Food and Chemical Toxicology 215 (2026) 116231

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Non-linear hair-to-blood mercury partitioning in a chronically exposed Amazonian population

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ARTICLE INFO

Handling Editor: Professor Matthew Wright

Keywords:
Mercury
Hair-to-blood ratio
Human biomonitoring
Amazon
Selenium

ABSTRACT

Human biomonitoring of mercury (Hg) exposure commonly relies on blood and hair measurements, often assuming a stable conversion ratio between these matrices. However, this assumption neglects dynamic toxicokinetic processes governing Hg distribution and elimination. Here, we characterized the distribution, determinants, and toxicokinetic implications of the hair-to-blood total Hg ratio in 453 individuals from Amazonian riverine communities chronically exposed to methylmercury (MeHg). Total Hg (THg) was determined in blood and hair, Hg speciation in hair by LC-ICP-MS, and selenium (Se) in blood was measured by ICP-MS. Model-based estimates of MeHg intake and Hg excretion were derived, and linear, non-linear, and multivariable analyses were applied. Blood and hair THg were strongly correlated ($R = 0.86$, $p < 0.0001$), confirming hair as a robust biomarker of chronic exposure. However, the hair-to-blood ratio showed high inter-individual variability (median 303; range 73.6–2132) and a significant inverse association with blood THg ($\beta = -0.394$, $p < 0.001$), indicating non-linear partitioning. Blood Se levels were elevated and positively associated with the ratio ($\beta = 1.081$, $p < 0.001$). Estimated MeHg intake exceeded the USEPA reference dose by over tenfold. These findings demonstrate that the hair-to-blood Hg ratio is a dynamic biomarker influenced by exposure intensity and potentially by Se status.

1. Introduction

Mercury (Hg) exposure remains a major global public health concern, particularly among populations with high fish consumption. This is largely due to methylmercury (MeHg), its organic form, which is widely distributed in the environment, bioaccumulates in aquatic food webs, and represents the main route of human exposure through fish consumption (Barrera-Oro, 2026; Córdoba-Tovar et al., 2025; Esplugas et al., 2025; Gutiérrez-Mosquera et al., 2021; Soares et al., 2026; Wesolowska et al., 2024). In exposed populations, the assessment of internal Hg burden primarily relies on measurements in whole blood and hair, which provide complementary information on exposure dynamics. Blood Hg concentrations reflect circulating levels and are generally interpreted as indicators of recent or ongoing exposure. In contrast, hair Hg represents an integrated biomarker of exposure over time, as MeHg is efficiently incorporated into the hair shaft during keratin synthesis through its strong affinity for sulfhydryl groups (Branco et al., 2017; Packull-McCormick et al., 2022; Ruggieri et al., 2017). Because hair grows at a relatively constant rate, proximal hair segments provide a retrospective record of systemic Hg concentrations during the period of hair formation (LeBeau et al., 2011; Nuttall, 2006).

The quantitative relationship between Hg concentrations in blood and hair has been widely used in exposure assessment and risk evaluation, where the hair-to-blood Hg ratio serves as a conversion factor to harmonize biomarker measurements across matrices (Bartell et al., 2000; Noisel et al., 2011; Phelps et al., 1980). Regulatory agencies,

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https://doi.org/10.1016/j.fct.2026.116231
Received 17 April 2026; Received in revised form 22 May 2026; Accepted 19 June 2026
Available online 20 June 2026
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including the World Health Organization, have adopted a default conversion ratio of approximately 250:1 to translate hair Hg concentrations into equivalent blood levels and to interpret exposure relative to established toxicological reference values (WHO, 1990). This assumption has been extensively applied in epidemiological studies and regulatory frameworks, implicitly presuming a stable proportional relationship between circulating Hg and its incorporation into keratinized tissues, despite limited empirical validation across different exposure scenarios. However, Hg partitioning between blood and hair reflects complex and dynamic toxicokinetic processes involving systemic distribution, protein binding, intracellular sequestration, tissue-specific affinities, and elimination pathways (Bartell et al., 2000; Denaro et al., 2025; Noisel et al., 2011), which are unlikely to remain constant across individuals or exposure levels. The incorporation of Hg into the growing hair shaft depends not only on circulating Hg concentrations but also on biological and metabolic factors that regulate Hg transport and tissue distribution. These processes may vary substantially across individuals depending on exposure intensity, nutritional status, metabolic capacity, and physiological variability, potentially leading to substantial inter-individual differences in Hg partitioning (LeBeau et al., 2011; Nuttall, 2006; Queiroz et al., 2025; Robledo-Moreno et al., 2025). Among potential modifiers, selenium (Se) is of particular interest due to its well-established interactions with Hg, which may influence Hg distribution, retention, and elimination. Hair Hg remains one of the most robust and widely accepted biomarkers of long-term MeHg exposure. Accordingly, the hair-to-blood Hg ratio should be considered a dynamic toxicokinetic parameter rather than a fixed conversion factor.

A more comprehensive characterization of the variability and determinants of Hg partitioning between blood and hair is essential to improve biomarker interpretation and refine exposure assessment. However, few studies have systematically evaluated how this ratio behaves across a wide range of exposure levels in real-world populations (Bartell et al., 2000; Noisel et al., 2011; Denaro et al., 2025). Identifying biological modifiers of Hg distribution may reduce exposure misclassification and strengthen risk evaluation in environmentally exposed populations.

Therefore, the present study aimed to critically evaluate the validity of the hair-to-blood Hg ratio as a conversion factor by: (i) characterizing its distribution in a chronically exposed population, (ii) identifying its biological and toxicokinetic determinants, and (iii) assessing whether Hg partitioning follows a linear or non-linear relationship across exposure levels.

2. Materials and methods

2.1. Study design and population

The present investigation is based on data derived from a comprehensive interdisciplinary research program aimed at characterizing Hg environmental dynamics, sources of exposure, and related health outcomes in populations residing in the Tapajós River basin, Brazilian Amazon (state of Pará, Brazil). A cross-sectional field study was conducted in 13 communities in the region, enrolling 453 individuals aged 15–87 years.

Participants were recruited based on residence in the study communities. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (CEP/FCFRP-71, approval date: 2006; CAAE: 77196924.5.0000.5403, approval date: March 22, 2024).

All procedures were performed in compliance with applicable Brazilian laws and institutional guidelines. The privacy rights of all participants were strictly protected throughout the study. Written informed consent was obtained from all participants prior to enrollment, including consent for biological sample collection, storage, and future research use.

2.2. Sample collection

Peripheral blood samples were collected using trace element-free vacuum tubes (3 mL) containing sodium heparin as an anticoagulant (BD Vacutainer®), following standardized procedures to minimize contamination. Sample collection was performed without prior fasting.

Immediately following collection, samples were aliquoted into 2 mL microtubes and stored at −20 °C aboard the research boat. Subsequently, they were then transported on dry ice to the Laboratory of Analytical and Systems Toxicology (ASTox, FCFRP-USP, Brazil), where they were stored at −80 °C until analysis.

On the day of peripheral blood sampling, hair samples were obtained from the occipital region near the scalp, cut as close as possible to the scalp to ensure temporal alignment with recent exposure. The strands were fixed at the proximal end to preserve orientation and kept in individually labeled Ziploc bags. Before analysis, only the proximal 1 cm hair segment, corresponding approximately to one month of hair growth, was separated and subjected to a cleaning procedure. An aliquot of 20 mg of this segment was then used for trace element analysis.

2.3. Sample preparation and determination of exposure levels

Peripheral blood concentrations of Hg and Se were quantified by inductively coupled plasma mass spectrometry (ICP-MS; PerkinElmer DRC II, USA) following the procedure described by Batista et al. (2009), using matrix-matching calibration in triplicate. For matrix matching a base pool of blood derived from undosed goats was used. Prior to analysis, blood samples were diluted 1:50 by mixing 40 μL of whole blood with 1.96 mL of 0.5% (v/v) HNO_3 and 0.005% (v/v) Triton X-100.

Hair samples were prepared according to the protocol described by de Souza et al. (2010). For Hg speciation analysis in hair, 50 mg aliquots were subjected to ultrasonic extraction using a solution containing 0.10% (v/v) HCl, 0.05% (m/v) L-cysteine, and 0.10% (v/v) 2-mercaptoethanol (5 mL for CRM IAEA-086). The resulting extracts were filtered through 0.20 μm nylon membranes. All extractions were performed in triplicate, including procedural blanks. Hg species were separated and quantified by liquid chromatography coupled to inductively coupled plasma mass spectrometry (LC-ICP-MS; Elan DRC II, PerkinElmer, USA), using external calibration based on peak height (de Souza et al., 2010). Total Hg concentrations in hair were also determined by ICP-MS following the same analytical protocol.

All solutions were prepared in a clean laboratory under a laminar-flow hood providing a class 100 environment. Ultra-pure deionized water (18.2 MΩ cm) used for sample and solution preparation was obtained from a Milli-Q purification system (Millipore RiOs-DI™, Bedford, MA, USA). All reagents were of analytical grade, except for HNO_3 (Merck, Germany), which was further purified by sub-boiling distillation in quartz stills prior to use.

2.4. Data validation

2.4.1. Whole blood

A Standard Reference Material (SRM; NIST 966 – Toxic Metals in Bovine Blood, Level 2) obtained from the National Institute of Standards and Technology (NIST, USA), as well as a secondary reference material provided through the external quality assessment scheme for trace elements operated by the Institut National de Santé Publique du Québec, Canada (QMEQAS 07B03), were analyzed after every 20 routine samples. Percentage recoveries ranged from 91 to 102% for Hg in the SRM and from 93 to 99% for Se in the QMEQAS reference material. Calibration curves for both elements covered the concentration range of 0–40 μg/L. Method detection limits (MDLs), calculated as three times the standard deviation (3σ) based on the analysis of 20 blank blood

samples, were 0.12 μg/L for Hg and 0.34 μg/L for Se.

2.4.2. Hair

A certified reference material (CRM) for human hair (IAEA-086), obtained from the International Atomic Energy Agency (IAEA, Vienna, Austria), was analyzed after every 20 routine samples. A paired *t*-test indicated no statistically significant differences at the 95% confidence level between certified and measured concentrations for both total Hg and MeHg, confirming the accuracy of the analytical results. Typical within-day precision was consistently below 7%, while between-day precision was lower than 9% (expressed as relative standard deviation, RSD). Method detection limits (3σ, n = 20), were 9 ng/g for MeHg and 11 ng/g for inorganic Hg.

2.5. Data analysis

Descriptive analyses were performed to provide a comprehensive characterization of the sociodemographic profile and dietary habits of the study population, as well as to describe Hg partitioning among biological compartments and to theoretically estimated daily Hg excretion, excretion rates (%), and estimated daily Hg intake. Results are reported as median, 25th, 75th, and 95th percentiles, and minimum–maximum values, depending on data distribution. The distribution of the hair-to-blood Hg ratio was visually assessed using histograms, and its variation across different blood Se levels was further explored through box plots stratified by Se quartiles. Several approaches have been proposed to estimate MeHg intake and excretion in humans, including physiologically based pharmacokinetic models and biomonitoring-based approaches using different biological matrices. In the present study, estimates of daily Hg excretion and the proportion of total body burden eliminated per day were derived from the toxicokinetic framework proposed by Magos and Clarkson (2008). These values were not directly measured, but were theoretically estimated by considering Hg incorporated into the growing hair shaft as a proxy of Hg elimination from the body. Daily MeHg intake from food consumption was calculated according to Eq. (1).

$$d = \frac{C^{*}b^{*}V}{A^{*}f^{*}BW} \quad \text{(Eq. 1)}$$

d = dose (μg/kg body weight per day), C=Hg concentration in whole blood (μg/L), b = elimination rate constant (0.014 per day), V = blood volume (9% of body weight), A = fraction of the dose absorbed (0.95), f = the absorbed fraction distributed to the blood (0.05) and BW = body weight (kg) (WHO, 2004).

Simple linear regression analyses were initially applied to evaluate associations between Hg concentrations measured in different biological matrices, including blood THg, hair THg, hair MeHg, hair IHg, blood Se concentrations, the hair-to-blood THg ratio, and the theoretically estimated daily Hg excretion via hair. Pearson correlation coefficients (R), regression coefficients (β), and corresponding p-values were calculated.

Model assumptions, including linearity, homoscedasticity, independence, and normality of residuals, were evaluated prior to the interpretation of regression outputs through residual-versus-fitted plots and Q–Q plots. Extreme observations were inspected for potential analytical, transcription, or processing errors and were retained when considered biologically plausible.

Additionally, non-parametric LOESS (locally estimated scatterplot smoothing) regression was employed to explore potential non-linear relationships between blood THg concentrations and the hair-to-blood THg ratio. The smoothing parameter (span) was selected after iterative visual inspection of curve stability and overfitting behavior to optimize local fit while preserving global trend interpretation.

Two separate multiple linear regression models were constructed using the following dependent variables: (i) the hair-to-blood THg ratio and (ii) the theoretically estimated daily Hg excretion via hair as dependent variables. Independent variables considered for inclusion were age, sex, education, blood THg, plasma THg, hair THg, hair MeHg, and hair IHg concentration, blood Se concentration, fish intake frequency, Brazil nut consumption, and community-related variables.

Predictor variables were selected based on biological plausibility and/or statistical significance in univariate analyses. Interaction terms were evaluated when biologically justified. Prior to model inclusion, multicollinearity among predictors was assessed using variance inflation factors (VIF). Variables presenting evidence of excessive collinearity were excluded from the final models. Multiple linear regression models followed the general structure described in Eq. (2):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n + \varepsilon \quad \text{(Eq. 2)}$$

Where Y represents the dependent outcome variable (hair-to-blood THg ratio or estimated daily Hg excretion), β_0 is the intercept, β_n are regression coefficients, X_n are predictor variables, and ε represents the residual error term.

Because concentration data showed non-normal distributions, logarithmic transformation was applied before regression analyses when appropriate. The adequacy of normalization was evaluated using the Shapiro–Wilk test in combination with graphical inspection of histograms and Q–Q plots.

Statistical significance was set at $p \leq 0.05$. Where appropriate, regression results are reported as β coefficients with corresponding 95% confidence intervals. All statistical analyses were performed using SPSS Statistics version 23, Microsoft Excel 365®, and R software (version 4.5.2).

3. Results and discussion

3.1. Characterization of the study population

The sociodemographic characteristics and lifestyle habits of the study participants are summarized in Table 1. A total of 453 participants were enrolled in this study, including adults and older individuals with a median age of 40 (range: 15 - 87 years). Most participants were aged between 18 and 59 years, with the highest percentage in the 18 - 29 age group (26.3%), followed by those aged 30 - 39 (19.6%) and 40 - 49 years (17.9%).

The median body mass index (BMI) was 23.9 (range: 16.1 - 41.5) kg/m^2. According to the World Health Organization (WHO, 2010) and the U.S. Centers for Disease Control and Prevention (CDCC. for D.C. and P, 2024) criteria, the median BMI value indicates a predominantly eutrophic population; however, the wide range reflects substantial inter-individual variability, including individuals classified as underweight, overweight, and obese.

Total mercury (THg) concentrations exhibited marked variability across biological matrices. Median total Hg concentrations were 41.05 (p25th – 75th: 23.3 – 69.9) μg/L in blood and 10.93 (p25th – 75th: 6.4 – 18.9) μg/g in hair. Median concentrations of MeHg and inorganic Hg (IHg) in hair were 9.47 (p25th – 75th: 5.6 – 16.07) μg/g and 1.62 (p25th – 75th: 0.9 – 2.7) μg/g, respectively. Both values markedly exceeded internationally recognized reference limits. For blood, the median concentration observed was substantially higher than the USEPA guideline of 5.8 μg/L, established as a level protective for the general population over a lifetime, which was exceeded by 97.6% of participants, and the WHO reference value of 10 μg/L considered the upper limit of normal concentration and which was exceeded by 93.2% of participants. In addition, this concentration exceeded the 95th percentile for total blood Hg reported for the general population by the U.S. Centers for Disease Control and Prevention (CDC) NHANES 2011–2016 (P95 = 4.25 μg/L; 95% CI: 3.44 – 4.94 μg/L). Similarly, for hair, the median concentration observed exceeded the WHO-defined normal level (2.0 μg/g), the threshold level (5.0 μg/g), and the no observed adverse effect level (NOAEL) of 10 μg/g associated with fetal neurotoxicity (CDC, N.C. for E.

Table 1
Sociodemographic profile and dietary habits of riverine communities in the Middle Tapajós River, Brazilian Amazon.

Characteristics	Median ($p25^{th}$ – 75^{th})	Range
Age (years)	40 (28 – 54)	15 - 87
BMI (kg/m^2)	23.92 (21.74 – 26.7)	16.1 - 41.5
THg blood (μg/L)	41.05 (23.3 – 69.9)	1.70 - 289
THg hair (μg/g)	10.9 (6.40 – 18.9)	0.97 - 62.4
MeHg hair (μg/g)	9.47 (5.60 – 16.07)	0.91 - 56.0
IHg hair (μg/g)	1.62 (0.90 – 2.70)	0.04 - 8.03
Se blood (μg/L)	225 (183 – 303)	103 - 1500
		n (%)
Age categories	15-17	17 (3.8)
	18-29	119 (26.3)
	30-39	89 (19.6)
	40-49	81 (17.9)
	50-59	72 (15.9)
	60-69	49 (10.8)
	70-79	17 (3.8)
	80-87	9 (2.0)
Sex	Females	232 (51.2)
	Males	221 (48.8)
Education	Illiterate	38 (8.4)
	Elementary school	331 (73.1)
	High school	74 (16.3)
	Higher education	8 (1.8)
	Not indicated	2 (0.4)
Fish intake frequency (servings per week)	Not consume	0
	Low	63 (13.9)
	Medium	349 (77.0)
	High	0
	Not indicated	41 (9.1)
Brazil nuts consumption (units per week)	Not consume	440 (97.1)
	Low	1 (0.2)
	Medium	3 (0.7)
	High	7 (1.5)
	Not indicated	2 (0.4)

H.. D. of L.S, 2019; NRC, 2000; USEPAU.S.E.P.A, 2000; WHO Department of Food Safety and UNEP DTIE Chemicals Branch, 2008). Blood Se concentrations also showed wide dispersion, with a median of 225.2 ($p25^{th}$ – 75^{th}: 182.5 – 303.2) μg/L. This median concentration approximated the 95th percentile (P95 = 233 μg/L; 95% CI: 227 - 242) for total blood Se reported for the general population by the CDC/NHANES 2011–2016, indicating elevated Se status in a substantial proportion of the study population (CDC, N.C. for E.H.. D. of L.S, 2019).

The sex distribution was balanced, with females representing 51.2% of the participants and males 48.8%. Educational attainment was predominantly elementary school (73.1%), followed by high school education (16.3%), while smaller proportions of participants were illiterate (8.4%) or had completed higher education (1.8%).

Fish consumption was highly prevalent, with most participants reporting a medium intake frequency (77.0%) and 13.9% reporting low intake; no participants reported high fish consumption. Brazil nut consumption was uncommon, with 97.1% of participants reporting no intake, and only a small fraction reporting low, medium, or high consumption. The natural availability of Brazil nuts is highly seasonal, occurring mainly at the beginning of the year when mature fruits fall from the trees (typically between January and March). In subsequent months, such as May and July, fresh fruits are no longer available in the environment, which markedly reduces local consumption (Jansen et al., 2021; Martins et al., 2018; Prance, 2003).

Low fish intake was defined as the consumption of one or fewer portions per week; moderate intake as two to four portions per week; and high intake as five or more portions per week. Similarly, for Brazil nuts consumption, low intake was defined as up to one unit per week, moderate intake as two to four units per week, and high intake as more than five units per week.

3.2. Hair-to-blood Hg ratio: distribution and international comparison

As shown in Table 2, the **median hair Hg/blood Hg ratio** in the Tapajós River population (n = 453; 15–87 years) median was 303, with a wide range (74–2132). The interquartile range (246–385) and the elevated 95th percentile (544) indicate marked inter-individual variability and a right-skewed distribution, suggesting heterogeneous Hg partitioning between circulating and keratin compartments. This distribution pattern can also be visually confirmed by the histogram (Fig. 1), which illustrates the asymmetry and the presence of higher extreme values. The median ratio (303) exceeded the value of 250 proposed by the WHO as a reference conversion factor between hair and blood Hg concentrations, although the skewed distribution indicates that median-based comparisons may be more appropriate (WHO, 1990).

Hair Hg was predominantly MeHg, with a median MeHg/THg ratio of 0.85 (IQR: 0.83–0.89), whereas IHg accounted for a minor fraction, confirming that hair THg reflects MeHg exposure in this fish-dependent population (Table 2). Se-related ratios, particularly hair THg/blood Se (63.4 ± 55.4) and hair MeHg/blood Se (54.3 ± 48.0), showed broad dispersion, indicating variability in the balance between Hg burden and Se status.

When compared with other populations (Table 3), the mean hair Hg/blood Hg ratio in the Tapajós population fell within the upper range reported for fish-consuming communities. Similar values were observed in the Persian Gulf (335 ± 104) (Okati and Esmaili-sari, 2018) and Japan (351 ± 54) (Yaginuma-Sakurai et al., 2012), whereas lower means were reported in Canada (293) (Singh et al., 2023), South Korea (261) (Kim et al., 2013), and in United States (234 ± 15) (McDowell et al., 2004). Higher ratios have been described in Sweden (366) (Berglund et al., 2005) and in children from the Faroe Islands (up to 370) (Budtz-Jørgensen et al., 2004), while lactating women in Sweden presented substantially lower values (median 131) (Oskarsson et al., 1996), highlighting the influence of age and physiological status.

The distribution of hair-to-blood Hg ratios across Se quartiles remained relatively stable, with median values showing a slight downward trend as Se concentrations increased (Fig. 2). Interquartile ranges were comparable across groups; however, increased dispersion was observed in the highest Se quartile (Q4), including an extreme value (>2000). This pattern suggests that Se may contribute to variability in Hg partitioning in some individuals, although its influence on central tendency appears limited within the observed range.

Overall, the observed heterogeneity likely reflects differences in exposure intensity, seasonal and dietary patterns, toxicokinetic factors, and Se status. Importantly, comparisons with populations characterized by lower Hg exposure levels, such as general populations from the United States, Sweden, and Slovenia, suggest that the hair-to-blood Hg relationship may vary according to exposure intensity and dietary context. In lower-exposure settings, Hg partitioning tends to present narrower distributions and lower variability, whereas highly exposed Amazonian populations exhibit broader and more heterogeneous ratios. These differences reinforce that the hair-to-blood Hg ratio is context-

Table 2
Summary of Hg species and Se concentration ratios in hair and blood.

Ratio	Min.	25^{th}	50^{th}	75^{th}	95^{th}	Max.
THg hair/THg blood	73	246	303	385	544	2132
THg blood/Se blood	0.005	0.091	0.16	0.27	0.55	1.47
THg hair/Se blood	4.27	26.6	46.5	82	186	338
MeHg hair/THg hair	0.72	0.83	0.85	0.89	0.93	1.00
IHg hair/THg hair	0.033	0.11	0.15	0.17	0.22	0.27
MeHg hair/Se blood	3.9	23	39	69	168	303

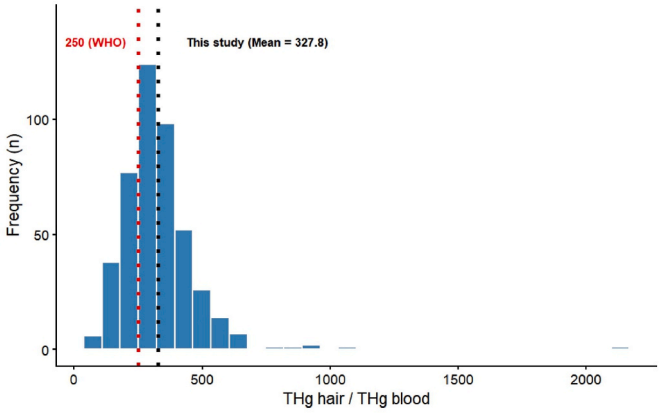

Fig. 1. Frequency distribution of the hair-to-blood THg ratio in the study population.

Table 3
Summary of hair-to-blood Hg ratios across different study populations and geographical locations.

Location	n	Study population	Ratio Hg hair/Hg blood mean ± S. D. (range)	Reference
Tapajós River, Brazil	453	Mixed-age riverine population (15 - 87 years old)	328 ± 154 (73.6 - 2132)	This study
Atlantic provinces, Canada	1168	Mixed-age riverine population (3 - 79 years old)	293 (273 - 316)	Singh et al. (2023)
Slovenia/ Croatioa		Pregnanty women	170[b]	Trdin et al. (2019)
Persian Gulf coast, Iran	80	Fishermen families Non-fishermen families	335 ± 104 (182 - 546) 264 ± 95 (182 - 509)	Okati and Esmaili-sari (2018)
South Korea	1197	Adults	261.32 (128.4 - 419.8)	Kim et al. (2013)
Sendai, Japan	27	Adults	351 ± 54 (263 - 478)	Yaginuma-Sakurai et al. (2012)
Slovenia	574	Pregnant women	200[b]	Miklavčič et al. (2011)
Stockholm, Sweden	28	Adults	366 (185 - 673)	Berglund et al. (2005)
Faroe Islands	1445	Children - 7 years old Children - 14 years old	370[a] (48 - 1324) 264[a] (18 - 1038)	Budtz-Jørgensen et al. (2004)
United States of America	3774	Children - 1 - 5 years old Mixed-age (16 - 49 years old)	342 ± 20 234 ± 15	McDowell et al. (2004)
Västerbotten, Sweden	30	Lactating Women	131 (28 - 263)	Oskarsson et al. (1996)

[a] Median.
[b] Estimated from reported median hair and blood Hg concentrations.

dependent and may not be directly generalizable across populations with distinct exposure profiles, nutritional patterns, and environmental conditions. These findings reinforce that, although hair THg is a reliable biomarker at the population level, individual hair-to-blood ratios exhibit substantial variability, highlighting the importance of contextual and population-specific interpretation.

3.3. Model-based assessment of Hg intake and elimination

Estimated Hg exposure parameters, calculated using established literature-based equations, are summarized in Table 4. The estimated daily Hg excretion showed substantial variability, with a median of 2.2 μg/day (range: 0.19–12.5 μg/day). When normalized to the estimated body burden, daily excretion corresponded to approximately 0.07% per day (IQR: 0.06–0.08%), indicating relatively consistent proportional elimination across individuals.

This apparent consistency in relative excretion contrasts with the known complexity of Hg toxicokinetics. The applied estimation is based on a simplified steady-state toxicokinetic model that assumes homogeneous distribution of Hg throughout the organism and fixed proportional elimination rates. However, Hg is known to undergo compartmentalized distribution, with preferential accumulation in tissues such as the brain, liver, kidneys, and hair (ATSDR et al., 2024; Denaro et al., 2025; Pope and Rand, 2021). As a result, the estimated daily excretion rates should be interpreted as simplified population-level indicators of Hg turnover rather than precise representations of individual elimination dynamics. Differences in tissue-specific retention, binding affinities, and biotransformation processes are not captured by this approach and may therefore lead to the under- or overestimation of true excretory fluxes in individuals with comparable total body burdens.

Estimated daily MeHg intake was calculated according to the approach proposed by the Joint FAO/WHO Expert Committee on Food Additives (WHO, 2004), yielding a mean intake of 1.30 ± 0.95 μg/kg body weight per day, with median and upper percentile values of 1.08 and 3.07 μg/kg BW/day, respectively, and a maximum estimated intakes reaching 7.66 μg/kg BW/day. In the same riverine communities, Passos et al. (2008a) reported estimated daily Hg intakes ranging from 0 to 11.8 μg/kg/day, with a mean of 0.92 and a median of 0.59 μg/kg/day. The overall concordance in the magnitude of exposure supports the persistence of elevated dietary Hg intake in this population. These values markedly exceed the reference dose established by the USEPA (0.1 μg/kg/day), indicating chronic dietary exposure in a large proportion of the study population (USEPAU.S.E.P.A, 2000). In riverine communities, where fish consumption represents the primary exposure pathway, such intake levels are consistent with sustained rather than episodic MeHg exposure (Cassulatti dos Santos et al., 2026; Cezarette et al., 2025; Cruz et al., 2024).

Although all exposure metrics were indirectly derived from mathematical models rather than direct measurements, these approaches are widely applied in epidemiological studies of Hg-exposed populations and enable comparison across studies and regions. Nevertheless, the assumptions of steady-state conditions, homogeneous distribution, and fixed toxicokinetic parameters must be acknowledged. Accordingly, the resulting estimates should be interpreted cautiously, particularly when extrapolating to individual-level exposure or risk assessment.

3.4. Linear regression analysis of Hg partitioning between blood and hair

A strong and statistically significant positive association was observed between THg concentrations in blood and hair ($R = 0.8597$, $p < 0.0001$), indicating a close coupling between internal exposure and Hg incorporation into hair (Fig. 3a). This corresponds to approximately 74% of the variance in hair Hg concentrations being explained by blood Hg levels ($R^2 \approx 0.74$), indicating a strong but not complete predictive relationship. This relationship supports the use of hair THg as a reliable biomarker of chronic Hg exposure in riverine populations with sustained dietary intake, particularly from fish consumption (Cassulatti dos Santos et al., 2026; Cezarette et al., 2025; Cruz et al., 2024; Passos et al., 2008b).

Despite this strong coupling, the ratio of THg in hair to THg in blood showed a significant inverse relationship with blood THg concentrations ($R = -0.2511$, $p < 0.0001$) (Fig. 3b). Non-parametric LOESS smoothing revealed a non-linear decrease in the hair-to-blood ratio with increasing

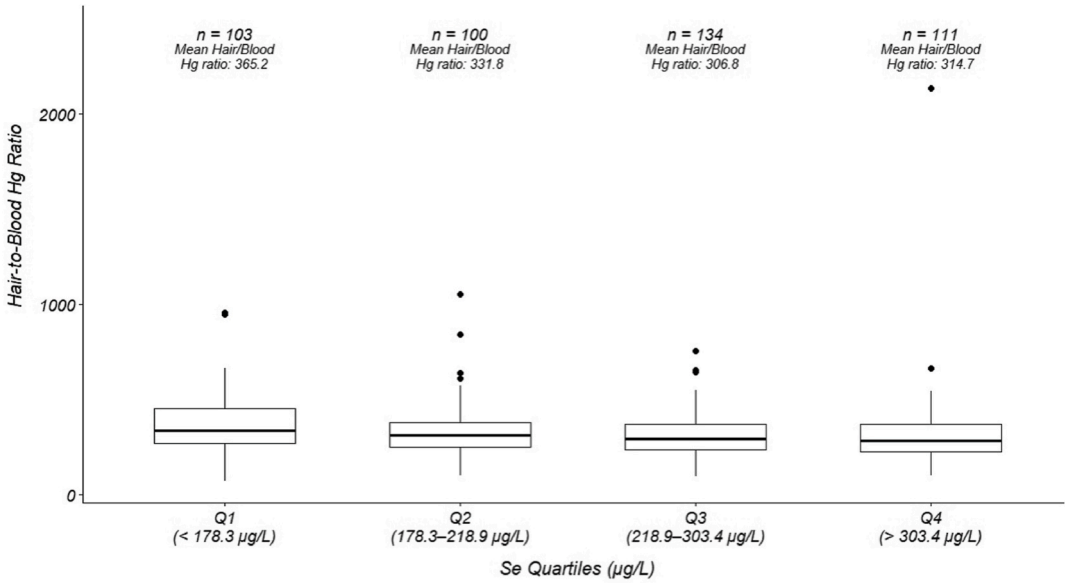

Fig. 2. Box-plot analysis of hair-to-blood Hg ratios stratified by blood Se quartiles in the studied Amazonian population. Boxes represent the interquartile range (IQR), horizontal lines indicate the median, whiskers represent 1.5 × IQR, and dots indicate outliers. The Se quartile ranges, sample size (n), and mean hair-to-blood Hg ratio for each quartile are displayed in the figure.

Table 4
Model-based estimates of daily MeHg intake and Hg excretion parameters in the study population.

	Mean ± SD	Min.	25th	50th	75th	95th	Max.
Daily excretion (µg Hg/day)	2.82 ± 2.06	0.19	1.3	2.2	3.8	7.12	12.5
Daily excretion of Hg (% of the body burden)	0.07 ± 0.01	0.04	0.06	0.07	0.08	0.09	0.12
Daily intake of MeHg (µg/kg BW/day)	1.30 ± 0.95	0.05	0.61	1.08	1.85	3.07	7.66

blood THg concentrations, reaching a plateau at approximately 70 µg/L. This pattern suggests that Hg partitioning becomes more stable at higher exposure levels but is not constant across the full exposure range. Notably, variability in the hair-to-blood ratio was proportionally greater at lower blood Hg concentrations, particularly near the USEPA reference level (5.8 µg/L), whereas dispersion progressively decreased at higher concentrations. These findings indicate that uncertainty associated with fixed hair-to-blood conversion factors may be more relevant near toxicological decision thresholds. Despite the strong correlation between matrices, the remaining unexplained variability highlights the influence of additional biological and environmental factors on Hg incorporation into hair. This pattern indicates that Hg incorporation into hair is not constant across all exposure levels, and may be influenced by toxicokinetic constraints, saturation of hair binding sites, or inter-individual differences in hair growth rates. (Basu et al., 2018; Budtz-Jørgensen et al., 2004; Singh et al., 2023).

This observation is consistent with multi-compartment toxicokinetic models, in which Hg distribution between blood and peripheral tissues is governed by dynamic equilibrium processes rather than fixed proportional relationships (Denaro et al., 2025). In addition, blood Hg reflects more recent exposure, whereas hair Hg integrates exposure over longer time periods, which may further contribute to variability in their relationship, particularly under fluctuating exposure conditions.

When hair-based Hg excretion was expressed as a daily rate, it showed a strong positive correlation with THg concentrations ($R = 0.8597$, $p < 0.0001$) (Fig. 4b), indicating that absolute Hg elimination via hair is proportional to internal Hg burden. This supports the concept that hair Hg reflects not only exposure but also a route of Hg removal from the body (Esteban-López et al., 2022; Koenigsmark et al., 2021; Magos and Clarkson, 2008). In contrast, the relationship between daily hair Hg excretion and the hair-to-blood ratio was weak and statistically insignificant ($R = 0.080$, $p = 0.092$) (Fig. 4a), suggesting that relative partitioning metrics do not adequately predict absolute Hg elimination.

The association between Se concentrations in blood and daily Hg excretion via hair was statistically significant but weak ($R = 0.1310$, $p < 0.005$) (Fig. 4c). Although the magnitude of this correlation was modest, it suggests a potential modulatory role of Se in Hg toxicokinetics. Se is known to interact with Hg through the formation of inert Hg–Se complexes, which may alter Hg distribution, retention, and elimination (Cezarette et al., 2025; Córdoba-Tovar et al., 2025; de Moraes Pontes et al., 2025; Raymond and Ralston, 2020; Singh et al., 2023; Spiller, 2018). However, the weak association indicates that Se is unlikely to be a primary determinant of Hg excretion via hair. This finding suggests that the variability observed is more plausibly explained by the combined influence of additional factors described in the literature, including exposure intensity, individual metabolic capacity, nutritional status, and genetic variability, all of which may contribute to inter-individual differences in Hg toxicokinetics (Dack et al., 2024; Esplugas et al., 2025; Kuras et al., 2019; Packull-McCormick et al., 2026; Queiroz et al., 2025).

To further characterize Hg partitioning, the relationship between blood THg and Hg speciation in hair was evaluated. Significant positive associations were observed between blood THg and both hair MeHg ($R = 0.8569$, $p < 0.0001$) and hair IHg ($R = 0.7835$, $p < 0.0001$), indicating efficient transfer of Hg species from the systemic circulation to the hair matrix (ATSDR et al., 2024;Carrier et al., 2001; Denaro et al., 2025). The stronger association observed for MeHg reflects its predominance in blood under chronic dietary exposure conditions, particularly in fish-consuming populations (Lino et al., 2018; Moriarity et al., 2020; Petrova et al., 2020).

MeHg readily binds to sulfhydryl groups in keratin and is efficiently incorporated into growing hair, which explains its tighter coupling with blood Hg levels (Branco et al., 2017). In contrast, IHg represents a smaller fraction of circulating Hg and may be more influenced by demethylation processes, renal handling, and intracellular

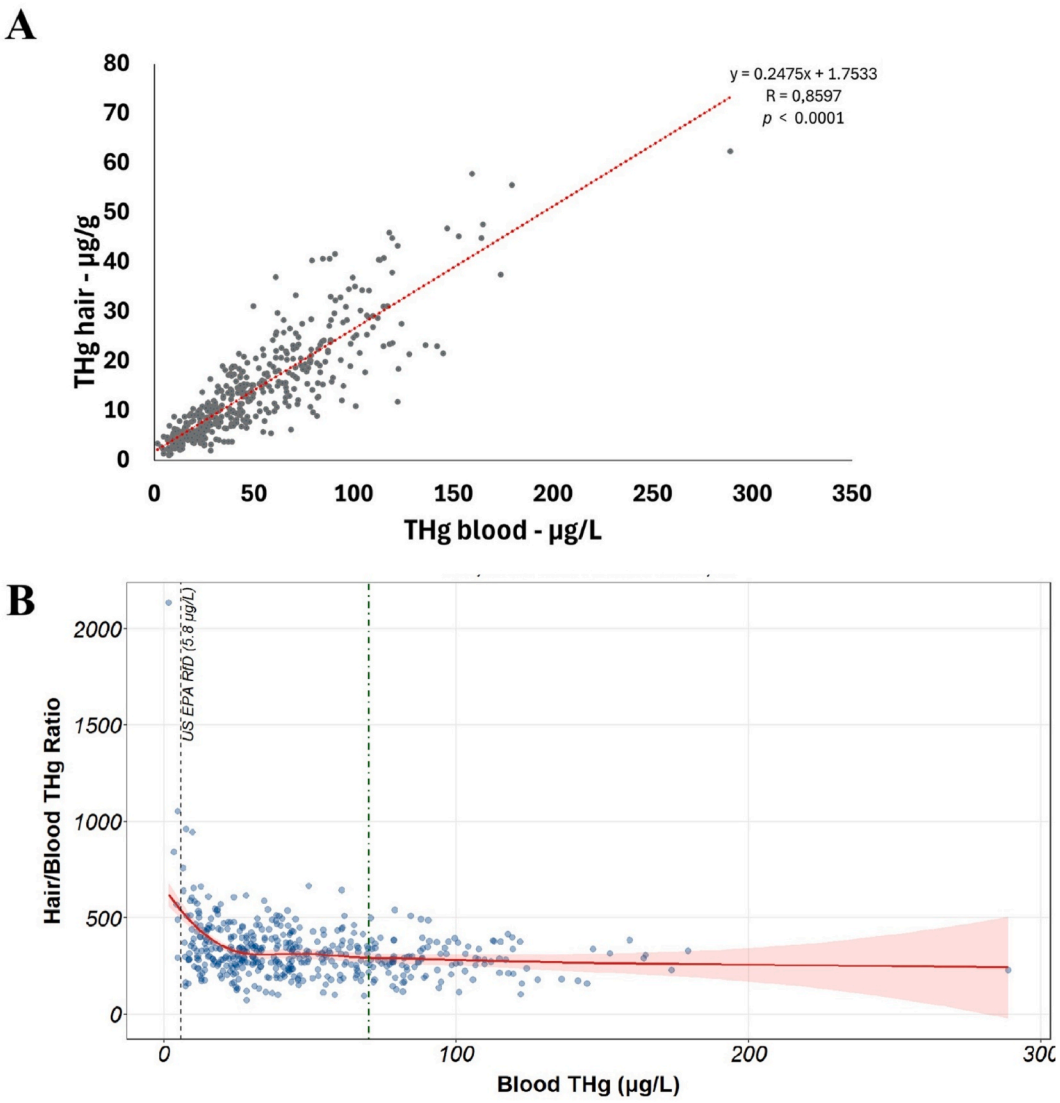

Fig. 3. Correlation between THg concentrations in hair and blood. (a) Linear regression of hair THg vs. blood THg. (b) Hair-to-blood THg ratio versus blood Hg levels. The black dashed line marks the US EPA RfD (5.8 µg/L), and the green dot-dashed line indicates the onset of the toxicokinetic stability plateau (70 µg/L). Trend line fitted via LOESS regression with a 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sequestration, contributing to the comparatively greater variability observed in its incorporation into hair (Branco et al., 2017).

Overall, these findings demonstrate that although blood and hair Hg concentrations are tightly linked, particularly for hair MeHg, Hg partitioning and elimination via hair are dynamic processes that vary across exposure levels and individuals. The progressive decrease in the hair-to-blood ratio with increasing blood Hg concentrations suggests the presence of adaptive or kinetic constraints at higher internal burdens, indicating that Hg transfer to hair is not constant across the exposure spectrum. At the same time, the strong association between blood Hg levels and estimated daily Hg excretion via hair highlights hair as a relevant elimination pathway in chronically exposed populations.

The modest influence of Se on Hg excretion further underscores its secondary role in shaping Hg toxicokinetics under real-world exposure conditions. From a biomonitoring and risk assessment perspective, these findings have important practical implications. In highly exposed populations such as the present study, where estimated MeHg intake substantially exceeded the USEPA reference dose, the observed variability in hair-to-blood Hg ratios may have limited impact on the overall identification of population-level risk, since exposure levels are consistently elevated well above toxicological thresholds. However, in populations with lower Hg exposure or in individuals whose biomarker levels are close to regulatory reference values, such variability may become critically important.

Under these scenarios, the use of a fixed hair-to-blood conversion factor may introduce substantial uncertainty into individual-level exposure assessment and clinical interpretation. Individuals with similar hair Hg concentrations may present markedly different circulating Hg levels due to toxicokinetic variability, potentially leading to exposure misclassification near decision thresholds. In practical terms, applying the conventional conversion factor of 250 may result in systematic overestimation or underestimation of blood Hg concentrations depending on the exposure level. This issue appears particularly relevant in highly exposed individuals, in whom the hair-to-blood ratio tends to show non-linear behavior, potentially leading to overestimation of circulating Hg levels inferred from hair measurements. Collectively, these findings indicate that hair Hg concentrations should be interpreted cautiously as direct surrogates of blood Hg levels, especially in epidemiological, clinical, and biomonitoring contexts involving heterogeneous exposure scenarios.

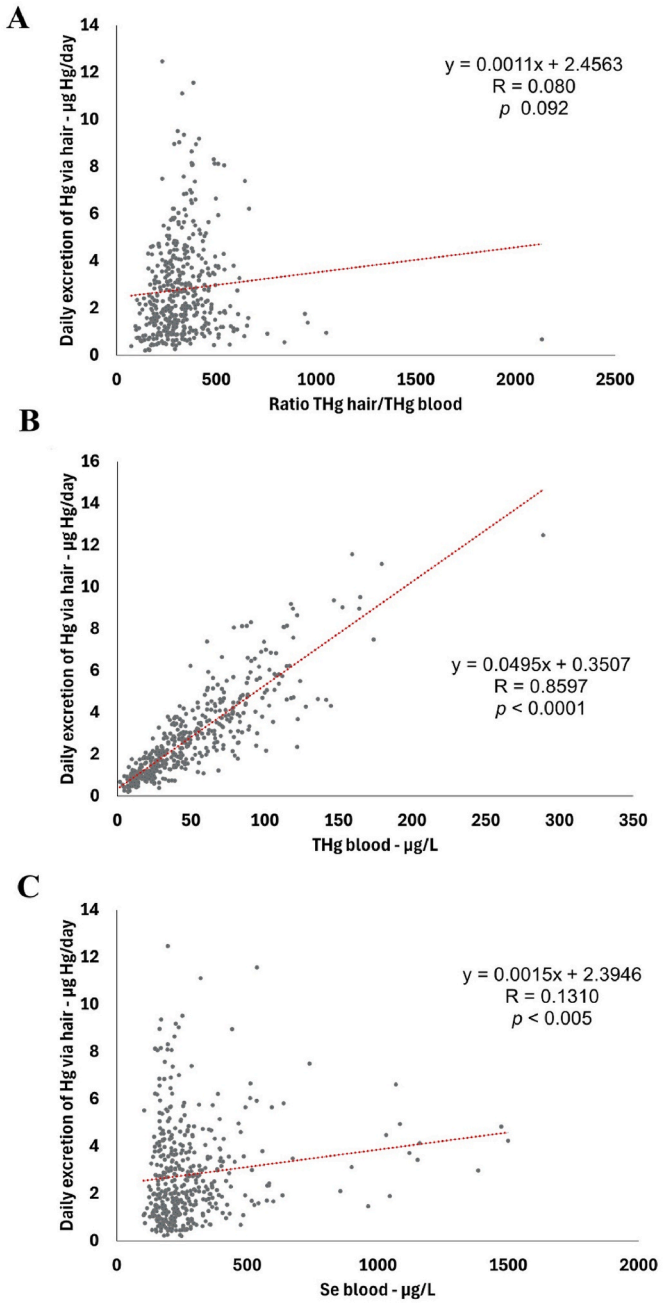

Fig. 4. Relationship between daily Hg excretion via hair and different biomarkers. (a) Daily Hg excretion versus hair/blood THg ratio. (b) Daily Hg excretion versus blood THg concentration. (c) Daily Hg excretion versus blood Se concentration.

Fig. 5 highlights the practical implications of the non-linear and heterogeneous relationship between hair and blood Hg concentrations. Although hair Hg was strongly correlated with blood Hg at the population level, substantial variability in predicted blood Hg concentrations was observed across the exposure range. At lower hair Hg concentrations, particularly near toxicological decision thresholds, this variability becomes especially relevant. For example, applying the conventional 250:1 conversion factor to a hair Hg concentration of 2 µg/g would predict a blood Hg concentration of approximately 8 µg/L, slightly above the USEPA reference level of 5.8 µg/L. However, the observed dispersion in the present study indicates that individuals with similar hair Hg concentrations may exhibit markedly different circulating Hg levels, ranging from values near the reference threshold to substantially

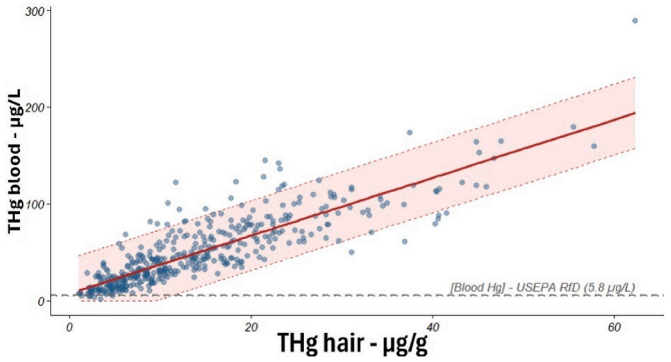

Fig. 5. Relationship between hair THg and blood THg concentrations. The solid red line represents the fitted regression model and the shaded area the 95% prediction interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

elevated concentrations. This finding suggests that the use of a fixed conversion factor at low exposure levels may introduce considerable uncertainty and increase the likelihood of exposure misclassification. In contrast, at higher hair Hg concentrations (e.g., ~50 µg/g), although the absolute variability in predicted blood Hg concentrations remained substantial, estimated values consistently remained far above health-based guidance values. Therefore, the practical impact of uncertainty in the hair-to-blood relationship appears proportionally more critical near regulatory and clinical decision thresholds than in highly exposed individuals. These findings reinforce that the hair-to-blood Hg ratio should be interpreted as a dynamic toxicokinetic parameter rather than a universal fixed conversion factor.

3.5. *Multivariate regression analysis of determinants of Hg partitioning and excretion*

The hair-to-blood THg ratio, used as an indicator of Hg partitioning between the hair matrix and circulating blood, was significantly associated with blood THg, blood Se concentrations, and the interaction between sex and Brazil nut non-consumption (Fig. 6). No associations were observed with age or sex alone, indicating that variability in Hg partitioning was not driven by demographic factors in isolation.

Blood THg showed a consistent inverse association with the hair/blood THg ratio ($\beta = -0.394$; $p < 0.001$; 95% CI: −0.531, −0.258), indicating that individuals with higher circulating Hg concentrations proportionally exhibited lower Hg incorporation into hair. This finding confirms that Hg transfer to hair is not linearly proportional to systemic Hg burden, consistent with the non-linear patterns observed in Section 3.4. Given that blood Hg reflects more recent exposure, whereas hair Hg integrates exposure over longer time periods, elevated blood THg may represent recent increases in intake not yet fully expressed in hair, or a relative limitation in Hg transfer to the growing hair shaft at higher circulating concentrations (Liberda et al., 2014; Lukina et al., 2021; Packull-McCormick et al., 2022).

Blood Se concentrations were strongly and positively associated with the hair/blood THg ratio ($\beta = 1.081$; $p < 0.001$; 95% CI: 0.967, 1.194), indicating a potential shift in Hg partitioning towards the hair compartment with increasing Se levels. Notably, Se concentrations in this population were markedly elevated, with a median of 225.2 ($p25^{th}$ – 75^{th}: 182.5 – 303.2) µg/L, approaching the 95th percentile reported for the general population in the U.S. NHANES 2015–2016 (P95 = 233 µg/L). This suggests that Se is not merely a background nutritional factor, but rather may represent a biological factor associated with variability in Hg toxicokinetics in this population. (Basta et al., 2023; Cezarette et al., 2025; de Moraes Pontes et al., 2025; Tinggi and Perkins, 2022).

Although Brazil nuts are widely recognized as a major dietary source of Se in the Amazon, the elevated blood Se concentrations observed

Variables	β	p value	95% CI
THg blood	-0.394	< 0.001	[-0.531; -0.258]
Se blood	1.081	< 0.001	[0.967; 1.194]
Brazil nuts intake (not consume) * Sex	-0.812	0.005	[-1.379; -0.245]

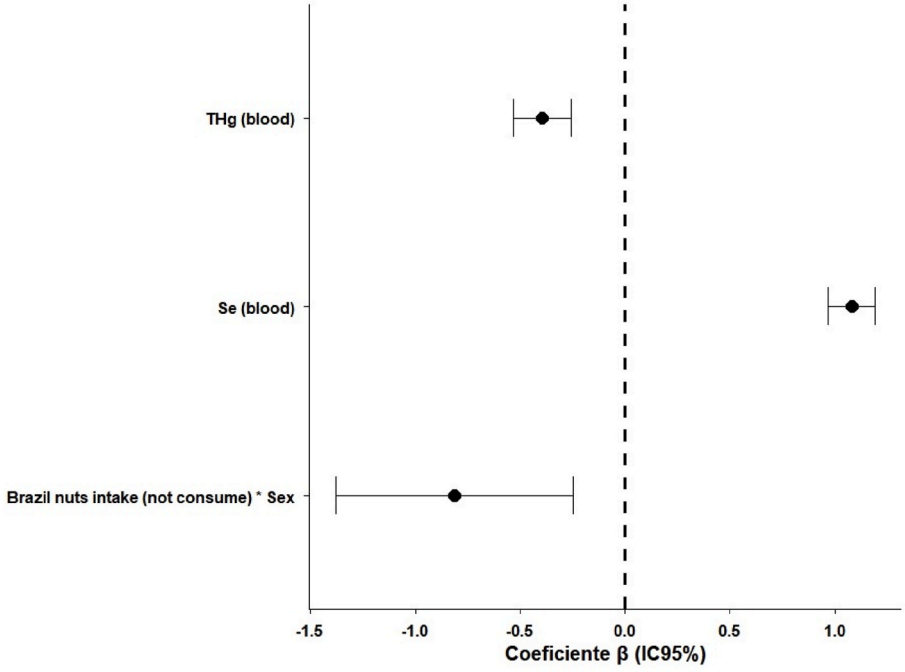

Fig. 6. Multivariate predictors of the THg hair/blood ratio: Parameter estimates and forest plot visualization.

despite low reported Brazil nut consumption indicate the contribution of alternative and sustained exposure pathways (Lemire et al., 2010; Silva Junior et al., 2017). Fish consumption, which is frequent and continuous among riverine populations, represents a relevant source of highly bioavailable organic Se and may substantially contribute to chronic Se intake. Many Amazonian fish species present Se concentrations sufficient to sustain high Se intake, often occurring alongside Hg exposure, and are consumed throughout the year, unlike the highly seasonal availability of Brazil nuts (Lino et al., 2018, 2020; Oliveira et al., 2023). In addition, local geochemical characteristics may promote Se presence in drinking water, in foods cultivated in Se-rich soils, such as cassava and other staple crops, fish and aquatic organisms, offal, eggs, and meat (Lemire et al., 2006, 2010; Passos et al., 2003; Silva Junior et al., 2017).

From a toxicokinetic perspective, Se, particularly in the form of selenomethionine, has a long biological half-life and can be nonspecifically incorporated into body proteins, acting as a reservoir of Se (Pons et al., 2020). Under conditions of elevated and chronic Se status, Hg may preferentially form stable Hg–Se complexes, reducing its bioavailability in blood and altering its distribution among biological compartments (Bjørklund et al., 2017; Tinggi and Perkins, 2022). This mechanism provides biological plausibility for the observed redistribution of Hg toward hair at higher Se levels. Nevertheless, given the cross-sectional nature of the study, these associations should not be interpreted as evidence of causality. Elevated Se concentrations and higher hair-to-blood Hg ratios may also reflect shared dietary sources, exposure patterns, or other unmeasured toxicokinetic determinants. In addition, because blood and hair represent different exposure windows, temporal mismatches between recent and integrated exposure may contribute to the observed associations.

The significant interaction between sex and non-consumption of Brazil nuts ($\beta = -0.812$; $p = 0.005$; 95% CI: −1.379, −0.245) indicates that the absence of this dietary source differently affects Hg partitioning in men and women. This suggests that sex-specific physiological factors may modulate the relationship between Se status and Hg distribution, potentially through differences in metabolism, hormonal regulation, or antioxidant capacity (Park et al., 2011; Ruszkiewicz et al., 2016; Spiller, 2018).

Taken together, these results demonstrate that the hair-to-blood THg ratio is a dynamic biomarker influenced by systemic Hg burden, elevated and heterogeneous Se status, and sex-dependent dietary factors. In Amazonian riverine populations, where Se intake may substantially exceed reference population levels due to combined dietary and environmental sources, Se appears to be an important determinant of Hg distribution between biological compartments. These results highlight the importance of explicitly considering Se status and exposure pathways when interpreting Hg biomarkers, as failure to do so may bias estimates of exposure intensity and obscure biologically relevant inter-individual variability in biomonitoring studies.

The multivariate regression analysis of daily Hg excretion provides important complementary evidence to the results observed for the hair-to-blood THg ratio, reinforcing the role of dietary and biological modifiers in Hg toxicokinetics. While the hair/blood ratio reflects Hg partitioning between systemic and peripheral compartments, daily excretion represents a downstream process related to detoxification and elimination. Together, these metrics provide an integrated view of Hg distribution and removal within the organism.

Medium consumption of Brazil nuts was positively associated with daily Hg excretion ($\beta = 8.80$; $p < 0.05$; 95% CI: 0.516, 17.084). However, this finding should be interpreted cautiously given the very small number of participants reporting Brazil nut consumption. Although Brazil nuts are recognized as Se-rich foods, the present study did not directly demonstrate higher blood Se concentrations among consumers, and causality cannot be inferred from these associations. Therefore, the observed relationship may reflect broader dietary, environmental, or toxicokinetic variability. (Cezarette et al., 2025; Oliveira et al., 2023; Tinggi and Perkins, 2022).

Fish intake frequency showed context-dependent associations with daily Hg excretion, further underscoring the dual role of fish

consumption in Hg exposure and metabolism. In some community contexts, medium fish consumption was inversely associated with Hg excretion ($\beta = -3.72$; $p < 0.04$; 95% CI: −7.207, −0.273), potentially reflecting higher Hg retention due to increased intake. In contrast, a strong sex-dependent positive interaction between medium fish consumption and Hg excretion was observed ($\beta = 9.35$; $p < 0.01$; 95% CI: 3.224, 15.468), suggesting that biological sex modifies the balance between Hg intake and elimination. These results reinforce that Hg toxicokinetics are shaped not only by exposure intensity, but also by sex-specific physiological and nutritional factors.

Independent community-level effects on daily Hg excretion indicate that local environmental and dietary conditions contribute to inter-individual variability in Hg elimination. Such contextual factors likely operate upstream of both biomarker outcomes, influencing exposure sources, nutrient co-exposures, and metabolic capacity (Eagles-Smith et al., 2018; Feingold et al., 2020). This suggests that variability in Hg biomarkers reflects not only individual-level processes, but also broader environmental and community-specific influences.

Overall, the concordant patterns observed between Hg partitioning (hair-to-blood THg ratio) and Hg elimination (daily excretion) support a coherent toxicokinetic framework in which Se availability, dietary habits, and sex-specific factors jointly shape Hg handling in the body. These results reinforce the interpretation that differences in Hg biomarkers among individuals and communities reflect not only variations in exposure but also biologically meaningful differences in distribution and elimination processes. Such an integrated interpretation strengthens the use of multiple biomarkers to characterize Hg exposure and risk in Amazonian riverine populations.

3.6. Study limitations

This study has limitations that should be considered when interpreting the findings. The cross-sectional design precludes causal inference and does not allow assessment of temporal variability in Hg exposure or biomarker dynamics. Blood and hair represent different exposure windows, and the lack of longitudinal data limits the evaluation of intra-individual changes in Hg partitioning. In addition, seasonal variation in dietary habits, particularly fish consumption patterns that are characteristic of Amazonian riverine populations, was not specifically evaluated in the present study. Such seasonal differences may influence Hg exposure levels and potentially affect the hair-to-blood Hg relationship and biomarker interpretation.

Additionally, key toxicokinetic parameters used in the model, including the excretion rate constant and distribution fractions, were derived from literature-based average values and therefore do not account for inter-individual variability in Hg kinetics. Differences in metabolism, physiological status, and exposure patterns may influence these parameters and contribute to uncertainty in the estimated intake and excretion values. Therefore, these estimates should be interpreted as population-level approximations rather than precise individual measures.

Although the sample size was large, unmeasured factors such as genetic variability, renal function, hormonal status, and hair growth rate were not assessed. In addition, Hg speciation was performed only in hair, not in blood. In addition, dietary intake variables were based on self-reported information, which may be subject to recall bias and misclassification.

Analytical uncertainty, although minimized through quality assurance/quality control procedures, may also contribute to variability in measured concentrations. Furthermore, the findings are based on a specific Amazonian riverine population characterized by chronic Hg exposure and high fish consumption, and therefore may not be directly generalizable to populations from other geographical regions or to populations with substantially lower Hg exposure levels and different dietary profiles. Studies conducted in lower-exposure populations have generally reported narrower distributions and lower variability in hair-to-blood Hg ratios, suggesting that Hg partitioning dynamics may differ according to exposure intensity and nutritional context. Additionally, because of the cross-sectional design, associations observed between Se concentrations and the hair-to-blood Hg ratio may reflect reverse causality or shared determinants, including dietary habits, fish consumption patterns, metabolic variability, and other unmeasured toxicokinetic factors, rather than direct causal effects of Se alone.

Despite these limitations, the study provides a robust toxicokinetic assessment based on a large and well-characterized population with rigorous analytical methods.

3.7. Conclusions

This study reinforces the value of hair Hg as a biomarker of chronic MeHg exposure while demonstrating that the hair-to-blood Hg relationship is influenced by exposure intensity and biological modifiers. Rather than supporting a universal fixed conversion factor, the present findings suggest that interpretation of hair Hg measurements may benefit from consideration of toxicokinetic variability and contextual biological factors. Despite the strong overall correlation between blood and hair Hg concentrations, the inverse and non-linear relationship between blood Hg levels and the hair-to-blood ratio demonstrates that Hg partitioning between circulating and keratin compartments is not constant across exposure gradients. These findings highlight important limitations that may be particularly relevant in populations or individuals with Hg exposure levels near toxicological reference values, where variability in hair-to-blood Hg partitioning may increase uncertainty in exposure classification and individual risk assessment. Se status emerged as an important determinant of Hg partitioning, with elevated blood Se strongly associated with increased Hg redistribution towards hair. This observation highlights the potential role of nutritional and biochemical modifiers in regulating Hg toxicokinetics and provides biological evidence that co-exposure to essential elements can influence Hg biomarker relationships. In parallel, model-based estimates confirmed sustained and elevated MeHg exposure, with intake levels substantially exceeding international reference doses, reinforcing the chronic nature of Hg exposure in Amazonian riverine populations.

Collectively, these results suggest that the relationships between Hg biomarkers may not be fully explained by strict, static proportionality and could reflect underlying toxicokinetic influences. Although the present cross-sectional design does not allow direct kinetic determination, the observed associations indicate that Hg biomarker relationships may be affected by multiple biological and exposure-related factors. These findings support a more cautious interpretation of fixed hair-to-blood Hg conversion approaches in biomonitoring and exposure assessment.

Future research should prioritize longitudinal designs, direct measurement of Hg species across biological matrices, and integration of key biological modifiers to better capture inter-individual variability in Hg toxicokinetics. Such advances will strengthen epidemiological inference and support more reliable environmental health risk evaluation in populations chronically exposed to Hg.

Ethics approval and consent to participate

The study conducted by the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Brazil, was approved by the Institutional Research Ethics Committee.

Availability of data and materials

All data generated or analyzed during this study are with the corresponding author. If necessary, he can answer any questions about the datasets, which can be requested by reasonable request.

CRediT authorship contribution statement

Lucas Cassulatti dos Santos: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Carlos José Sousa Passos:** Conceptualization, Writing – review & editing. **Alexey A. Tinkov:** Conceptualization, Writing – review & editing. **Michael Aschner:** Conceptualization, Writing – review & editing. **Milena Horvat:** Conceptualization, Writing – review & editing. **Fernando Barbosa:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

Acknowledgments and Funding

We thank São Paulo Research Foundation - FAPESP for the financial support and for granting research fellowships (FAPESP - process number 2018/24069-3; 2021/05059-0; 2022/03476-5 and 2025/10516-1), the Brazilian National Council for Scientific and Technological Development (CNPq - 406442/2022-3). A.A.T. received support from the Ministry of Science and Higher Education of Russia (FENZ-2023-0004). Slovenian funding though the programme of ARIS P1-0143 is also acknowledged.

Data availability

Data will be made available on request.

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