Environmental Research 299 (2026) 124369

Contents lists available at ScienceDirect

Environmental Research

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

Serum concentrations of selenium, selenium species and metals in children newly diagnosed with leukemia: a hospital-based case-control study

Marco Vinceti [a,b,*], Teresa Urbano [a], Bernhard Michalke [c], Lauren A. Wise [b], Maria Caterina Putti [d], Eloise Pulvirenti [e], Claudia Favara [e], Silvia Di Federico [a], Federico Zagnoli [a,f], Giorgia Adani [a,g], Annadiletta Donà [h,i], Roberta Patti [h], Giada Biddeci [d], Enrica Romano [d], Giovanna Russo [j], Marta Arabbito [j], Gea Oliveri Conti [e], Maria Fiore [e], Margherita Ferrante [e], Vincenzo Di Benedetto [h], Maria Grazia Scuderi [h], Piergiorgio Gamba [k], Pier Luca Ceccarelli [l], Giovanni Palazzi [m], Alessia Pancaldi [m], Silvia Fustinoni [n,o], Marcella Malavolti [a], Tommaso Filippini [a,p]

[a] Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN), University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[c] Research Unit Analytical BioGeoChemistry, Helmholtz Center Munich German Research Center for Environmental Health GmbH, Neuherberg, Germany
[d] Department of Women's and Children's Health, Pediatric Haemato-Oncology, University of Padua, Padua, Italy
[e] Section of Public Health, Department of Medical Sciences, Surgical and Advanced Technologies "G.F. Ingrassia", University of Catania, Catania, Italy
[f] Health Directorate, Local Health Authority, Reggio Emilia, Italy
[g] Head Office, Sassuolo Hospital, Modena, Italy
[h] Department of Pediatric Surgery, Azienda Policlinico Rodolico San Marco, Catania, Italy
[i] Pediatric Surgery Unit, Department of Pediatrics, IRCCS-ISMETT, Palermo, Italy
[j] Pediatric Onco-hematology Unit, Azienda Policlinico Rodolico San Marco, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[k] Department of Women's and Children's Health, Pediatric Surgery, University of Padua, Padua, Italy
[l] Department of Pediatric Surgery, University of Modena and Reggio Emilia, Policlinico University Hospital, Modena, Italy
[m] Pediatric Onco-Hematology Unit, Policlinico University Hospital, Modena, Italy
[n] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[o] IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Milan, Italy
[p] School of Public Health, University of California Berkeley, Berkeley, CA, USA

ARTICLE INFO

Keywords:
Case-control study
Childhood leukemia
Metals
Selenium species

ABSTRACT

Exposure to metalloids and metals has been associated with childhood cancer, specifically acute leukemia, though studies are limited. During 2020-2023, we conducted a hospital-based case-control study in Italy to evaluate the association between trace element status and childhood leukemia. We enrolled 77 cases with newly-diagnosed acute childhood leukemia and 74 controls referred to the hospital for minor medical procedures. In blood samples collected at hospital admission, we used inductively-coupled plasma mass spectrometry to measure serum concentrations of selenium (and its species), copper, iron, manganese, and cadmium. We estimated odds ratios and 95% confidence intervals using restricted cubic spline regression. Dose-response, confounder-adjusted analyses showed positive monotonic associations of selenium, copper and iron, above a certain level of exposure, with childhood leukemia. Two selenium species, selenoprotein P-bound selenium and selenomethionine, showed similar results to total selenium. Zinc showed an inverse association with leukemia, while there was no appreciable relation with manganese. Copper concentrations in the top tertile were associated with the highest odds ratio of leukemia, though the association was imprecise. These findings indicate the need for further investigation of the potential adverse role of some selenium species and copper in childhood leukemia. However, reverse causation bias and residual confounding could not be ruled out as possible explanations for our findings.

* Corresponding author at: Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, Modena 41125, Italy
E-mail address: marco.vinceti@unimore.it (M. Vinceti).

https://doi.org/10.1016/j.envres.2026.124369
Received 29 December 2025; Received in revised form 12 March 2026; Accepted 25 March 2026
Available online 25 March 2026

1. Introduction

Acute leukemia is the most common childhood cancer, with an incidence of 5 cases per 100,000 in Western countries (Hu et al., 2024; Wang et al., 2025). Despite advancements in its therapy, a deeper understanding of the biochemical and toxicological mechanisms underpinning disease development and some promising indications from the epidemiologic literature (Metayer et al., 2016), its causes are still largely unknown. While some evidence indicates an etiologic role for environmental factors such as ionizing radiation (Smith-Bindman et al., 2025), non-ionizing radiation (Malagoli et al., 2023; Malavolti et al., 2024), pesticides (Malagoli et al., 2016), air pollution (Filippini et al., 2019; Heck et al., 2016; Vinceti et al., 2012), petroleum compounds (Soliman et al., 2026), infections (He et al., 2020) and nutrition (Metayer et al., 2014; Schraw et al., 2022), exposure to metals or metalloids is understudied. Some evidence of their association with leukemia has, however, been provided in a study of atmospheric lead (Pb), chromium (Cr), and selenium (Se) concentrations (Heck et al., 2014). Some though not all studies have suggested an association between elevated cadmium (Cd) concentrations and childhood leukemia (Asenjo et al., 2022; Demir et al., 2011; Sherief et al., 2015; Whitehead et al., 2015), and a consistent pattern of higher blood copper (Cu) concentrations among children with leukemia compared with controls (Carpentieri et al., 1986; Demir et al., 2011; Legutko, 1978; Mehdi et al., 2015; Sgarbieri et al., 2006). Evidence for zinc (Zn) has been sparse and inconsistent (Demir et al., 2011; Infante-Rivard et al., 2001; Ladas et al., 2016; Whitehead et al., 2015).

Children are exposed to metals and metalloids via breastfeeding, dermal absorption, drinking water, dietary ingestion, inhalation, and non-dietary ingestion of soil or dust (Filippini et al., 2018; Glorennec et al., 2016; Sáez et al., 2025; Venturelli et al., 2025). While measures of environmental and dietary factors can provide useful exposure information, biological matrices such as blood, urine, and, in some cases, nails or hair, may instead offer a more comprehensive and integrated measure of internal dose, reflecting overall exposure from multiple sources over time (Ashton et al., 2009; Gutiérrez-González et al., 2019; Martinez-Morata et al., 2023; Vinceti et al., 2018b). In addition, there is strong evidence that for some metals and metalloids, especially Se, but also Cu, iron (Fe) and manganese (Mn) (Mandrioli et al., 2017; Urbano et al., 2025a, 2025b; Vinceti et al., 2025; Violi et al., 2020), exposure to different chemical species may matter, given the marked differences of nutritional and toxicological properties of various chemical forms of the same element.

In the present study, we assessed associations of children's serum concentrations of six heavy metals and metalloids, including selenium species, with childhood leukemia in three Italian regions.

2. Methods

2.1. Study population

We carried out a hospital-based case-control study, approved by the Ethics Committee of the Coordinating Center in Modena (approval no. 432/2019/OSS/AUSLMO) at three Italian university hospitals—Modena (Emilia-Romagna), Catania (Sicily) and Padua (Veneto) during 2020-2023. All cases of newly diagnosed childhood (<18 years) leukemia identified at the pediatric hematology or oncology clinics of these three hospitals were eligible for inclusion. Additional eligibility criteria were having an Italian or English-speaking parent, and no previous cancer diagnosis or ongoing pharmacological treatment. We selected sex-matched controls (1:1) from pediatric surgical units of the same university hospitals as the cases, applying the same eligibility criteria. Among controls, reasons for hospital admission were check-up visits for mild heterogeneous symptoms with no subsequent disease diagnosis (n = 6, 8.1%) and minor surgical interventions (n = 68, 91.9%), mainly for sebaceous cysts, benign dermal pigmented lesions, hypospadias, varicocele, hydrocele, inguinal hernia and phimosis. We did not include children affected by gastrointestinal, thoracic or vascular malformations, lymph node masses, infectious disease, acute metabolic and inflammatory conditions, or acute emergencies.

2.2. Laboratory analyses

We collected blood samples from fasting children in the morning for all participants, immediately after diagnosis for cases, within 2 days after hospital admission and before the start of any therapy or surgical intervention. We also collected a fasting urinary sample to estimate environmental tobacco smoke exposure though cotinine determination. Blood samples were centrifugated at 2500 × g to obtain serum and aliquoted in 1.5 mL sterile polypropylene tubes, and eventually stored at −80 °C within 30 min from collection. Samples were kept continuously frozen and transported by air courier, deep frozen with dry ice, to the Laboratory of Helmholtz Centrum in Munchen, Germany.

We used inductively-coupled plasma atomic emission spectrometry (ICP-AES; Optima 7300 DV, PerkinElmer, Rodgau-Jügesheim, Germany) (Schramel et al., 1982) to measure serum concentrations of Cu, Fe, Mn, and Zn. Sample introduction was performed via a peristaltic pump connected to a Seaspray nebulizer and a cyclonic spray chamber. The emission lines used for quantification were: Cu: 324.754 nm, Fe: 259.941 nm, Mn: 257.611 nm, and Zn: 213.857 nm. Instrumental settings were as follows: RF power, 1400 W; plasma gas flow, 13 L Ar/min; and nebulizer gas flow, ~0.6 L Ar/min (optimized daily). The limits of quantification (LOQs) were 0.8 μg/L for Cu, 0.9 μg/L for Fe, 0.5 μg/L for Mn, and 1.5 μg/L for Zn. As cadmium (Cd) and total selenium (Se) concentrations were below the detection limits of ICP-AES, these elements were analyzed using inductively coupled plasma sector field mass spectrometry (ICP-sf-MS; Element 2, Thermo Scientific, Bremen, Germany). For Cd, we measured ^{111}Cd in low-resolution (LR) mode; for Se, ^{77}Se and ^{78}Se were measured in high-resolution (HR) mode. Instrumental parameters were: RF power, 1260 W; plasma gas flow, 16 L Ar/min; auxiliary gas flow, 0.85 L Ar/min; and nebulizer gas flow, 1.085 L Ar/min (optimized daily). The dwell time was set to 300 ms. The LOQs were 0.05 μg/L for ^{77}Se and 0.07 μg/L for ^{78}Se. We generated five-point calibration curves for each element, demonstrating excellent linearity (R^2 better than 0.99968 for all elements). Quality control measures included the analysis of three blanks and a certified reference standard for each analyzed element (CPI International, Santa Rosa, CA, USA) after every ten samples. We calculated final concentrations using a laboratory information management system (LIMS), integrating calibration data, blanks, and control standards to ensure accuracy and reproducibility.

We performed Se speciation using a hyphenated system consisting of a NexSAR gradient HPLC pump, autosampler, and a NexION 300D ICP-DRC-MS (PerkinElmer, Rodgau, Germany), operated via Clarity software. Se species were separated using an anion-exchange column (AG-11 pre-column combined with AS-11 analytical column, Thermo Dionex, Idstein, Germany) with a 50 μL sample injection volume. Chromatographic separation employed a gradient elution with two eluents: Eluent A – 10 mM Tris-HAc with 5% methanol (MeOH), pH 8.0; Eluent B – 50 mM sodium carbonate (Na_2CO_3), 20 mM ammonium acetate (NH_4Ac), and 5% MeOH, pH 8.0. We applied the gradient profile as recently described (Urbano et al., 2025a; Vinceti et al., 2025). A constant flow rate of 0.80 mL/min was maintained throughout the run. ICP-DRC-MS operational settings were: RF power, 1250 W; plasma gas flow, 15 L Ar/min; auxiliary gas flow, 1.05 L/min; and nebulizer gas flow, 0.92 L/min (optimized daily). Se was detected via the ^{77}Se, ^{78}Se, and ^{80}Se isotopes. The dynamic reaction cell (DRC) was operated with methane (CH_4) as the reaction gas at a flow rate of 0.58 mL/min, with a DRC rejection parameter (q) of 0.6. We quantified the following Se species: selenite (Se IV), selenate (Se VI), selenomethionine (Se-Met), selenocystine (Se-Cys_2), thioredoxin reductase-bound selenium (Se-TXNRD), glutathione peroxidase-bound selenium (Se-GPX), selenoprotein P

Table 1
Characteristics of the study population (urinary cotinine and trace elements as μg/L). *Calculated on samples with serum metal determinations.

Variable	N Controls	Median (IQR) Controls	Min - Max Controls	N Cases	Median (IQR) Cases	Min - Max Cases
Age	74	7.00 (4.00 - 11.00)	0.00 - 18.00	77	4.00 (3.00 - 9.00)	0.00 - 16.00
Urinary cotinine	68	0.05 (0.05 - 0.50)	0.05 - 17.84	72	0.52 (0.05 - 1.38)	0.05 - 488.06
Total Se	74	106.42 (79.74 - 145.00)	18.28 - 221.00	77	113.00 (80.90 - 154.00)	31.10 - 310.00
Se-SELENOP	74	64.33 (33.12 - 80.88)	1.77 - 153.85	77	64.71 (46.69 - 103.95)	4.18 - 292.10
Se-Met	74	1.79 (0.52 - 4.04)	0.01 - 10.07	77	2.09 (1.09 - 4.18)	0.01 - 48.22
Se-Cys	74	2.06 (0.74 - 4.71)	0.01 - 24.57	77	1.80 (0.42 - 3.68)	0.01 - 35.94
Se-GPX	74	5.69 (2.15 - 22.05)	0.34 - 106.49	77	5.70 (2.86 - 16.30)	0.19 - 95.29
Se-TXNRD	74	0.65 (0.34 - 1.60)	0.00 - 18.77	77	1.96 (0.78 - 3.73)	0.12 - 17.53
Se IV	74	11.02 (2.40 - 21.21)	0.01 - 70.56	77	6.34 (3.33 - 12.83)	0.58 - 41.19
Se VI	74	3.47 (1.22 - 15.69)	0.01 - 63.11	77	3.63 (1.64 - 7.61)	0.01 - 102.88
Se-HSA	74	0.58 (0.31 - 2.23)	0.01 - 18.84	77	1.74 (0.63 - 4.00)	0.01 - 36.14
Age*	17	6.00 (5.00 - 9.00)	1.00 - 12.00	58	5.00 (3.00 - 9.00)	0.00 - 16.00
Urinary Cotinine*	17	0.28 (0.05 - 0.99)	0.04 - 17.84	55	0.62 (0.16 - 1.62)	0.05 - 488.06
Cd	17	0.02 (0.01 - 0.03)	0.01 - 0.31	58	0.02 (0.02 - 0.03)	0.01 - 0.28
Cu	17	953 (874 - 1010)	100 - 1800	58	1620 (1310 - 2310)	339 - 3270
Fe	17	1920 (1050 - 2630)	543 - 6610	58	1900 (1210 - 2980)	511- 19300
Mn	17	0.68 (0.61 - 1.22)	0.46 - 2.53	58	0.99 (0.70 - 1.45)	0.07 - 2.44
Zn	17	949 (812 - 1090)	741 - 1660	58	824 (706 - 990)	445 - 1880

(Se-SELENOP), and human serum albumin-bound selenium (Se-HSA). Species were identified by retention time matching with respective standard compounds. We determined the oxidized Se species selenocystine (a dimer, (R-CH_2-Se)2) instead of the physiological form of the element, the monomer selenocysteine (R-CH_2-SeH), being the latter unstable and therefore not suitable to be determined as such.

Due to the unavailability of commercial SELENOP, we isolated the protein from human serum using a modified protocol based on previously published methods (Jitaru et al., 2008; Shigeta et al., 2007; Solovyev et al., 2013). Purification was conducted using a heparin-affinity column (Amersham, GE Healthcare Europe GmbH, Munich, Germany). Human serum albumin (HSA) was prepared at a concentration of 1000 mg/L. For preparation of Se-HSA, we added selenite to the HSA stock solution to reach a final Se concentration of 10 mg/L, followed by incubation for a minimum of 14 days. Identification of Se-HSA in sample chromatograms was based on comparisons with both Se-HSA and unmodified HSA standards, using selenium-specific mass signals and UV absorbance profiles. We processed chromatographic data using Clarity software for peak area integration of Se-specific chromatograms. We determined limits of quantification (LOQs) for individual Se species using a 10σ noise criterion near each respective peak. LOQs were consistently set at 0.025 μg/L (as Se) for all quantified species. For Cu, Fe, Mn, and Zn and Se species the limit of detection (LOD) was 0.02 μg/L, while for Cd it was 0.007 μg/L, with a LOQ of 0.025 μg/L. Urinary cotinine concentrations (μg/L) were measured using a validated LC–MS/MS method (Campo et al., 2016; Fustinoni et al., 2013), with a LOQ of 0.1 μg/L. Details about the sample distribution with respect to LOQ are reported in Supplementary Table S1.

2.3. Data analysis

We replaced values below the LOD with LOD/2 and values below the LOQ with LOQ/2 (Finkelstein and Verma, 2001). We used crude and multivariable unconditional logistic regression models, to calculate the odds ratio (OR) of leukemia according to Se, Se species and metal serum concentration categories as computed in controls, alongside 95% confidence interval (CI). We adjusted for sex and age in all analyses, and for urinary cotinine in an additional model. ORs were assessed across the entire range of exposure by using a restricted cubic spline model, placing knots at the 10th, 50th and 90th percentiles, and also tertiles, for each exposure variable.

3. Results

Of 178 eligible study participants, 151 (77 cases of which 70 acute lymphoblastic leukemia and 7 acute myeloid leukemia, and 74 controls) had sufficient blood collected to allow determinations of overall Se levels and single Se species (Table 1). For 75 participants (58 cases and 17 controls), the amount of blood also allowed for determination of metals (Cd, Cu, Fe, Mn and Zn). Among participants, 64.9% were males, and median age was 6 years. Distribution of selenium species and metals by type of leukemia is reported in Supplementary Table S2. Median cotinine concentrations were higher among cases (0.52 μg/L, interquartile range 0.05 – 1.38) than controls (0.05 μg/L, interquartile range 0.05 – 17.84).

Table 2 shows the ORs for leukemia associated with tertiles of serum selenium concentrations, in both crude analysis and after adjustment for age and sex, and for these factors and urinary cotinine. Total selenium showed a slightly and imprecise increase in odds of leukemia only in the upper category (OR 1.09, 95% CI 0.47-2.52). Concerning selenium species, there was a dose-response positive association between Se-SELENOP, Se-TXNRD, and the odds of leukemia, while other species exhibited high ORs in the middle and upper tertiles but no indication of dose-response. Spline regression analyses generally indicated non-linear patterns of association (Fig. 1), with a clear positive association above 150 μg/L for total Se, as also observed for Se-SELENOP, whose increase was steeper and more linear. We also observed a monotonic linear positive pattern of association for Se-Met. Conversely, four other Se species – namely, Se-Cys, Se-GPX, Se IV and Se VI – showed inverse associations with leukemia, consistent with categorical analyses, indicating a non-linear pattern for Se-GPX, Se IV. Finally, both Se-TXNRD and Se-HSA showed an inverted U-shaped pattern with a positive association at relatively low exposure levels, a feature not observed in categorical analyses.

In categorical analyses (Table 3) based on a smaller sample size, we observed positive associations with Cd and Fe, but with highest odds in the middle tertile. Cu was associated with higher odds only in the upper category (OR 5.33, 95% CI 1.23-23.19), as was Mn (OR 3.38, 95% CI 0.82-13.89), while Zn was inversely associated with leukemia. Spline regression analysis showed a more comprehensive pattern of association between metals and leukemia (Fig. 2), demonstrating a positive association above a certain threshold only for Fe and Cu, i.e., above 5000 μg/L and 2000 μg/L, respectively. The pattern of association with Cd, Mn and Zn did not indicate any positive association with the odds of

Table 2
Risk of childhood leukemia according to tertiles of Se and Se species distribution.

Variable	Min and max in the exposure tertiles (μg/L)	Median in the exposure tertile (μg/L)	N Cases/ Controls	Adjusted for age and sex OR (95% CI)	Adjusted for age, sex, and urinary cotinine OR (95% CI)
Total Se					
Ref	<85.85	69.37	24/24	Ref	Ref
2nd tertile	85.85 - 129.99	107.21	23/25	0.94 (0.41 - 2.14)	0.95 (0.39 - 2.27)
3rd tertile	>129.99	167.00	30/25	1.15 (0.52 - 2.56)	1.09 (0.47 - 2.52)
Se-SELENOP					
Ref	<40.30	25.83	14/24	Ref	Ref
2nd tertile	40.30 - 76.38	59.02	26/25	2.16 (0.91 - 5.15)	2.07 (0.83 - 5.16)
3rd tertile	>76.38	105.46	30/25	2.14 (0.91 - 5.03)	1.82 (0.74 - 4.47)
Se-Met					
Ref	<0.88	0.40	16/24	Ref	Ref
2nd tertile	0.88 - 3.55	1.91	37/25	2.17 (0.95 - 4.97)	2.68 (1.10 - 6.51)
3rd tertile	>3.55	5.52	24/25	1.40 (0.59 - 3.33)	1.57 (0.64 - 3.89)
Se-Cys					
Ref	<1.09	0.29	31/24	Ref	Ref
2nd tertile	1.09 - 4.08	2.13	29/25	0.95 (0.43 - 2.09)	0.86 (0.37 - 2.00)
3rd tertile	>4.08	5.58	17/25	0.56 (0.24 - 1.29)	0.50 (0.21 - 1.20)
Se-GPX					
Ref	<2.90	1.54	20/24	Ref	Ref
2nd tertile	2.90 - 16.19	5.54	37/25	1.66 (0.75 - 3.69)	1.47 (0.63 - 3.43)
3rd tertile	>16.19	30.49	20/25	1.00 (0.42 - 2.35)	0.89 (0.37 - 2.16)
Se-TXNRD					
Ref	<0.39	0.22	8/24	Ref	Ref
2nd tertile	0.39 - 1.12	0.68	16/25	2.07 (0.74 - 5.81)	3.22 (1.03 - 10.05)
3rd tertile	>1.12	2.77	53/25	5.75 (2.24 - 14.77)	7.34 (2.58 - 20.88)
Se IV					
Ref	<4.61	2.30	30/24	Ref	Ref
2nd tertile	4.61 - 15.63	8.11	34/25	1.17 (0.54 - 2.53)	1.52 (0.67 - 3.46)
3rd tertile	>15.63	24.78	13/25	0.41 (0.17 - 0.99)	0.52 (0.21 - 1.32)
Se VI					
Ref	<1.83	0.74	22/24	Ref	Ref
2nd tertile	1.83 - 7.37	3.56	35/25	1.12 (0.49 - 2.54)	0.89 (0.37 - 2.12)
3rd tertile	>7.37	15.76	20/25	0.67 (0.28 - 1.59)	0.68 (0.27 - 1.70)
Se-HSA					
Ref	<0.36	0.21	10/24	Ref	Ref
2nd tertile	0.36 - 1.15	0.60	15/25	1.54 (0.57 - 4.15)	1.90 (0.66 - 5.48)
3rd tertile	>1.15	3.00	52/25	4.62 (1.90 - 11.28)	4.55 (1.77 - 11.71)

leukemia, consistent with the categorical analysis, also suggesting for Zn an inverse association with the disease at the lowest levels of exposure.

Analyses further adjusted for urinary cotinine yielded comparable results (Tables 2–3, and Supplementary Figs. S1–S2), as did analyses limited to the 70 cases with lymphoblastic leukemia (Supplementary Tables S3–S4, and Supplementary Figs. S3–S4).

4. Discussion

In this Italian hospital-based case-control study, higher concentrations of total Se and some Se species, and of Cu and to a lesser extent Fe, were associated with childhood leukemia at diagnosis, either suggesting an etiologic role of these trace elements or that disease progression induces derangements in their metabolism.

With reference to Se and Se species, we found complex patterns, since total Se and two Se species showed positive associations with the disease, but this was not observed for other forms of the element. Total Se showed a monotonic positive association at concentrations above 120 μg/L, i.e. about an approximate intake of 80 μg/day (Haldimann et al., 1996), slightly higher than the recommended dietary intake by the European Food Safety Authority (EFSA Panel on Nutrition Novel Foods Food Allergens et al., 2023a). Given the strong toxicity of Se above the dietary recommendations (EFSA Panel on Nutrition Novel Foods Food Allergens et al., 2023a; Vinceti et al., 2017b), some epidemiologic evidence linking increased Se intake to hematological malignancies (Duffield-Lillico et al., 2002; Heck et al., 2014; Vinceti et al., 2016, 2018c), and the capacity of Se to promote oxidative stress and DNA damage (Vinceti et al., 2022), it is biologically plausible that excess intake of Se could be associated with increased leukemia risk in children.

In the present study, very low Se concentrations were positively associated with childhood leukemia, framing a U-shaped relation between Se exposure and odds that has been frequently described with other endpoints, as well as other essential but also toxic elements, depending on amount of exposure and its chemical form (Vinceti et al., 2018b). Accordingly, the specific Se species that showed positive (stronger and monotonic) associations with leukemia were Se-SELENOP and Se-Met, both being species of strong toxicological interest (Urbano et al., 2021, 2023; Vinceti et al., 2018b). Se-SELENOP is a protein Se-transporter whose excess has been associated with a broad spectrum of adverse effects, mainly altered glucose metabolism and type 2 diabetes (Ishikura et al., 2014; Misu et al., 2010; Mita et al., 2017; Oo et al., 2018, 2022), in line with the results of randomized controlled trials (Vinceti et al., 2018a, 2021) and Mendelian randomization studies (Cheng et al., 2025), cognitive impairment and pulmonary arterial hypertension (Kikuchi et al., 2019; Saito, 2020; Vinceti et al., 2017a, 2023). Se-Met, in turn, has been shown to be a pro-oxidant and toxic, non-physiological Se species (Vinceti et al., 2018b, 2022).

The associations of total Se, Se-SELENOP, and Se-Met with leukemia could result from reverse causation bias, which is when exposure is a downstream effect of the disease and not a factor of etiologic relevance. The altered redox status and increased oxidative stress characterizing childhood leukemia onset could elicit a compensatory response, upregulating antioxidant enzymes, some of which contain Se atoms (Vinceti et al., 2022). In fact, some studies investigating conditions associated with free radical damage in humans and in laboratory settings have shown the potential for reactive increase of antioxidant enzymes, including selenoproteins, following the induction of oxidative stress (EFSA Panel on Nutrition Novel Foods Food Allergens et al., 2023a;

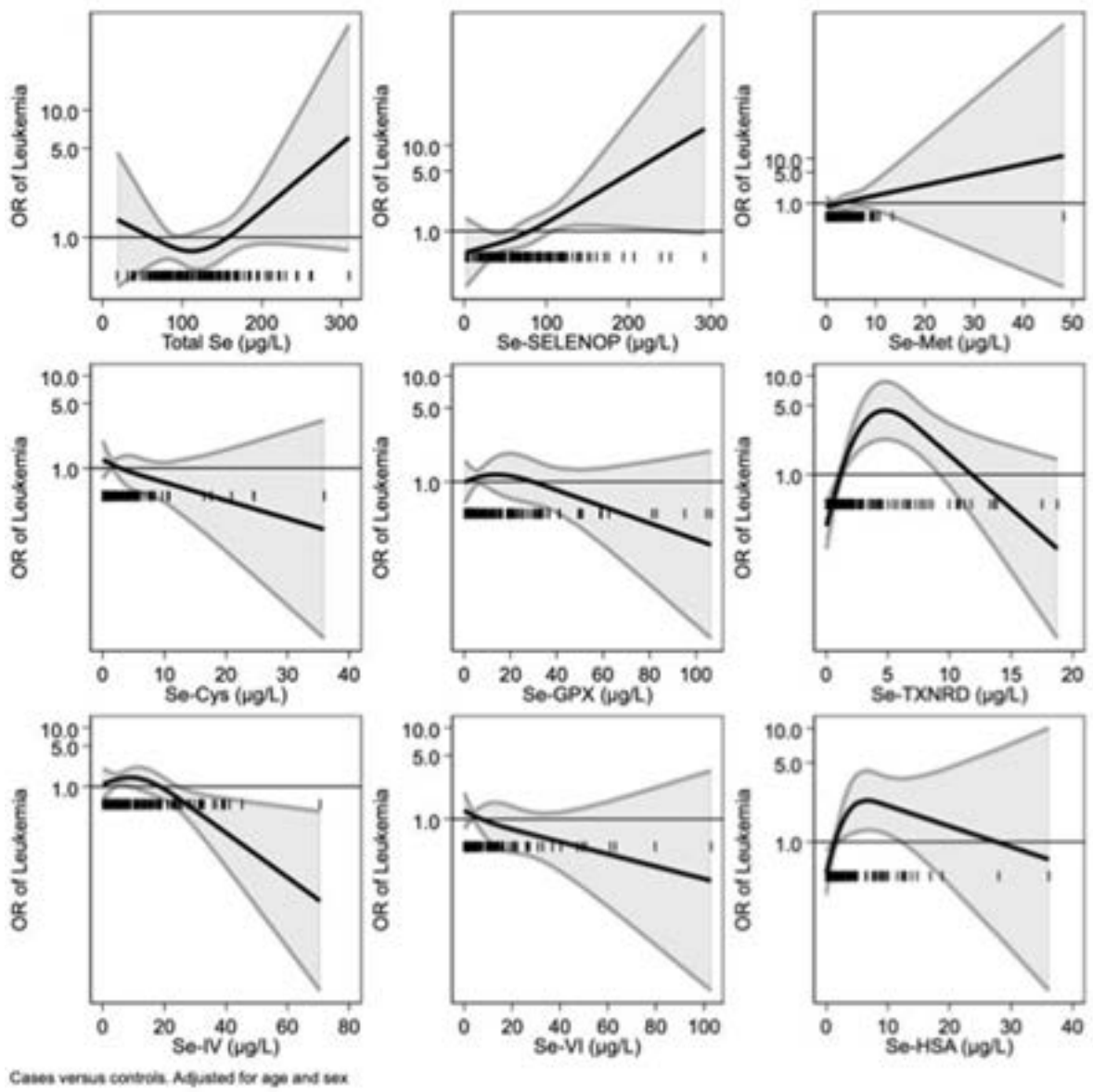

Fig. 1. Dose-response odds ratio of childhood leukemia according to serum selenium and selenium species metal concentrations (solid black line OR curve, gray area 95% confidence interval), adjusting for age and sex.

Vinceti et al., 2022). Thus, we urge caution in the interpretation of findings from cross-sectional and case-control studies, including ours. Longitudinal studies are needed to better understand if differences in Se status precede or accompany leukemia onset in children and, in the former case, whether they are of independent etiologic relevance or simply a marker of disease occurrence.

In this study, results for the other Se species were either inconsistent or unclear. The organic 'physiological' forms of Se, Se-cystine and Se-containing glutathione peroxidase, and two potentially toxic inorganic Se species, selenite and selenate, showed an inverse association with leukemia. Conversely, Se-TXNRD- and Se-HSA showed more inconsistent pattern, with an indication of inverted U-shaped association in non-linear analyses, and with heterogenous results compared with analyses based on exposure categories (documenting positive monotonic associations), thus providing limited and unclear evidence of involvement in disease etiology.

We found a strong though imprecise association between high Cu concentrations, an element with both nutritional and toxicological properties, and leukemia. Though high blood Cu concentrations have been already described in some studies of children affected by leukemia (Asenjo et al., 2022; Carpentieri et al., 1986; Demir et al., 2011; Kim et al., 2019; Legutko, 1978; Sgarbieri et al., 1999; Wang et al., 2010), no dose-response assessment has been performed to date. It remains to be ascertained if elevated Cu is a determinant of childhood leukemia, a biomarker of diagnostic interest, a potential target to counteract disease progression, or simply an effect induced by disease onset and progression. Cu has a high potential for inducing free radical damage and promoting cell proliferation, tumor growth and inflammation, and eventually inducing other effects involved in cancer initiation and promotion (Gupte and Mumper, 2009; Liao et al., 2020). Conversely, the immunological, metabolic, inflammatory and redox processes associated with childhood leukemia could increase circulating levels of the primary copper-carrying protein in human blood, ceruloplasmin oxidase (Ma et al., 2020; Mehdi et al., 2015; Rodriguez-Gonzalez et al., 2026), and this mechanism could partly or wholly explain our findings.

The positive and non-linear association between serum Fe concentrations and leukemia resembles the pattern detected for Cu, despite a much lower odds in the intermediate and high ranges of exposure, and

Table 3
Risk of childhood leukemia according to tertiles of metal distribution.

Variable (μg/L)	Min and max in the exposure tertiles (μg/L)	Median in the exposure tertile (μg/L)	N Cases/Controls	Adjusted for age and sex OR (95% CI)	Adjusted for age, sex, and urinary cotinine OR (95% CI)
Cd					
Ref	<0.0153	0.0114	12/5	Ref	Ref
2nd tertile	0.0153 - 0.0252	0.02075	26/6	1.39 (0.33 - 5.87)	1.67 (0.39 - 7.20)
3rd tertile	>0.0252	0.04205	20/6	1.24 (0.30 - 5.10)	1.47 (0.34 - 6.27)
Cu					
Ref	<882.00	546.5	7/5	Ref	Ref
2nd tertile	882.00 - 1009.97	927.5	2/6	0.27 (0.03 - 2.03)	0.27 (0.03 - 2.04)
3rd tertile	>1009.97	1690	49/6	5.72 (1.32 - 24.77)	5.33 (1.23 - 23.19)
Fe					
Ref	>1069.99	870	11/5	Ref	Ref
2nd tertile	1069.99 - 2349.78	1770	26/6	2.07 (0.51 - 8.43)	2.18 (0.52 - 9.11)
3rd tertile	>2349.78	3840	21/6	1.52 (0.37 - 6.29)	1.67 (0.40 - 7.02)
Mn					
Ref	<0.618	0.489	9/5	Ref	Ref
2nd tertile	0.618 - 0.770	0.682	9/6	0.82 (0.17 - 3.85)	0.76 (0.16 - 3.60)
3rd tertile	>0.770	1.27	40/6	3.68 (0.90 - 15.10)	3.38 (0.82 - 13.89)
Zn					
Ref	<867.97	747	34/5	Ref	Ref
2nd tertile	867.97 - 1079.90	958	15/6	0.41 (0.10 - 1.61)	0.46 (0.12 - 1.82)
3rd tertile	>1079.90	1260	9/6	0.22 (0.05 - 0.90)	0.21 (0.05 - 0.92)

the imprecision of associations at the highest levels of exposure due to small numbers of participants. Altered Fe metabolism and overload have been documented during and after the treatment of childhood leukemia, but little is known about their levels at or before disease onset, and therefore our findings require confirmation. Reverse causation bias may also affect the results for Fe, though a potential (though weaker) role of Fe in both childhood leukemia etiology and pathogenesis could exist, also taking into account the potential relation between Fe availability and altered metabolism on the induction of cancer (Salnikow, 2021; Torti et al., 2025), including specifically leukemia (Brissot et al., 2020; Lan et al., 2022; Wang et al., 2019), and the capacity of Fe to induce oxidative stress and DNA damage, for instance through ferroptosis (Garcia-Gimenez et al., 2025).

For Zn, we found an inverse dose-response non-linear association between circulating concentrations and leukemia, in the lowest range of exposure. A decrease in Zn concentrations in adult and childhood leukemia has been reported, a finding of interest also considering the biological functions of Zn related to redox status and antioxidant properties and immune response (Consolo et al., 2013; Kim et al., 2019; Mocchegiani et al., 1994; Ullah et al., 2025; Yao et al., 2024), that point to a potential deleterious effect of Zn deficiency in leukemogenesis, consistently with what has been suggested for other cancers (Chen et al., 2024). As for the other elements, however, we cannot rule out reverse causation as an explanation of these findings, including a role of inflammation or cancer itself in intracellular-extracellular Zn redistribution (Chen et al., 2024; Gammoh and Rink, 2017; McDonald et al., 2020).

Cd is a toxic heavy metal (Rasin et al., 2025) with weak ecologic evidence linking it to with childhood leukemia (Asenjo et al., 2022), while Mn is an essential element characterized however by severe neurotoxicity at high levels (EFSA Panel on Nutrition Novel Foods Food Allergens et al., 2023b; Filippini et al., 2017; Violi et al., 2020). These two elements showed little association with leukemia when investigated in their entire range of exposure, despite a suggestive positive association in categorical analyses, with a dose-response trend for Cd. While a positive association of Cd and Mn with disease at low levels cannot be entirely ruled out, the lack of association at high exposure levels considerably weakens the plausibility for a causal association.

We adjusted our analyses for urinary cotinine concentrations as an indicator of potential (passive) smoking, and levels were considerably higher in cases compared with controls. Parental or more generally environmental smoking could have played a key role in triggering leukemia onset, but is also able to influence trace element status by affecting both their intake and metabolism, as shown for Se and Cd (Nakayama et al., 2019; Snoj Tratnik et al., 2022; Vacchi-Suzzi et al., 2016; Vinceti et al., 2015), and suggested for Zn and Cu (Di Gioacchino et al., 2000; Nwogueze et al., 2024).

A study limitation was the case-control study design, making us unable to establish temporality between trace element status and leukemia. This limitation applies to all trace elements and Se species investigated in the present study, calling for the implementation of longitudinal studies to overcome it, and for caution in inferring causality from our findings. In addition, hospital controls were selected to represent the exposure distribution in the source population from which the cases arose. Specifically, their medical conditions were likely unrelated to exposure (i.e., trace element status) and to metabolic and inflammatory alterations, thereby reducing potential for selection bias, though this possibility could not be entirely ruled out. Furthermore, the number of study participants was not sufficient to allow for subgroup analyses according to sex, age, and other factors, or to generate precise OR estimates apart for Se, given the much larger sample size for that element. Finally, the observational study design leaves room for confounding, since unmeasured environmental and lifestyle variables could have biased our results. However, the positive associations detected for total Se and Fe, Se-SELENOP and Se-Met, including the strong but imprecise association with Cu, warrant further investigation.

CRediT authorship contribution statement

Marco Vinceti: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Teresa Urbano:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Bernhard Michalke:** Writing – review & editing, Formal analysis, Data curation. **Lauren A. Wise:** Writing – review & editing, Writing – original draft, Supervision. **Maria Caterina Putti:** Writing – review & editing, Resources, Data curation. **Eloise Pulvirenti:** Writing – review & editing, Resources. **Claudia Favara:** Writing – review & editing, Resources. **Silvia Di Federico:** Writing – review & editing, Resources. **Federico Zagnoli:** Writing – review & editing, Resources. **Giorgia Adani:** Writing – review & editing, Resources, Conceptualization. **Annadiletta Donà:** Writing – review & editing, Resources. **Roberta Patti:** Writing – review & editing, Resources. **Giada Biddeci:** Writing – review & editing, Resources. **Enrica Romano:** Writing – review & editing, Resources. **Giovanna Russo:**

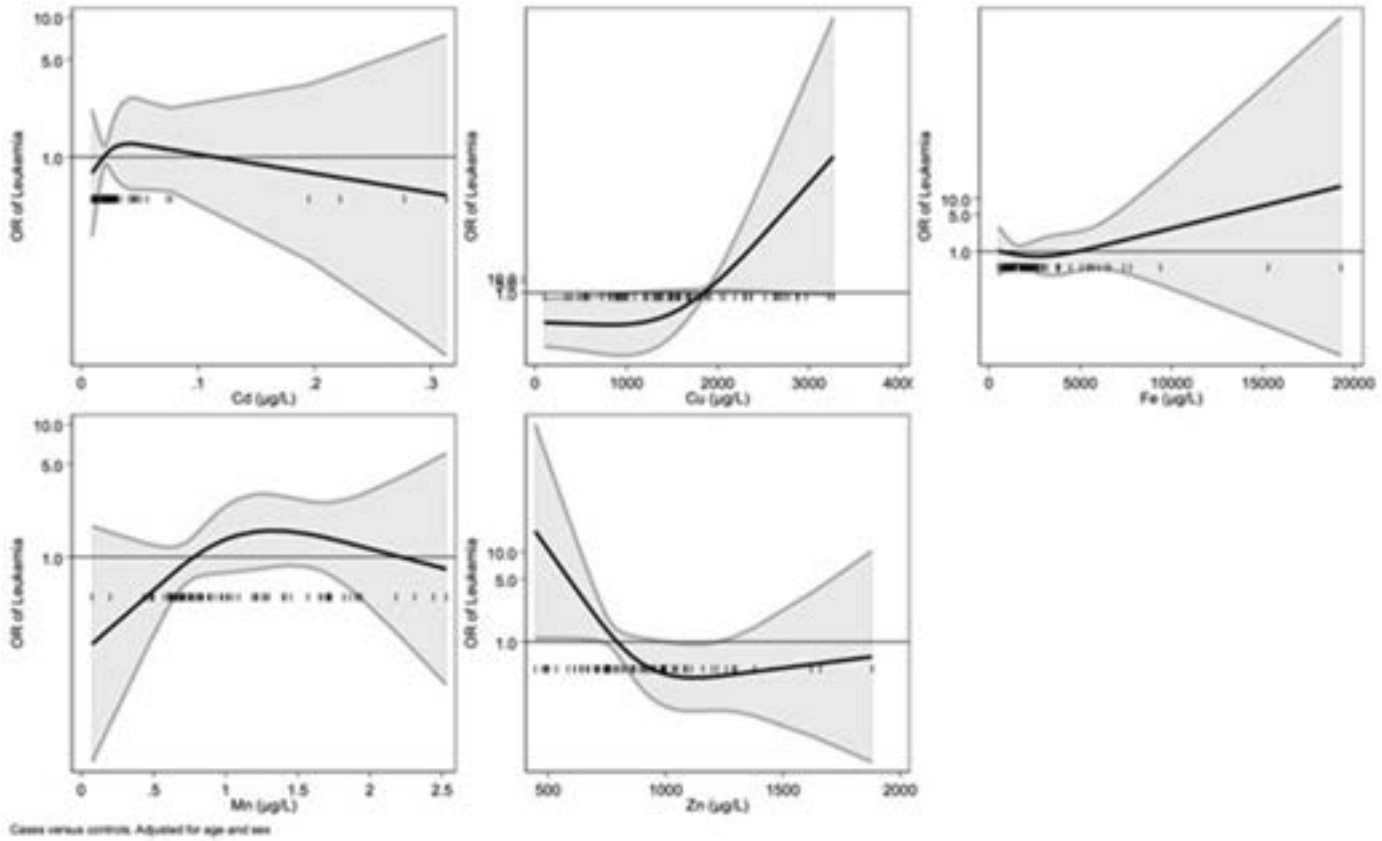

Fig. 2. Dose-response odds ratio of childhood leukemia according to serum metal concentrations (solid black line OR curve, gray area 95% confidence interval), adjusting for age and sex.

Writing – review & editing, Resources, Data curation. **Marta Arabbito:** Writing – review & editing, Resources. **Gea Oliveri Conti:** Writing – review & editing, Resources. **Maria Fiore:** Writing – review & editing, Resources. **Margherita Ferrante:** Writing – review & editing, Resources. **Vincenzo Di Benedetto:** Writing – review & editing, Resources. **Maria Grazia Scuderi:** Writing – review & editing, Resources. **Piergiorgio Gamba:** Writing – review & editing, Resources. **Pier Luca Ceccarelli:** Writing – review & editing, Resources. **Giovanni Palazzi:** Writing – review & editing, Resources. **Alessia Pancaldi:** Writing – review & editing, Resources. **Silvia Fustinoni:** Writing – review & editing, Formal analysis. **Marcella Malavolti:** Writing – review & editing, Writing – original draft, Conceptualization. **Tommaso Filippini:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, 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.

Acknowledgements

This study was supported by Children with Cancer UK grant no. 19-309, and by Associazione Sostegno Oncologia Ematologia Pediatrica - ASEOP of Modena, Italy (grants to Dr. Vinceti). The authors declare they have no actual or potential competing financial interests. The authors kindly acknowledge the cooperation of children and their parents participating in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2026.124369.

Data availability

The data presented in this study are not publicly available due to privacy restrictions and may be available on reasonable request from the corresponding author.

References

Asenjo, S, Nuñez, O, Segú-Tell, J, Pardo Romaguera, E, Cañete Nieto, A, Martín-Méndez, I, Bel-Lan, A, García-Pérez, J, Cárceles-Álvarez, A, Ortega-García, JA, Ramis, R., 2022. Cadmium (Cd) and lead (Pb) topsoil levels and incidence of childhood leukemias. Environ. Geochem. Health 44, 2341–2354. https://doi.org/10.1007/s10653-021-01030-w.

Ashton, K, Hooper, L, Harvey, LJ, Hurst, R, Casgrain, A, Fairweather-Tait, SJ, 2009. Methods of assessment of selenium status in humans: a systematic review. Am. J. Clin. Nutr. 89, 2025S–2039S. https://doi.org/10.3945/ajcn.2009.27230A.

Brissot, E, Bernard, DG, Loréal, O, Brissot, P, Troadec, MB, 2020. Too much iron: a masked foe for leukemias. Blood Rev. 39, 100617. https://doi.org/10.1016/j.blre.2019.100617.

Campo, L, Polledri, E, Bechtold, P, Gatti, G, Ranzi, A, Lauriola, P, Goldoni, CA, Bertazzi, PA, Fustinoni, S, 2016. Determinants of active and environmental exposure to tobacco smoke and upper reference value of urinary cotinine in not exposed individuals. Environ. Res. 148, 154–163. https://doi.org/10.1016/j.envres.2016.03.02.

Carpentieri, U, Myers, J, Thorpe, L, Daeschner 3rd, CW, Haggard, ME, 1986. Copper, zinc, and iron in normal and leukemic lymphocytes from children. Cancer Res. 46, 981–984.

Chen, B, Yu, P, Chan, WN, Xie, F, Zhang, Y, Liang, L, Leung, KT, Lo, KW, Yu, J, Tse, GMK, Kang, W, To, KF, 2024. Cellular zinc metabolism and zinc signaling: from biological functions to diseases and therapeutic targets. Signal Transduct. Target. Ther. 9, 6. https://doi.org/10.1038/s41392-023-01679-y.

Cheng, L, Zeng, Z, Quan, H, 2025. Association of selenium with type 2 diabetes and obesity: a univariate and multivariate Mendelian randomization study. Medicine (Baltim.) 104, e45338. https://doi.org/10.1097/MD.0000000000045338.

Consolo, LZ, Melnikov, P, Cônsolo, FZ, Nascimento, VA, Pontes, JC, 2013. Zinc supplementation in children and adolescents with acute leukemia. Eur. J. Clin. Nutr. 67, 1056–1059. https://doi.org/10.1038/ejcn.2013.146.

Demir, C, Demir, H, Esen, R, Sehitogullari, A, Atmaca, M, Alay, M, 2011. Altered serum levels of elements in acute leukemia cases in Turkey. Asian Pac. J. Cancer Prev. 12, 3471–3474.

Di Gioacchino, M, Forcucci, R, Tiboni, GM, Kouri, S, Di Gioacchino, F, Boscolo, P, 2000. The influence of menopause and habitual smoking upon serum zinc, serum copper and the cardiovascular and immune parameters of women. Int. J. Immunopathol. Pharmacol. 13, 91–97.

Duffield-Lillico, AJ, Reid, ME, Turnbull, BW, Combs Jr., GF, Slate, EH, Fischbach, LA, Marshall, JR, Clark, LC, 2002. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the nutritional prevention of cancer trial. Cancer Epidemiol. Biomarkers Prev. 11, 630–639.

EFSA Panel on Nutrition Novel Foods and Food Allergens (NDA), Turck, D., Bohn, T., Castenmiller, J, de Henauw, S, Hirsch-Ernst, KI, Knutsen, HK, Maciuk, A, Mangelsdorf, I, McArdle, HJ, Peláez, C, Pentieva, K, Siani, A, Thies, F, Tsabouri, S, Vinceti, M, Aggett, P, Crous Bou, M, Cubadda, F, Ciccolallo, L, de Sesmaisons Lecarré, A, Fabiani, L, Titz, A, Naska, A, 2023a. Scientific opinion on the tolerable upper intake level for selenium. EFSA J. 21, e07704. https://doi.org/10.2903/j.efsa.2023.7704.

EFSA Panel on Nutrition Novel Foods and Food Allergens (NDA), Turck, D, Bohn, T, Castenmiller, J, de Henauw, S, Hirsch-Ernst, KI, Knutsen, HK, Maciuk, A, Mangelsdorf, I, McArdle, HJ, Pentieva, K, Siani, A, Thies, F, Tsabouri, S, Vinceti, M, Bornhorst, J, Cubadda, F, Dopter, A, FitzGerald, R, de Sesmaisons Lecarré, A, das Neves Ferreira, P, Fabiani, L, Horvath, Z, Matijević L, Z, Naska, A., 2023b. Scientific opinion on the tolerable upper intake level for manganese. EFSA J. 21, e8413. https://doi.org/10.2903/j.efsa.2023.841.

Filippini, T, Cilloni, S, Malavolti, M, Violi, F, Malagoli, C, Tesauro, M, Bottecchi, I, Ferrari, A, Vescovi, L, Vinceti, M, 2018. Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a northern Italy community. J. Trace Elem. Med. Biol. 50, 508–517. https://doi.org/10.1016/j.jtemb.2018.03.001.

Filippini, T, Hatch, EE, Rothman, KJ, Heck, JE, Park, AS, Crippa, A, Orsini, N, Vinceti, M, 2019. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. Environ. Health Perspect. 127, 46002. https://doi.org/10.1289/EHP4381.

Filippini, T, Michalke, B, Grill, P, Malagoli, C, Malavolti, M, Vescovi, L, Sieri, S, Krogh, V, Cherubini, A, Maffeis, G, Lucchini, R, Ferrante, M, Vinceti, M, 2017. Determinants of serum manganese levels in an Italian population. Mol. Med. Rep. 15, 3340–3349. https://doi.org/10.3892/mmr.2017.6379.

Finkelstein, MM, Verma, DK, 2001. Exposure estimation in the presence of nondetectable values: another look. Am. Ind. Hyg. Assoc. J. 62, 195–198. https://doi.org/10.1080/15298660108984622.

Fustinoni, S, Campo, L, Polledri, E, Mercadante, L, Erspamer, L, Ranzi, A, Lauriola, P, Goldoni, CA, Bertazzi, P, 2013. A validated method for urinary cotinine quantification used to classify active and environmental tobacco smoke exposure. Curr. Anal. Chem. 9, 447–456. https://doi.org/10.2174/1573411011309030014.

Gammoh, NZ, Rink, L, 2017. Zinc in infection and inflammation. Nutrients 9, 624. https://doi.org/10.3390/nu9060624.

Garcia-Gimenez, A, Ditcham, JE, Azazi, DMA, Giotopoulos, G, Asby, R, Meduri, E, Bagri, J, Sakakini, N, Lopez, CK, Narayan, N, Beinortas, T, Agrawal-Singh, S, Fung, K, O'Connor, D, Mansour, MR, Alabed, HBR, Jenkins, B, Koulman, A, Murphy, MP, Horton, SJ, Huntly, BJP, Richardson, SE, 2025. CREBBP inactivation sensitizes B cell acute lymphoblastic leukemia to ferroptotic cell death upon BCL2 inhibition. Nat. Commun. 16, 4274. https://doi.org/10.1038/s41467-025-59531-6.

Glorennec, P, Lucas, JP, Mercat, AC, Roudot, AC, Le Bot, B, 2016. Environmental and dietary exposure of young children to inorganic trace elements. Environ. Int. 97, 28–36. https://doi.org/10.1016/j.envint.2016.10.009.

Gupte, A, Mumper, RJ, 2009. Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. Cancer Treat. Rev. 35, 32–46. https://doi.org/10.1016/j.ctrv.2008.07.004.

Gutiérrez-González, E, García-Esquinas, E, de Larrea-Baz, NF, Salcedo-Bellido, I, Navas-Acien, A, Lope, V, Gómez-Ariza, JL, Pastor, R, Pollán, M, Pérez-Gómez, B, 2019. Toenails as biomarker of exposure to essential trace metals: a review. Environ. Res. 179, 108787. https://doi.org/10.1016/j.envres.2019.108787.

Haldimann, M, Venner, TY, Zimmerli, B, 1996. Determination of selenium in the serum of healthy Swiss adults and correlation to dietary intake. J. Trace Elem. Med. Biol. 10, 31–45. https://doi.org/10.1016/S0946-672X(96)80006-X.

He, JR, Ramakrishnan, R, Hirst, JE, Bonaventure, A, Francis, SS, Paltiel, O, Håberg, SE, Lemeshow, S, Olsen, S, Tikellis, G, Magnus, P, Murphy, MFG, Wiemels, JL, Linet, MS, Dwyer, T, 2020. Maternal infection in pregnancy and childhood leukemia: a systematic review and meta-analysis. J. Pediatr. 217, 98–109e8. https://doi.org/10.1016/j.jpeds.2019.10.046.

Heck, JE, Park, AS, Contreras, ZA, Davidson, TB, Hoggatt, KJ, Cockburn, M, Ritz, B, 2016. Risk of childhood cancer by maternal birthplace: a test of the Hispanic paradox. JAMA Pediatr. 170, 585–592. https://doi.org/10.1001/jamapediatrics.2016.0097.

Heck, JE, Park, AS, Qiu, J, Cockburn, M, Ritz, B, 2014. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int. J. Hyg Environ. Health 217, 662–668. https://doi.org/10.1016/j.ijheh.2013.12.003.

Hu, Y, Liu, Y, Fu, J, Liu, Y, Wang, H, Song, Y, 2024. Global, regional, and national burden of acute lymphoblastic leukemia in children: epidemiological trends analysis from 1990 to 2021. iScience 27, 111356. https://doi.org/10.1016/j.isci.2024.111356.

Infante-Rivard, C, Olson, E, Jacques, L, Ayotte, P, 2001. Drinking water contaminants and childhood leukemia. Epidemiology 12, 13–19. https://doi.org/10.1097/00001648-200101000-00004.

Ishikura, K, Misu, H, Kumazaki, M, Takayama, H, Matsuzawa-Nagata, N, Tajima, N, Chikamoto, K, Lan, F, Ando, H, Ota, T, Sakurai, M, Takeshita, Y, Kato, K, Fujimura, A, Miyamoto, K, Saito, Y, Kameo, S, Okamoto, Y, Takuwa, Y, Takahashi, K, Kidoya, H, Takakura, N, Kaneko, S, Takamura, T, 2014. Selenoprotein P as a diabetes-associated hepatokine that impairs angiogenesis by inducing VEGF resistance in vascular endothelial cells. Diabetologia 57, 1968–1976. https://doi.org/10.1007/s00125-014-3306-9.

Jitaru, P, Prete, M, Cozzi, G, Turetta, C, Cairns, W, Seraglia, R, Traldi, P, Cescon, P, Barbante, C, 2008. Speciation analysis of selenoproteins in human serum by solid-phase extraction and affinity HPLC hyphenated to ICP-quadrupole MS. J. Anal. At. Spectrom. 23, 402–406. https://doi.org/10.1039/B712693J.

Kikuchi, N, Satoh, K, Satoh, T, Yaoita, N, Siddique, MAH, Omura, J, Kurosawa, R, Nogi, M, Sunamura, S, Miyata, S, Misu, H, Saito, Y, Shimokawa, H, 2019. Diagnostic and prognostic significance of serum levels of SeP (selenoprotein P) in patients with pulmonary hypertension. Arterioscler. Thromb. Vasc. Biol. 39, 2553–2562. https://doi.org/10.1161/ATVBAHA.119.313267.

Kim, S, Freeland-Graves, JH, Babaei, M, Sachdev, PK, Beretvas, SN, 2019. Quantifying the association between acute leukemia and serum zinc, copper, and selenium: a meta-analysis. Leuk. Lymphoma 60, 1548–1556. https://doi.org/10.1080/10428194.2018.1540043.

Ladas EJ, Orjuela M, Stevenson K, Cole PD, Lin M, Athale UH, Clavell LA, Leclerc JM, Michon B, Schorin MA, Welch JG, Asselin BL, Sallan SE, Silverman LB, Kelly KM. 2016. Dietary intake and childhood leukemia: the diet and acute lymphoblastic leukemia treatment (DALLT) cohort study. Nutrition 32, 1103–1109 e1. doi: 10.1016/j.nut.2016.03.014.

Lan, H, Gao, Y, Zhao, Z, Mei, Z, Wang, F, 2022. Ferroptosis: redox imbalance and hematological tumorigenesis. Front. Oncol. 12, 834681. https://doi.org/10.3389/fonc.2022.834681.

Legutko, L, 1978. Serum copper investigations in children with acute lymphoblastic leukemia. Folia Haematol. Int. Mag. Klin. Morphol. Blutforsch. 105, 248–254.

Liao, Y, Zhao, J, Bulek, K, Tang, F, Chen, X, Cai, G, Jia, S, Fox, PL, Huang, E, Pizarro, TT, Kalady, MF, Jackson, MW, Bao, S, Sen, GC, Stark, GR, Chang, CJ, Li, X, 2020. Inflammation mobilizes copper metabolism to promote colon tumorigenesis via an IL-17-STEAP4-XIAP axis. Nat. Commun. 11, 900. https://doi.org/10.1038/s41467-020-14698-y.

Ma, J, Xie, Y, Zhou, Y, Wang, D, Cao, L, Zhou, M, Wang, X, Wang, B, Chen, W, 2020. Urinary copper, systemic inflammation, and blood lipid profiles: Wuhan-Zhuhai cohort study. Environ. Pollut. 267, 115647. https://doi.org/10.1016/j.envpol.2020.115647.

Malagoli, C, Costanzini, S, Heck, JE, Malavolti, M, De Girolamo, G, Oleari, P, Palazzi, G, Teggi, S, Vinceti, M, 2016. Passive exposure to agricultural pesticides and risk of childhood leukemia in an Italian community. Int. J. Hyg Environ. Health 219, 742–748. https://doi.org/10.1016/j.ijheh.2016.09.015.

Malagoli, C, Malavolti, M, Wise, LA, Balboni, E, Fabbi, S, Teggi, S, Palazzi, G, Cellini, M, Poli, M, Zanichelli, P, Notari, B, Cherubini, A, Vinceti, M, Filippini, T, 2023. Residential exposure to magnetic fields from high-voltage power lines and risk of childhood leukemia. Environ. Res. 232, 116320. https://doi.org/10.1016/j.envres.2023.116320.

Malavolti, M, Malagoli, C, Wise, LA, Poli, M, Notari, B, Taddei, I, Fabbi, S, Teggi, S, Balboni, E, Pancaldi, A, Palazzi, G, Vinceti, M, Filippini, T, 2024. Residential exposure to magnetic fields from transformer stations and risk of childhood leukemia. Environ. Res. 245, 118043. https://doi.org/10.1016/j.envres.2023.118043.

Mandrioli, J, Michalke, B, Solovyev, N, Grill, P, Violi, F, Lunetta, C, Conte, A, Sansone, VA, Sabatelli, M, Vinceti, M, 2017. Elevated levels of selenium species in cerebrospinal fluid of amyotrophic lateral sclerosis patients with disease-associated gene mutations. Neurodegener. Dis. 17, 171–180. https://doi.org/10.1159/000460253.

Martinez-Morata, I, Sobel, M, Tellez-Plaza, M, Navas-Acien, A, Howe, CG, Sanchez, TR, 2023. A state-of-the-science review on metal biomarkers. Curr. Environ. Health Rep. 10, 215–249.

McDonald, CM, Suchdev, PS, Krebs, NF, Hess, SY, Wessells, KR, Ismaily, S, Rahman, S, Wieringa, FT, Williams, AM, Brown, KH, King, JC, 2020. Adjusting plasma or serum zinc concentrations for inflammation: biomarkers reflecting inflammation and nutritional determinants of anemia (BRINDA) project. Am. J. Clin. Nutr. 111, 927–937. https://doi.org/10.1093/ajcn/nqz304.

Mehdi WA, Yusof F, Mehde AA, Zainulabdeen JA, Raus RA, Abdulbari AS. Mehdi, W.A., et al., 2015. Effects of acute lymphoblastic leukemia on ceruloplasmin oxidase, copper and several markers of oxidative damage, in children. Asian Pac. J. Cancer Prev. 16, 5205–5210. doi: 10.7314/apjcp.2015.16.13.5205.

Metayer, C, Dahl, G, Wiemels, J, Miller, M, 2016. Childhood leukemia: a preventable disease. Pediatrics 138, S45–S55. https://doi.org/10.1542/peds.2015-4268H.

Metayer, C, Milne, E, Dockerty, JD, Clavel, J, Pombo-de-Oliveira, MS, Wesseling, C, Spector, LG, Schüz, J, Petridou, E, Ezzat, S, Armstrong, BK, Rudant, J, Koifman, S, Kaatsch, P, Moschovi, M, Rashed, WM, Selvin, S, McCauley, K, Hung, RJ, Kang, AY, Infante-Rivard, C, 2014. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a childhood leukemia international consortium study. Epidemiology 25, 811–822. https://doi.org/10.1097/EDE.0000000000000141.

Misu, H, Takamura, T, Takayama, H, Hayashi, H, Matsuzawa-Nagata, N, Kurita, S, Ishikura, K, Ando, H, Takeshita, Y, Ota, T, Sakurai, M, Yamashita, T, Mizukoshi, E, Yamashita, T, Honda, M, Miyamoto, K, Kubota, T, Kubota, N, Kadowaki, T, Kim, HJ, Lee, IK, Minokoshi, Y, Saito, Y, Takahashi, K, Yamada, Y, Takakura, N, Kaneko, S, 2010. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metab. 12, 483–495. https://doi.org/10.1016/j.cmet.2010.09.015.

Mita, Y, Nakayama, K, Inari, S, Nishito, Y, Yoshioka, Y, Sakai, N, Sotani, K, Nagamura, T, Kuzuhara, Y, Inagaki, K, Iwasaki, M, Misu, H, Ikegawa, M, Takamura, T, Noguchi, N, Saito, Y, 2017. Selenoprotein P-neutralizing antibodies improve insulin secretion and glucose sensitivity in type 2 diabetes mouse models. Nat. Commun. 8, 1658. https://doi.org/10.1038/s41467-017-01863-z.

Mocchegiani, E, Paolucci, P, Granchi, D, Cavallazzi, L, Santarelli, L, Fabris, N, 1994. Plasma zinc level and thymic hormone activity in young cancer patients. Blood 83, 749–757. https://doi.org/10.1182/blood.V83.3.749.749.

Nakayama, SF, Iwai-Shimada, M, Oguri, T, Isobe, T, Takeuchi, A, Kobayashi, Y, Michikawa, T, Yamazaki, S, Nitta, H, Kawamoto, T, 2019. Blood mercury, lead, cadmium, manganese and selenium levels in pregnant women and their determinants: the Japan environment and Children's study (JECS). J. Expo. Sci. Environ. Epidemiol. 29, 633–647. https://doi.org/10.1038/s41370-019-0139-0.

Nwogueze, BC, Ofili, MI, Uzuegbue, UE, Brotobor, D, Esievo, NJ, 2024. Modulatory role of welding fumes on serum zinc and copper levels and oxidative stress markers among welders: considering smoking as a possible implication. Toxicol. Rep. 12, 48–55. https://doi.org/10.1016/j.toxrep.2023.12.007.

Oo, SM, Misu, H, Saito, Y, Tanaka, M, Kato, S, Kita, Y, Takayama, H, Takeshita, Y, Kanamori, T, Nagano, T, Nakagen, M, Urabe, T, Matsuyama, N, Kaneko, S, Takamura, T, 2018. Serum selenoprotein P, but not selenium, predicts future hyperglycemia in a general Japanese population. Sci. Rep. 8, 16727. https://doi.org/10.1038/s41598-018-35067-2.

Oo, SM, Oo, HK, Takayama, H, Ishii, KA, Takeshita, Y, Goto, H, Nakano, Y, Kohno, S, Takahashi, C, Nakamura, H, Saito, Y, Matsushita, M, Okamatsu-Ogura, Y, Saito, M, Takamura, T, 2022. Selenoprotein P-mediated reductive stress impairs cold-induced thermogenesis in brown fat. Cell Rep. 38, 110566. https://doi.org/10.1016/j.celrep.2022.110566.

Rasin, P, V, AA, Basheer, S, Haribabu, J, Santibanez, JF, Garrote, CA, Arulraj, A, Mangalaraja, RV, 2025. Exposure to cadmium and its impacts on human health: a short review. J. Hazard. Mater. Adv. 17, 100608. doi: 10.1016/j.hazadv.2025.100608.

Rodriguez-Gonzalez, H, Arias, A, Poyatos, E, de Los Santos, MM, Minguez, B, Meavilla, S, Garcia-Volpe, C, Loverdos, I, Molera, C, Casado, M, Ormazabal, A, Perera-Lluna, A, Artuch, R, 2026. Proof of concept for an age- and inflammation-adjusted model for the establishment of pediatric serum copper reference intervals. Clin. Nutr. 58, 106586. https://doi.org/10.1016/j.clnu.2026.106586.

Sáez, C, Sánchez, A, Dualde, P, Vento, M, Aguirre, MÁ, Canals, A, Coscollà, C, 2025. Infant exposure and risk assessment to metals through breast milk from Spanish lactating mothers. Environ. Sci. Pollut. Res. Int. 32, 18832–18853. https://doi.org/10.1007/s11356-025-36770-0.

Saito, Y, 2020. Selenoprotein P as an in vivo redox regulator: disorders related to its deficiency and excess. J. Clin. Biochem. Nutr. 66, 1–7. https://doi.org/10.3164/jcbn.19-31.

Salnikow, K, 2021. Role of iron in cancer. Semin. Cancer Biol. 76, 189–194. https://doi.org/10.1016/j.semcancer.2021.04.001.

Schramel, P, Klose, BJ, Hasse, S, 1982. Efficiency of ICP emission spectroscopy for the determination of trace elements in bio-medical and environmental samples. Fresenius' Z. für Anal. Chem. 310, 209–216. https://doi.org/10.1007/BF00484034.

Schraw, JM, Bailey, HD, Bonaventure, A, Mora, AM, Roman, E, Mueller, BA, Clavel, J, Petridou, ET, Karalexi, M, Ntzani, E, Ezzat, S, Rashed, WM, Marcotte, EL, Spector, LG, Metayer, C, Kang, AY, Magnani, C, Miligi, L, Dockerty, JD, Mejía-Aranguré, JM, Nuñez-Enriquez, JC, Infante-Rivard, C, Milne, E, Scheurer, ME, 2022. Infant feeding practices and childhood acute leukemia: findings from the childhood cancer & leukemia international consortium. Int. J. Cancer 151, 1013–1023. https://doi.org/10.1002/ijc.34062.

Sgarbieri, UR, Fisberg, M, Tone, LG, 1999. Nutritional assessment and serum zinc and copper concentration in leukemic children. Sao Paulo Med. J. 117, 13–18. https://doi.org/10.1590/s1516-31801999000100003.

Sgarbieri, UR, Fisberg, M, Tone, LG, Latorre Mdo, R, 2006. Nutritional assessment and serum zinc and copper concentration among children with acute lymphocytic leukemia: a longitudinal study. Sao Paulo Med. J. 124, 316–320. https://doi.org/10.1590/s1516-31802006000600003.

Sherief, LM, Abdelkhalek, ER, Gharieb, AF, Sherbiny, HS, Usef, DM, Almalky, MAA, Kamal, NM, Salama, MA, Gohar, W, 2015. Cadmium status among pediatric cancer patients in Egypt. Medicine (Baltim.) 94, e740. https://doi.org/10.1097/MD.0000000000000740.

Shigeta, K, Sato, K, Furuta, N, 2007. Determination of selenoprotein P in submicrolitre samples of human plasma using micro-affinity chromatography coupled with low flow ICP-MS. J. Anal. At. Spectrom. 22, 911–916. https://doi.org/10.1039/B701206C.

Smith-Bindman, R, Alber, SA, Kwan, ML, Pequeno, P, Bolch, WE, Bowles, EJA, Greenlee, RT, Stout, NK, Weinmann, S, Moy, LM, Stewart, C, Francisco, M, Kofler, C, Duncan, Ducore, J, Mahendra, M, Pole, JD, Miglioretti, DL, 2025. Medical imaging and pediatric and adolescent hematologic cancer risk. N. Engl. J. Med. 393, 1269–1278. https://doi.org/10.1056/NEJMoa2502098.

Snoj Tratnik, J, Kocman, D, Horvat, M, Andersson, AM, Juul, A, Jacobsen, E, Ólafsdóttir, K, Klanova, J, Andryskova, L, Janasik, B, Wasowicz, W, Janev Holcer, N, Namorado, S, Coelho, I, Rambaud, L, Riou, M, Van Nieuwenhuyse, A, Appenzeller, B, Kolossa-Gehring, M, Weber, T, Esteban-López, M, Castaño, A, Gilles, L, Rodriguez Marti, L, Schoeters, G, Sepai, O, Govarts, E, 2022. Cadmium exposure in adults across Europe: results from the HBM4EU aligned studies survey 2014-2020. Int. J. Hyg. Environ. Health 246, 114050. doi: 10.1016/j.ijheh.2022.114050.

Soliman, HMH, Hassan, WY, Mostafa, M, Gomaa, MK, Soliman Jnr, MH, Hussein, MF, 2026. Association between petroleum compounds exposure and risk of childhood leukemia: a systematic review. Blood Lymphat. Cancer 16, 571340. https://doi.org/10.2147/BLCTT.S571340.

Solovyev, N, Berthele, A, Michalke, B, 2013. Selenium speciation in paired serum and cerebrospinal fluid samples. Anal. Bioanal. Chem. 405, 1875–1884. https://doi.org/10.1007/s00216-012-6294-y.

Torti, SV, Tesfay, L, Torti, FM, 2025. Iron and cancer. Adv. Exp. Med. Biol. 1480, 271–289. https://doi.org/10.1007/978-3-031-92033-2_18.

Ullah, MI, Manni, E, Shakil, M, Hussain, S, Awan, AN, Hussain, S, Alameen, AAM, Farhana, A, Atif, M, Naveed, MA, 2025. Association of serum copper, zinc and copper to zinc ratio in patients with acute myeloid leukemia. Sci. Rep. 15, 34091. https://doi.org/10.1038/s41598-025-14812-4.

Urbano, T., et al., 2025a. Biomarkers of total selenium and selenium species in paired serum and cerebrospinal fluid samples. J. Trace Elem. Med. Biol. 92, 127765.

Urbano, T, Filippini, T, Lasagni, D, De Luca, T, Grill, P, Sucato, S, Polledri, E, Djeukeu Noumbi, G, Malavolti, M, Santachiara, A, Pertinhez, TA, Baricchi, R, Fustinoni, S, Michalke, B, Vinceti, M, 2021. Association of urinary and dietary selenium and of serum selenium species with serum alanine aminotransferase in a healthy Italian population. Antioxidants 10, 1516. https://doi.org/10.3390/antiox10101516.

Urbano, T, Filippini, T, Wise, LA, Sucato, S, Polledri, E, Malavolti, M, Fustinoni, S, Michalke, B, Vinceti, M, 2023. Selenium exposure and urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine: major effects of chemical species and sex. Sci. Total Environ. 870, 161584. https://doi.org/10.1016/j.scitotenv.2023.161584.

Urbano, T., et al., 2025b. Iron species in cerebrospinal fluid and dementia risk in subjects with mild cognitive impairment: a cohort study. Neurotoxicology.

Vacchi-Suzzi, C, Kruse, D, Harrington, J, Levine, K, Meliker, JR, 2016. Is urinary cadmium a biomarker of long-term exposure in humans? A review. Curr. Environ. Health Rep. 3, 450–458. https://doi.org/10.1007/s40572-016-0107-y.

Venturelli, F, Filippini, T, Ferrari, A, Paduano, S, Marchesi, I, Casali, ME, Righi, E, Bargellini, A, 2025. Risk assessment of trace elements in human breastmilk in a northern Italy population. J. Trace Elem. Med. Biol. 89, 127641. https://doi.org/10.1016/j.jtemb.2025.127641.

Vinceti, M, Ballotari, P, Steinmaus, C, Malagoli, C, Luberto, F, Malavolti, M, Giorgi Rossi, P, 2016. Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water. Environ. Res. 150, 348–356. https://doi.org/10.1016/j.envres.2016.06.009.

Vinceti, M., Chiari, A, Eichmüller, M, Rothman, KJ, Filippini, T, Malagoli, C, Weuve, J, Tondelli, M, Zamboni, G, Nichelli, PF, Michalke, B, 2017a. A selenium species in cerebrospinal fluid predicts conversion to Alzheimer's dementia in persons with mild cognitive impairment. Alzheimers Res. Ther. 9, 100. https://doi.org/10.1186/s13195-017-0323-1.

Vinceti, M., Filippini, T, Cilloni, S, Bargellini, A, Vergoni, AV, Tsatsakis, A, Ferrante, M, 2017b. Health risk assessment of environmental selenium: emerging evidence and challenges (Review). Mol. Med. Rep. 15, 3323–3335. https://doi.org/10.3892/mmr.2017.637.

Vinceti, M, Filippini, T, Jablonska, E, Saito, Y, Wise, LA, 2022. Safety of selenium exposure and limitations of selenoprotein maximization: molecular and epidemiologic perspectives. Environ. Res. 211, 113092. https://doi.org/10.1016/j.envres.2022.113092.

Vinceti, M., Filippini, T, Rothman, KJ, 2018a. Selenium exposure and the risk of type 2 diabetes: a systematic review and meta-analysis. Eur. J. Epidemiol. 33, 789–810. https://doi.org/10.1007/s10654-018-0422-8.

Vinceti, M., Filippini, T, Wise, LA, 2018b. Environmental selenium and human health: an update. Curr. Environ. Health Rep. 5, 464–485. https://doi.org/10.1007/s40572-018-0213-0.

Vinceti, M, Filippini, T, Wise, LA, Rothman, KJ, 2021. A systematic review and dose-response meta-analysis of exposure to environmental selenium and the risk of type 2 diabetes in nonexperimental studies. Environ. Res. 197, 111210. https://doi.org/10.1016/j.envres.2021.111210.

Vinceti, M, Grill, P, Malagoli, C, Filippini, T, Storani, S, Malavolti, M, Michalke, B, 2015. Selenium speciation in human serum and its implications for epidemiologic research: a cross-sectional study. J. Trace Elem. Med. Biol. 31, 1–10. https://doi.org/10.1016/j.jtemb.2015.02.001.

Vinceti, M, Rothman, KJ, Crespi, CM, Sterni, A, Cherubini, A, Guerra, L, Maffeis, G, Ferretti, E, Fabbi, S, Teggi, S, Consonni, D, De Girolamo, G, Meggiato, A, Palazzi, G, Paolucci, P, Malagoli, C, 2012. Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: a case-control study in an Italian population. Eur. J. Epidemiol. 27, 781–790. https://doi.org/10.1007/s10654-012-9727-1.

Vinceti, M, Urbano, T, Chiari, A, Filippini, T, Wise, LA, Tondelli, M, Michalke, B, Shimizu, M, Saito, Y, 2023. Selenoprotein P concentrations and risk of progression from mild cognitive impairment to dementia. Sci. Rep. 13, 8792. https://doi.org/10.1038/s41598-023-36084-6.

Vinceti, M, Urbano, T, Filippini, T, Bedin, R, Simonini, C, Sorarù, G, Trojsi, F, Michalke, B, Mandrioli, J, 2025. Changes in cerebrospinal fluid concentrations of selenium species induced by tofersen administration in subjects with amyotrophic lateral sclerosis carrying SOD1 gene mutations. Biol. Trace Elem. Res. 203, 2355–2364.doi. https://doi.org/10.1007/s12011-024-04311-4.

Vinceti, M., Vicentini, M, Wise, LA, Sacchettini, C, Malagoli, C, Ballotari, P, Filippini, T, Malavolti, M, Giorgi Rossi, P, 2018c. Cancer incidence following long-term consumption of drinking water with high inorganic selenium content. Sci. Total Environ. 635, 390–396. https://doi.org/10.1016/j.scitotenv.2018.04.097.

Violi, F, Solovyev, N, Vinceti, M, Mandrioli, J, Lucio, M, Michalke, B, 2020. The study of levels from redox-active elements in cerebrospinal fluid of amyotrophic lateral

sclerosis patients carrying disease-related gene mutations shows potential copper dyshomeostasis. Metallomics 12, 668–681. https://doi.org/10.1039/d0mt00051e.
Wang, F, Lv, H, Zhao, B, Zhou, L, Wang, S, Luo, J, Liu, J, Shang, P, 2019. Iron and leukemia: new insights for future treatments. J. Exp. Clin. Cancer Res. 38, 406. https://doi.org/10.1186/s13046-019-1397-3.
Wang, J., Wu, Y., Chen, Y. -J., Li, H. -Y., Fu, Q., 2010. Changes of some trace elements and nutritional proteins in children with acute lymphoblastic leukemia and acute myeloid leukemia at stages of onset. Chin. J. Clin. 18, 19–23. https://doi.org/10.3760/cma.j.issn.1674-635X.2010.01.006.
Wang, M, Bi, Y, Fan, Y, Fu, X, Jin, Y, 2025. Global incidence of childhood cancer by subtype in 2022: a population-based registry study. eClinicalMedicine 89, 103571. https://doi.org/10.1016/j.eclinm.2025.103571.
Whitehead, TP, Ward, MH, Colt, JS, Dahl, G, Ducore, J, Reinier, K, Gunier, RB, Katharine Hammond, S, Rappaport, SM, Metayer, C, 2015. Dust metal loadings and the risk of childhood acute lymphoblastic leukemia. J. Expo. Sci. Environ. Epidemiol. 25, 593–598. https://doi.org/10.1038/jes.2015.9.
Yao, G, Wang, Z, Xie, R, Zhanghuang, C, Yan, B, 2024. Trace element zinc metabolism and its relation to tumors. Front. Endocrinol. 15, 1457943. https://doi.org/10.3389/fendo.2024.1457943.