)	0.0744 (0.161)
Median [Min, Max]	0.0450 [0.0160, 4.29]
Missing	54 (2.9%)
Manganese	
Mean (SD)	0.166 (0.330)
Median [Min, Max]	0.0920 [0.0920, 10.9]
Missing	54 (2.9%)
Lead	
Mean (SD)	0.478 (0.706)
Median [Min, Max]	0.320 [0.0200, 19.3]
Missing	54 (2.9%)
Tin	
Mean (SD)	1.25 (3.56)
Median [Min, Max]	0.480 [0.0640, 92.2]
Missing	54 (2.9%)
Thallium	
Mean (SD)	0.200 (0.144)
Median [Min, Max]	0.170 [0.0130, 1.28]
Missing	54 (2.9%)
Tungsten	
Mean (SD)	0.120 (0.446)
Median [Min, Max]	0.0590 [0.0130, 16.2]
Missing	54 (2.9%)

Table 2

term	estimate	std.error	statistic	p.value	conf.low	conf.high	model
Barium	-0.0192507734	0.065588830	-0.29350689	0.78826805	-0.22798370	0.189482155	Barium
Cadmium	1.1694782492	0.383815803	3.04697785	0.05556032	-0.05199493	2.390951432	Cadmium
Cobalt	-0.0051564242	0.060566247	-0.08513693	0.93751599	-0.19790525	0.187592404	Cobalt
Cesium	0.0294729225	0.040200625	0.73314588	0.51656284	-0.09846341	0.157409253	Cesium
Molybdenum	-0.0003380207	0.003015853	-0.11208130	0.91783759	-0.00993581	0.009259768	Molybdenum
Antimony	0.2725423129	0.764607095	0.35644753	0.74510066	-2.16077871	2.705863338	Antimony
Manganese	0.0246741499	0.318940750	0.07736280	0.94320570	-0.99033766	1.039685960	Manganese
Lead	0.0076523071	0.369820868	0.02069193	0.98479070	-1.16928275	1.184587363	Lead
Tin	-0.0235496063	0.046124691	-0.51056400	0.64485267	-0.17033896	0.123239745	Tin
Thallium	0.2514831706	0.869466790	0.28923839	0.79123552	-2.51554820	3.018514545	Thallium
Tungsten	-0.1017848471	0.211188103	-0.48196298	0.66280795	-0.77387965	0.570309951	Tungsten

Table 3