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Environmental burden of lead (Pb) and methylmercury (MeHg) exposure on IQ loss in children in Europe – single substance and mixture approach

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ABSTRACT

Lead (Pb) and methylmercury (MeHg) are well-established developmental neurotoxicants, associated with adverse effects on cognition in children. This study estimates the environmental burden of disease associated with Pb and MeHg on IQ loss of children.

Human biomonitoring surveys from five European countries were used to estimate exposure for children and women of childbearing age, covering all exposure sources and routes. Coupled with exposure–response functions we derived from *meta*-analyses, IQ points lost attributable to each metal were estimated. Assuming a normal distribution of IQ points, we calculated the resulting IQ score due to exposure and applied disability weights to calculate DALYs. Uncertainty (on model parameters) and intra-populational variability (exposure differences) were propagated through Monte Carlo simulations. The burden due to combined exposure to both substances was estimated for the French dataset, which met data requirements for a mixture assessment.

The estimated IQ shift between exposed and theoretically unexposed individuals was higher for Pb than for MeHg. Pb was responsible for a median shift in IQ points of −0.36 (Sweden) to −0.47 (Czech Republic), while MeHg contributed to −0.03 (Czech Republic) to −0.08 (France) IQ points. We estimated a mean attributable burden from 950 to 1173 DALYs per 100,000 individuals for Pb, and 96 to 251 DALYs per 100,000 for MeHg across the studied countries. The burden of combined exposure in the French population was estimated at an average of −0.49 IQ points lost per individual, and 1,367 DALYs per 100,000 births.

Our results highlight the necessity to strengthen regulatory measures to reduce lead exposure through key sources such as dust, tap water, and food, despite decreasing blood levels in Europe in the last few decades. Regarding MeHg, our study highlights the importance of maintaining targeted communication towards current and future parents, especially because dietary exposure remains the main exposure source.

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1. Introduction

Lead (Pb) and methylmercury (MeHg) are two metals with well-established neurotoxic effects (EFSA, 2010; ATSDR, 2024). The presence of MeHg in the environment is a result of biotransformation of inorganic mercury (Hg) via aquatic microorganisms (Peng et al., 2024). Soil naturally contains Hg, originating from volcanoes, forest fires or geothermal springs (accounting for 50–85 % of total Hg emissions), but is contamination also results from anthropogenic activities (15 to 50 % of total emissions), such as coal burning, oil refining and metallurgy, in particular small-scale gold mining (Al-Sulaiti et al., 2022; Ray et al., 2025). Hg can be deposited or leached into aquatic bodies, and methylated into its more toxic form, methylmercury (MeHg), which is bioaccumulated in aquatic organisms (Ray et al., 2025). Humans are exposed to methylmercury through, for e.g., seafood and big predator fish consumption. Mediterranean populations tend to have higher MeHg levels due to their food habits (Cossa et al., 2022). Pb is present naturally in the earth's crust, and used for various purposes, e.g., in soldering, waterpipes and lead-based paint. It is hence introduced as a contaminant into the direct human environment. Young children are particularly vulnerable to its neurotoxic effects due to the biological immaturity of the developing brain (Abelsohn and Sanborn, 2010). They can be exposed through drinking tap water (Caudeville et al., 2012; Tebby et al., 2022), and also through hand-to-mouth behavior with soil and house dust which is an important pathway for children (Sowers et al., 2024; Santoro et al., 2024). Historically, Pb used in industrial processes, gasoline, and paint has resulted in environmental contamination. Food also contributes to Pb exposure, particularly grains and grain-based products, vegetables, and milk and dairy products (EFSA, 2010). Some trace elements are simultaneously present in the same environmental media, which cause a combined human exposure to several metals (Merced-Nieves et al., 2021).

Since 1970, measures have been taken to reduce lead contamination in the environment in the EU, the most important one being the ban on lead in fuel in 2000 (Directive 98/70/EC). Lead was banned in paints in Europe in 2003, in water distribution pipes since 1995, and is restricted in consumer products such as jewelry in 2007, toys in 2009 (Directive 2009/48/EC) and electrical and electronic equipment in 2011 (Directive 2011/65/EU). In 2021, the European Commission put into place a new restriction on lead in ammunition (Commission Regulation (EU) 2021/57 2021). However, populations are still exposed to lead and methylmercury at present due to their persistence in the environment.

The prenatal and childhood phases are very critical windows of exposure for neurodevelopment with possible life-lasting effects (Kou et al., 2025). The brain is a very sensitive organ that starts its development in utero and then continues to develop until adulthood. Methylmercury is transported across the placenta into the fetus, crosses the blood–brain barrier and accumulates in the brain (Gundacker and Hengstschläger, 2012). The neurotoxic mechanisms of lead involve disruption of synaptogenesis, interferences with neurotransmitter release, and induction of oxidative stress (Bressler and Goldstein, 1991; Virgolini and Aschner, 2021; ATDSR, 2020).

Environmental burden of disease estimates are useful to rank chemical hazards according to their public health impacts and to define public health strategies to mitigate chemical exposure and health loss. European (Bierkens et al., 2012; Thomsen et al., 2022) and global (Carrington et al., 2019; Bellinger et al., 2019) burden of disease estimates based on dietary exposure to these substances have been estimated previously. According to the WHO's Global Health Estimates, dietary exposure to lead was responsible for nearly one million deaths globally in 2019 due to cardiovascular diseases (X. Chen et al., 2025), and represented 30 % of the global burden of idiopathic intellectual disability. The global health cost of lead exposure in 2019 was estimated to be 6.0 trillion US$, including US$1.38 trillion per year due to future income losses from IQ loss (Larsen and Sánchez-Triana, 2023). The global incidence of intellectual disability due to prenatal MeHg exposure was > 200,000, resulting in almost 2 million DALYs globally in 2015 (Bellinger et al., 2019).

As no safe threshold exists for exposure to lead (WHO, 2021; Vorvolakos et al., 2016), it is still necessary to monitor and assess human exposure and risk. Furthermore, most existing burden of disease or health impact assessments have only considered substances in isolation, while individuals are exposed to chemical mixtures in real life. Considering combined exposures allows to capture correlations between substances, and, given that the burden is not always linearly correlated with exposure, considering the effects of both substances together can lead to a higher degree of precision in the burden estimation.

The present study aimed to assess the environmental burden of disease of intellectual disability in European children associated with chronic exposure to Pb and MeHg using human biomonitoring data (HBM) to assess exposure. We considered populational HBM data available across Europe that encompass all exposure sources and routes, and not only dietary exposure. We explored different approaches for the evaluation of exposure to the mixture, Pb and MeHg, using individual data from ESTEBAN (France).

This work has been carried out under the Partnership for the Assessment of Risks from Chemicals (PARC; https://www.eu-parc.eu/). This study is closely aligned with the European Green Deal's Chemical Strategy for Sustainability (CSS), which seeks to better protect citizens and the environment from harmful chemicals, and to promote the use of safer and more sustainable chemicals (Chemicals Strategy for Sustainability; https://environment.ec.europa.eu/strategy/chemicals-strategy_en).

2. Material and methods

2.1. Human biomonitoring data

Data collection

We identified human biomonitoring (HBM) data from the European Human Biomonitoring (https://hbm.vito.be/eu-hbm-dashboard) Dashboard and the Information Platform for Chemical Monitoring (IPCHEM; https://ipchem.jrc.ec.europa.eu/). We searched for total Hg, MeHg, and Pb concentrations among children (6 to 11 years of age) and women of childbearing age (18 to 45 years of age). The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the exposure distribution were available for nine studies in five European countries (see Table S1 and Table S2 in Supplementary Material for full information on available percentiles of exposure): ESTEBAN (France), CzechHBM_AE (Czech Republic), CzechHBM_CE (Czech Republic), ESB (Germany), GerES IV (Germany), GerES V (Germany), SLO-HBM-I (Slovenia) and POPUP study (Sweden). For the French ESTEBAN dataset, individual-level exposure data was also available.

In the selected HBM surveys, ESTEBAN dataset and German Environmental Survey (GerES) were representative of the whole country (Oleko et al., 2024; Vogel et al., 2021), while the remaining datasets were representative of specific regions, such as the Swedish survey which was conducted in two cities in southern Sweden (Stajnko et al., 2024). Children aged 6–11 were the most surveyed population, representing postnatal exposure, and all data were collected in blood except for ESTEBAN (France) and POPUP study (Sweden) where mercury was analysed in hair. Sampling took place between 2000 and 2022, but we chose to restrict the timeline from 2010 onwards for Pb due to important decreases in Pb internal exposures linked to several regulatory measures (for e.g., the 2009 Directive (2009/48/EC) of the European Parliament and Council, regarding the safety of toys, and the 2011 Directive 2011/65/EU on the restriction of the use of hazardous substances in electrical and electronic equipment) (HBM4EU, 2022). Data on women of childbearing age or mothers were available for women from 18 to 49 years of age, and the studies were conducted from 2004 to 2023.

It is to be noted that the 5th and 10th percentiles of MeHg exposure were missing from the Czech datasets.

Data Distribution Modelling

We simulated a theoretical population by drawing a random sample out of the exposure distribution for each dataset in order to capture variability within the population. The individual data from the French ESTEBAN study was used to identify the most relevant distribution by comparing observed percentiles and simulated ones from tested distributions (log-normal and gamma). The accuracy of each distribution was evaluated using the coefficient of determination (R^2). The log-normal distribution was selected since it provided the highest R^2 for both Pb and MeHg.

Since, for all remaining datasets, no individual-level data was available to test for the accuracy of different distributions, we assumed that exposure was also lognormally distributed. This assumption is supported by the fact that it has been frequently observed that exposure in populations follow the lognormal distribution (Andersson, 2021; Jiang et al., 2024). Furthermore, exposure data are typically strictly positive, with occasional high values which are characteristics can be modelled with a lognormal distribution. For each of these countries, distribution parameters (meanlog and sdlog) were estimated from their available observed percentiles, and the goodness-of-fit was estimated using the R^2. These analyses were conducted in R using the MASS, stats, dplyr, and tidyr packages.

It was assumed that total mercury was a valid proxy for methylmercury as in the general population, most mercury exposure comes from organic mercury compounds in diet, such as MeHg in seafood, fish and rice (ATSDR, 2024). In a Swedish survey, about 90 % of the mercury in red blood cells was indeed MeHg (Berglund et al., 2005). For datasets in which total mercury was analysed in blood, a matrix conversion was applied using a blood-hair ratio of 250 to express total mercury in hair in order to ensure consistency across data (WHO, 1990).

2.2. Exposure-response functions (ERFs)

Epidemiological studies have shown that children with elevated blood lead levels, or prenatally exposed to MeHg, exhibit lower IQ scores and cognitive skills (Lanphear et al., 2005; Cohen et al., 2005; Axelrad et al., 2007; Crump et al., 2013). There is a documented high level of evidence regarding neurodevelopmental effects of Pb and MeHg in children (Stacy et al., 2024). Neurological impacts such as IQ deficits can significantly impair the quality of life of an individual as well as society on a larger scale (education, academic achievement, and employment). Due to the robust evidence supporting a causal relationship between Pb and (Me)Hg and IQ loss in children, intellectual disability is considered a valid indicator for the neurological impact of these substances on children.

We conducted a literature review to identify recent studies investigating associations between prenatal or postnatal exposure to Pb, MeHg or Hg and IQ loss in children. We searched for articles published between January 2005 (i.e., publication year of the oldest previously used ERFs) and July 2023. Search queries in PubMed and Scopus included the following terms: substance (Pb, MeHg, Hg – including Mesh terms), outcome (IQ and neurodevelopment), population (children) and results (association, ERF). All identified articles were screened for title, abstract, and full text. Papers were considered relevant according to predefined PECOTS – Population (children, pregnant women and women of childbearing age), Exposure (biological measures of Pb, MeHg or Hg from all matrices), Comparator (no exposure or lower levels of exposure), Outcome (FSIQ score measured by WISC, WASI or WPPSC), Timing of exposure (no restriction) and Setting (no restriction). The list of considered papers for lead and mercury is presented in Supplementary Tables S4 and S5. We collected several descriptive key data from these papers using a grid based on the one proposed by NTP OHAT (NTP, 2019). When mercury speciation was not clearly stated, we considered total mercury to be methylmercury (Berglund et al., 2005). Detailed search queries, selection criteria, and flow diagrams are available in the supplementary material.

To quantitatively integrate results from the selected articles, we conducted *meta*-analyses of the effect estimates of Pb and MeHg exposure on IQ loss. Separate analyses were performed for each substance, considering windows of exposure and biological matrix. Before entering the *meta*-analysis, reported effect estimates were standardised for one-unit linear increment of exposure using the approach proposed by Rodríguez-Barranco et al. (2017). Linear associations were preferred to facilitate interpretability. Meta-estimates were derived using random-effects models to account for heterogeneity between publications. Standardised results were combined into *meta*-analyses considering each pollutant, matrix, and windows of exposure separately. Only one result per study was allowed to avoid correlated estimates.

As we were interested in population-level burden, we only included results for the overall population rather than stratified estimates (e.g., by sex or by co-exposure levels). Within studies, results from the most-adjusted models were chosen to enter the *meta*-analysis; unadjusted results were not considered. Estimates adjusted for co exposures to other neurotoxicants were not used (or included) unless no alternative was available. This choice ensures consistency across studies, limits the introduction of heterogeneity and eases the interpretation of the aggregation of pollutant-specific estimates. The I^2 statistic was used as a quantitative indication of heterogeneity. Sensitivity analyses were performed to test the robustness of the results, such as redoing the analysis excluding visual outlier value. All *meta*-analyses were conducted using the *metafor* R package (Viechtbauer, 2010, 2025). Further details are available in the supplementary material and in Sell et al. (2026, submitted).

2.3. Attributable IQ shift, cases and DALYs calculation

The framework to estimate IQ shift and the incidence-based burden to both Pb and MeHg is presented in Fig. 1.

IQ shift

Combining random samples from the exposure concentration distributions with the selected ERF, we estimated the shift in IQ (ΔIQ) attributable to exposure to Pb and MeHg in children separately. ΔIQ represents the difference in IQ points between theoretically unexposed and exposed (ex) populations (i.e., counterfactual hypothesis or absence of exposure). This difference is always negative since Pb and MeHg negatively affect neurodevelopment in children (loss of IQ points). Due to existing evidence of the absence of a threshold for the neurodevelopmental effects of Pb exposure (Vorvolakos et al., 2016; Hänninen et al., 2014), we assumed no threshold for both Pb and MeHg in our calculations, which means that effects can occur at any non-zero dose. In the absence of exposure, IQ is assumed to be normally distributed with a mean of 100 and a standard deviation of 15 (Bellinger et al., 2019; Carrington et al., 2019), and each individual is attributed a random reference IQ score based on this distribution (IQ_{ref}). The IQ shift due to exposure, ΔIQ, is subtracted from the reference IQ score to derive the IQ score distribution of the exposed population, IQ_{ex}.

For each metal m (where m = Pb or MeHg), the individual IQ shift was calculated as:

$$\Delta IQ_{m,i} = expo_{m,i} \times \beta_m \quad (1)$$

where β_m is the slope of the exposure–response function for metal m(reflecting the decrease in IQ points per unit of exposure) and $expo_{m,i}$ is the exposure level of individual i to metal m. Exposure values were randomly selected from the fitted exposure distribution for a simulated population of n = 10,000 individuals per country, in order to reflect interindividual variability in exposure levels. A weighted shift is calculated by multiplying the resulting ΔIQ by a probability of causation of 0.9 (95 % CI: 0.8, 1), which is the likelihood that the shift results from exposure to Pb or MeHg, as defined by Stacy et al. (2024).

Attributable cases of intellectual disability

This shift towards decreasing IQ scores increases the proportion of

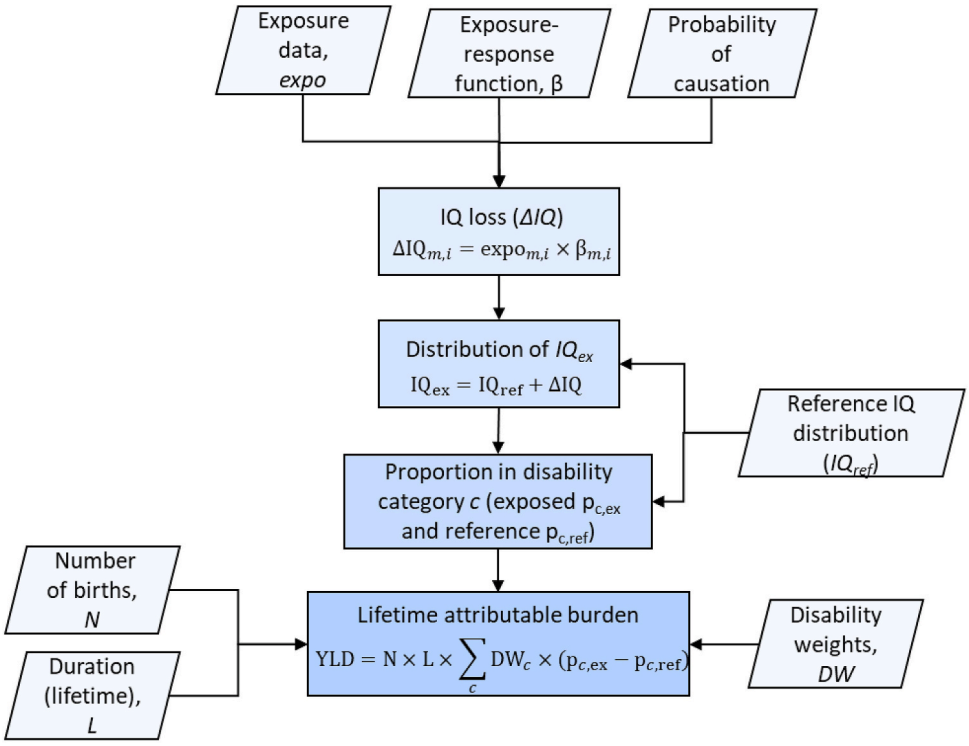

Fig. 1. Framework for the calculation of the environmental incidence-based burden of lead and methylmercury on cognitive disability in children using bio-monitoring (exposure) data. The indices m and i represent the metal (Pb or MeHg) and the individual respectively.

children with intellectual disability. (K. Lee et al., 2023). A case of intellectual disability is defined by an IQ score beneath 70 points (K. Lee et al., 2023). Given the expected normal distribution of IQ (IQ_{ref}), we were able to calculate the number of cases of intellectual disability attributable to exposure to Pb or to MeHg (equation (2)).

$$N_{attributablecases,m} = N_{cases_{exposed},m} - N_{cases_{ref,m}} \quad (2)$$

Calculation of environmental burden in DALYs

Finally, we used the disability weights estimated by the Institute for Health Metrics and Evaluation (IHME) to translate intellectual disability cases into DALYs (sum of Years Lived with Disability and Years of Life Lost) for each substance separately (Institute For Health Metrics And Evaluation, 2024). The total number of incidence DALYs attributable to lead or methylmercury exposure is given by the difference in DALYs in the exposed population and the reference population, as expressed in equation (4).

$$AttributableDALYs = L \times N \times \sum_{c=1}^{5} DW_c \times \left(p_{c,exposed} - p_{c,reference}\right) \quad (4)$$

N represents the total number of births for each country (incidence). L is the duration of the disability (the life expectancy of the country is considered here since the disability lasts a lifetime), which was relatively similar across countries, ranging from 79 to 82 years, with a mean of 81. p_c is the proportion of individuals in the cognitive impairment class c, different for the exposed population and the reference population. DW_c is the disability weight for five classes of cognitive impairment c: 1) profound (IQ score between 0 and 19), 2) severe (IQ between 20 and 34), 3) moderate (IQ between 35 and 49), 4) mild (IQ between 50 and 69) and 5) borderline (between 70 and 85) (Institute For Health Metrics And Evaluation, 2024). The term $N \times p_C$ estimates the number of individuals falling under category c in the population (N_c). Country-level burden estimates of ΔIQ, attributable cases and *DALYs* were computed separately for Pb and MeHg. The standardised burden in DALYs per 100,000 births is also calculated. The total number of births per country, and the life expectancy are given in supplementary material.

Monetised social cost of IQ loss

We applied the willingness-to-pay (WTP) method to evaluate the cost of IQ points lost, based on the OECD estimates (OECD, 2023) for five European countries: Denmark, Netherlands, Poland, Portugal and Sweden. The reported mean WTP per year were used for Sweden: 2800 USD_{2022} Purchasing Power Parity (PPP) per IQ point over 5 years as defined by the scenario studied (OECD, 2023). For the remaining countries, the mean of the five European countries were used: 3220 USD PPP per IQ point per year.

The monetised social cost was calculated as the product of the IQ points lost attributable to Pb and MeHg exposure (equation (1)) with the WTP of the country. The monetisation method considers all IQ points lost across individuals, and not only those falling under defined categories of IQ points, unlike the method applied for the DALY estimation.

2.4. Postnatal Pb-MeHg mixture burden of disease

Since exposure occurs to multiple substances, it is important to evaluate the burden of mixtures. While classic EBD studies treat substances separately, and results are summed to obtain the total burden, we explored two other approaches to consider the effects of exposure to both substances together as a mixture. This assessment is made possible because we studied the same outcome (cognitive disability) using the same metrics (IQ points lost and DALYs). In order to estimate the burden of disease of the Pb-MeHg mixture, the following data were necessary:

1. Concurrent exposure values of substances of interest for the same individual, over the same exposure window;
2. ERFs that allow to estimate the effect linked to the exposure matrix and exposure window of interest;
3. Conversion factors, if the biological exposure matrix is not the same as the one of the exposure–response functions.

In our case, only the French Esteban dataset meets requirement 1):

exposures to both Pb in blood and MeHg in hair at individual level. 2) For the exposure–response function, our *meta*-analysis (Table 3) resulted in a statistically significant beta-estimate for postnatal concurrent blood exposure to Pb, and prenatal hair levels in mothers for MeHg. As the effect of Pb is strongest after childbirth, we decided to use the postnatal period, even though the beta estimate for MeHg in postnatal hair was not statistically significant.

In this case study, since biomonitoring data for Pb and MeHg are not available for the same matrices (blood for Pb and hair for MeHg), an additional hair-to-blood conversion factor $\alpha_{\text{hair-blood}}$ is used so that hair MeHg exposure is converted to blood exposure to match the exposure matrix of the reference compound Pb, as shown in equation (5).

$$\alpha_{hair-blood} = \rho_{hair} \times 250 \times \alpha_{blood-plasma} \quad (5)$$

where ρ_{hair} is the hair density (1320 g/L) and $\alpha_{\text{blood-plasma}}$ is the blood-to-plasma conversion factor (0.21).

In this exploratory approach, we study possible methods to consider the effects of both Pb and MeHg for the ESTEBAN population.

Total burden of both substances

After the calculation of single-substance IQ shift linked to Pb and MeHg exposure for each individual in the ESTEBAN dataset, using the postnatal ERFs, there are two main options to evaluate the burden of both substances as a mixture: 1) calculating the disease burden in DALYs for each substance from their respective attributable IQ shift, then summing the DALYs for each individual to obtain the total burden and 2) summing the IQ shifts of the two substances to obtain a total shift linked to exposure to both of them, and then calculating the DALYs linked to this total. The two methods do not necessarily yield the same results because the conversion of IQ score to DALY is non-linear: disability-weights are different for different IQ categories. Both approaches are tested to compare results, but the second approach is retained because it is the one that accounts best for the non-linear relationship between the disability weights and the IQ score.

Scaling factor

Another approach we studied is the use of a scaling factor, with expresses the toxicity of a given compound as that of another index compound. In our study, Pb is defined as the index compound due to its high potential toxicity and widely available toxicological data, consistently with previous mixture risk assessments of metals conducted under the dose-addition hypothesis (Sprong et al., 2023; Mhungu et al., 2023; Wang et al., 2021). We thus describe the toxicity of MeHg in terms of Pb toxicity, using a scaling factor (SF), which is defined as the quotient of the Pb exposure dose divided by the MeHg dose required for an equal IQ shift using derived exposure–response functions. The equation for the exposure dose (6) is obtained from equation (1), with the exposure dose of metal *m* for individual *i* as the subject of the formula. The IQ shift ΔIQ represents a unit shift of 1 IQ point.

$$expo_{m,i} = \frac{\Delta IQ}{\beta_s} \quad (6)$$

Since no threshold was considered for the neurodevelopmental effects of Pb and MeHg exposure, and since ΔIQ is the same for both metals, the ratio of the exposure dose is equivalent to the ratio of the linear slope of the ERF in blood of MeHg to that of Pb in blood, as shown in equation (7).

$$SF = \frac{\beta_{MeHg}}{\beta_{Pb} \times \alpha_{hair-blood}} \quad (7)$$

The scaling factor was then applied to MeHg individual exposure data using the ESTEBAN dataset (France), to express MeHg exposure in Pb-equivalents, as show in equation (8).

$$expo_{MeHg}[eqPb] = expo_{MeHg} \times SF \quad (8)$$

Using the Pb-equivalent exposure, the total IQ shift can be calculated as expressed in equation (9):

$$IQ_{shift,tot} = \left((expo_{MeHg} \times SF) + expo_{Pb} \right) \times \beta_{Pb} \quad (9)$$

Exposure to the Pb-MeHg mixture was obtained by summing the Pb and Pb-equivalent exposures. This result can be used as input in the EBD calculation, using the derived beta-estimate of the Pb ERF. However, since the IQ shift is calculated using the ERF (beta-estimate) of each substance, and as the scaling factor is derived using the same ERFs, the calculated burden would be equivalent to method 2) described above for the calculation of the total burden (total IQ shifts of both substances obtained using the scaling factor, followed by the calculation of DALYs).

The three approaches used are summarised in Table 1 below:

The mixture approaches 2) and 3) have a major advantage over single-substance approach: they allow to account for possible correlations in exposure between the different substances. Furthermore, as it is the case in this study, relationships between exposure and burden are not always linear. Thus, introducing the combined exposure in the DALY calculation as proposed in approaches 2 and 3enables a better estimation of the burden of the associated outcome.

2.5. Probabilistic calculations

For both the individual-substance and mixture approaches, a probabilistic approach based on two-dimensional Monte Carlo simulations was used to calculate the burden (IQ loss and DALYs) and provide 95 % uncertainty intervals. This approach allows to propagate variability among individual exposures and uncertainty related to several model input parameters separately. 10,000 individual exposure values were randomly drawn from the associated lognormal distributions for each country to simulate a theoretical population, accounting for inter-populational variability. The size of the simulated population was set at 10,000 because it allowed to have stable results with reasonable computing time.

For each simulated individual, to account for uncertainty in model parameters, a random selection of 1,000 different values for each of the following parameters was taken from their respective distributions: 1) the exposure–response relationships (β_m), assumed to follow a normal distribution with a mean set to the central estimate and the standard deviation estimated from the corresponding confidence interval, 2) the probability of causation, assumed to follow a normal distribution based on its confidence interval, and 3) the individual's reference IQ in absence of exposure which follows a normal distribution with mean 100 and standard deviation 15, and 4) the disability weights (DW), modelled using a beta distribution bounded by 0 and 1. Disability weights and parameters of the distribution for each cognitive disability category are given in Annex Table 5. Statistics such as the mean and percentiles of burdens (IQ loss and DALYs) were computed across individuals. Uncertainty intervals were derived from the 1,000 values of each statistic, in calculating the median and the 2.5th and 97.5th percentiles. For the mixture approach, the ESTEBAN population was directly used, without random draws. A synthetic figure representing the population simulation and probabilistic Monte-Carlo 2D calculations is presented in Supplementary material (Fig. S1).

Table 1
Approaches used to evaluate burden of combined exposure to lead and methylmercury.

Approach	Description
1) Sum of DALYs	Individual IQ shift and DALYs are calculated for each substance separately, and DALYs are summed to obtain the mixture burden
2) Sum of shifts	Individual IQ shift calculated for each substance separately are summed to obtain the total shift due to exposure to the mixture, then the DALYs are calculated for the mixture
3) Scaling factor	MeHg exposure is converted into an equivalent Pb-exposure, to obtain the total Pb-equivalent exposure, then the total individual IQ shift and DALYs are calculated

We adapted the code developed by Rocabois et al., to calculate IQ loss and DALYs from exposure data and ERFs (Cherfan et al., 2026, submitted). The *readxl*, *tidyverse*, *xlsx*, *gtsummary*, *truncnorm* and *rmarkdown* packages were used on R version 4.4.2.

From this simulated population, the proportions (p_C) of individuals falling under each cognitive disability category were calculated. These proportions were applied to the actual number of births to obtain the total estimated incident burden, and standardised to 100,000 births.

3. Results

3.1. Concentrations of lead in blood and methylmercury in hair

Observed internal exposure concentrations for the different countries are presented in Table 2 and Table 3 for lead and methylmercury respectively. For lead, concentrations are presented as blood level values for children (Czech Republic, France, Germany, and Sweden). In the case of methylmercury, hair concentrations are given for mothers or women of childbearing age (Czech Republic, Slovenia, France, and Sweden).

Testing the goodness of fit between the log-normal distributions and observed percentiles resulted in an R^2 between 92 and 100 % (See Table S3 in Supplementary Material).

3.2. Exposure response functions

We identified 974 papers in our first screening, of which 139 were selected for the second step. Then, we identified 49 publications with relevant exposure–response functions (ERF) in our literature search (see details in supplementary material). In total, 30 publications for lead and 19 publications for (methyl)mercury, published between 2005 and 2023, were identified, covering epidemiological studies from across Europe, Africa, Asia, North and South America.

We performed 4 *meta*-analyses considering prenatal and postnatal exposure windows, and blood and hair matrices, separately. Mercury *meta*-analyses were performed on 3 to 5 studies. The *meta*-analytic estimates using postnatal mercury exposure were not statistically significant (p-value of the central estimate is < 0.05) for hair or blood levels, reflected by 95 % confidence intervals for the beta coefficient containing zero. Table 4 shows the different results linked to different windows of exposure (prenatal/postnatal) for Pb and MeHg.

The *meta*-analytic beta coefficient for prenatal MeHg exposure (measured in maternal hair) was negative and significant: −0.17 (95 % CI: −0.31, −0.04). For lead, two *meta*-analyses yielded a negative association between lead exposure and IQ that was statistically significant: association between postnatal exposure and IQ using concurrent lead exposure (defined as blood lead measured closest to the IQ test) or early-life lead exposure (defined as mean blood lead from 6 to 24 months). The *meta*-analytic beta coefficients were −0.45 (95 % CI: −0.66, −0.24) and −0.28 (95 % CI: −0.46, −0.11) for concurrent and early life lead exposure, respectively.

For our burden of disease calculations, we selected the beta estimate associated with a statistically significant decrease in IQ (shown in bold and red for Pb, blue for MeHg). This corresponded, for MeHg, to the prenatal beta-coefficient. For Pb, two statistically significant beta-coefficient were obtained, one for concurrent exposure and one for early exposure. We selected the concurrent estimate due to availability of exposure data. The studies from which these beta-estimates were obtained are indicated in Tables S4 and S5 in Supplementary material.

3.3. Burden of disease for lead and methylmercury

It is to be noted that results present in this section have the same representativeness as the HBM datasets: the French and German results aim at being representative of the population, while the Swedish, Czech and Slovenian results are representative of the regions where they were conducted.

IQ loss

Fig. 2 describes the distribution of individual IQ losses due to lead and methylmercury for postnatal and prenatal exposure, respectively.

For postnatal lead exposure, among the four countries studied, the attributable individual IQ shift was lowest for Sweden (−0.36 IQ points) and highest for Czech Republic (−0.47 IQ points). The IQ shift attributable to prenatal methylmercury exposure ranged from −0.03 IQ points for Czech Republic to −0.08 IQ points for France. Data was available for exposure to both substances in two countries: France and Sweden. For the French population, the median attributable individual IQ shift was over five-fold higher for Pb than for MeHg (−0.44 vs −0.08), while the attributable shift was about 9 times higher for Pb than for MeHg in the Swedish population (−0.36 vs −0.04).

The attributable number of cases (IQ < 70) due to both lead and methylmercury exposure is presented in Table 5, using the number of births for year 2023 in each country.

Out of the datasets studied, the total number of attributable incident cases of intellectual disability (IQ < 70) due to postnatal lead exposure ranged between 150 (for Sweden) and 1220 (for France) (see Table 5). The attributable incident cases per 100,000 for postnatal lead ranged between 150 (for Sweden) and 190 (for Czech Republic). For prenatal exposure to methylmercury, the average number of attributable cases range from 3 (Slovenia) to 271 (France) while the number of attributable cases per 100,000 range from 10 (Czech Republic) to 40 (France).

Disability-Adjusted Life Years

Fig. 3 shows the mean disease burden resulting from intellectual disability attributable to lead and methylmercury exposure for different countries in DALYs per 100,000 individuals.

In general, the disease burden linked to intellectual disability due to postnatal lead exposure was higher than for prenatal exposure to methylmercury in all countries. The largest difference was found for France with an almost six-fold higher disease burden for lead than for methylmercury. The highest total DALYs due to lead exposure were estimated for Germany and France, with around 7,500 and 8,000 DALYs respectively. However, considering the number of births, the DALY-rates for Pb exposure in Czech Republic and Sweden is comparable to the two countries: 950 DALYs/100,000 for Sweden, 1,079 DALYs/100,000 for Germany, 1,146 for Czech Republic and 1173 DALYs/100,000 for France. France had the highest burden linked to methylmercury exposure (1,705 DALYs in total and 251 DALYs/100,000).

The distribution of mean individual attributable DALYs within the population is given in histograms in the supplementary material (the mean for each individual, across 1,000 values calculated considering uncertainty of different model parameters as explained in section 2.5.).

Monetised social cost of IQ loss

The total cost linked to IQ loss in each country for Pb and MeHg are presented in Table 6.

Table 2
Percentiles of blood lead concentrations in 6 to 11-year-old children in μg/dL.

Country	Time period (range)	P5	P10	P25	P50	P75	P90	P95
Czech Republic	2016	0.64	0.71	0.95	1.17	1.50	1.80	2.08
France	2014–2016	0.26	0.63	0.79	1.08	1.44	1.88	2.40
Germany	2017	0.47	0.62	0.81	1.08	1.41	1.75	2.03
Sweden	2011–2017	0.44	0.54	0.66	0.88	1.15	1.53	1.89

Table 3
Percentiles of hair methylmercury concentrations in mothers or women of childbearing age (18–49 years) in μg/g.

Country	Time period (range)	P5	P10	P25	P50	P75	P90	P95
Czech Republic*	2005–2015	0.06	0.09	0.14	0.22	0.35	0.57	0.71
Slovenia*	2008–2014	0.08	0.11	0.18	0.28	0.48	0.77	1.01
France	2014–2016	0.05	0.19	0.28	0.59	0.91	1.31	1.8
Sweden	2004–2023	0.08	0.12	0.22	0.33	0.48	0.65	0.75

*Hair concentrations were obtained from the conversion of the total mercury from blood to total mercury (considered as methylmercury) in hair, using a blood-to-hair matrix conversion ratio of 250.

Table 4
Beta-coefficients from the *meta*-analysis for lead (Pb) and mercury (MeHg), with number of studies included (N), central estimate (CE), standard error (SE), 95 % confidence interval (95 % CI) and heterogeneity (I^2) for each *meta*-analysis.

Meta-analysis (i.e., window of exposure and biological matrix)	N	CE	SE	95 % confidence interval	I^2 (%)	Unit
Lead						
Prenatal exposure, blood (cord or mother)	7	-0.003	0.006	-0.015, 0.010	18.17	μg/dL
Postnatal concurrent exposure, blood (children)	**20**	**-0.452***	**0.106**	**-0.660, -0.243**	**99.21**	**μg/dL**
Postnatal lifetime average exposure, blood (children)	6	-0.869	0.484	-1.817, 0.080	98.54	μg/dL
Postnatal early exposure, blood (children)	**7**	**-0.280***	**0.089**	**-0.455, -0.105**	**56.46**	**μg/dL**
Methylmercury						
Prenatal exposure, blood	5	-0.044	0.181	-3981, 0.309	48.15	μg/L
Prenatal exposure, hair	**3**	**-0.173***	**0.068**	**-0.306, -0.041**	**0**	**μg/g**
Postnatal exposure, blood	4	0.293	0.534	-0.753, 1.338	71.91	μg/L
Postnatal exposure, hair	4	-0.159	0.172	-0.496, 0.178	0	μg/g

* Significant beta estimate (p-value < 0.05). Results are expressed for an increment of 1 unit of exposure.

The monetised cost of IQ loss linked to Pb exposure ranges from 22 million USD (Sweden) to 214 million USD (France) using the Willingness-to-Pay method. The cost of IQ loss linked to MeHg ranges from 0.6 million USD (Slovenia) to 47 million USD (France).

3.4. Postnatal burden of disease for the mixture

Results of the mixture burden of disease, applied to the French ESTEBAN dataset, are presented in Fig. 4 using the "sum of shifts" approach, where IQ shifts were calculated using the exposure values and beta-estimate **for each substance** (postnatal for lead and prenatal for MeHg as used for the single substance approach), then the total IQ shift was obtained as the sum at individual level, and using the "scaling factor" approach, whereby all MeHg exposures were converted to a Pb-equivalent and only the Pb beta-estimate was used to calculate resulting total IQ shifts (indicated as scaling factor in Fig. 4). The scaling factor calculated using beta-estimates for postnatal exposure to lead and methylmercury, together with the hair-to-blood conversion factor was of 0.142 $\mu g_{Pb}/dL_{blood}$ per $\mu g_{MeHg}/g_{hair}$.

The median sum of IQ shifts is −0.49 (95 % CI: −1.73, −0.07) for the "Sum of shifts" method, and −0.42 (95 % CI: −1.67, −0.12) using the scaling factor. The use of the scaling factor leads to a difference in estimated results as compared to summing the individual shifts linked to each substance, because of the matrix conversion factors used, but estimates remain within the uncertainty range, so the difference is not significant. It is to be noted that the total shift is mainly driven by Pb, which accounts for over 91 % of total impacts on average for the "Sum of shifts" scenario, and over 97 % for the "scaling factor" scenario.

Total DALYs are calculated using the three methods described in Table 1: 1) the sum of DALYs linked to postnatal Pb exposure and DALYs linked to prenatal MeHg exposure, 2) DALYs linked to the sum of shifts due to postnatal Pb and prenatal MeHg exposure, and 3) using the scaling factor to calculate the total Pb-equivalent exposure, followed by the total IQ shift and resulting DALYs. The scaling factor method hence

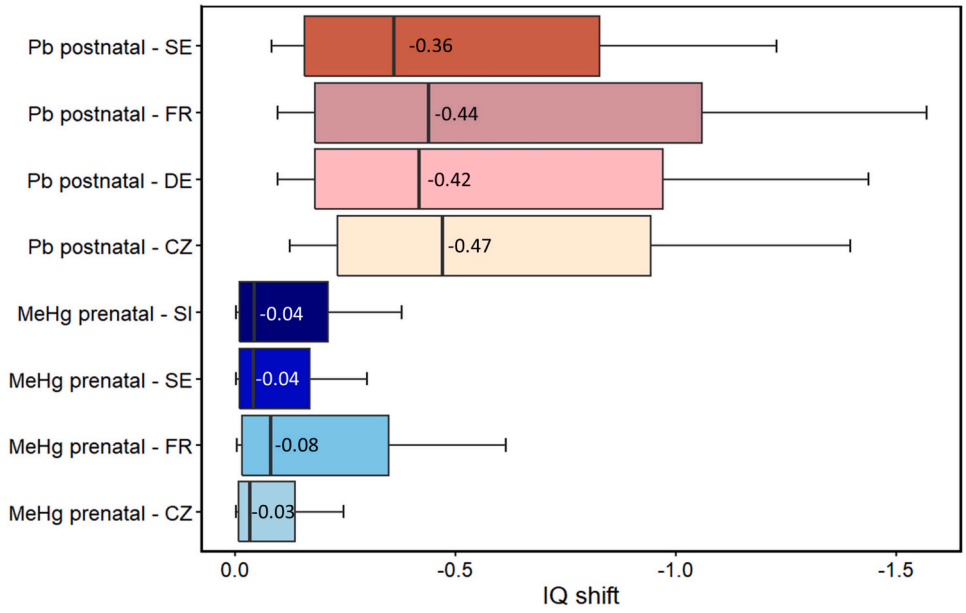

Fig. 2. Distribution of individual IQ shift due to exposure to lead (Pb) or methylmercury (MeHg) per country – SE: Sweden, FR: France, DE: Germany, SI: Slovenia, CZ: Czech Republic. The boxes represent variability in the population (2.5th and 97.5th percentiles of the population distribution) and the whiskers represent uncertainty on the outer percentiles: the 2.5th percentile of the confidence interval (CI) on the 2.5th percentile of the population distribution and the 97.5th percentile of the CI on the 97.5th percentile of the population.

Table 6
Mean number of attributable incident cases* and attributable incident cases* per 100,000 individuals (with 95 % uncertainty intervals) by country, substance and window of exposure.

Country	Total attributable cases		Mean attributable cases per 100,000	
	Postnatal Lead	**Prenatal Methylmercury**	**Postnatal Lead**	**Prenatal Methylmercury**
Czech Republic	173 (100, 255)	9 (0, 36)	190 (110, 280)	10 (0, 40)
France	1220 (678, 1831)	271 (68, 544)	180 (100, 270)	40 (10, 80)
Germany	1178 (693, 1801)	No data	170 (100, 260)	No data
Slovenia	No data	3 (0, 8)	No data	20 (0, 50)
Sweden	150 (70, 230)	20 (0, 50)	150 (70, 230)	20 (0, 50)

*A case of intellectual disability is defined as an IQ score beneath 70 points.

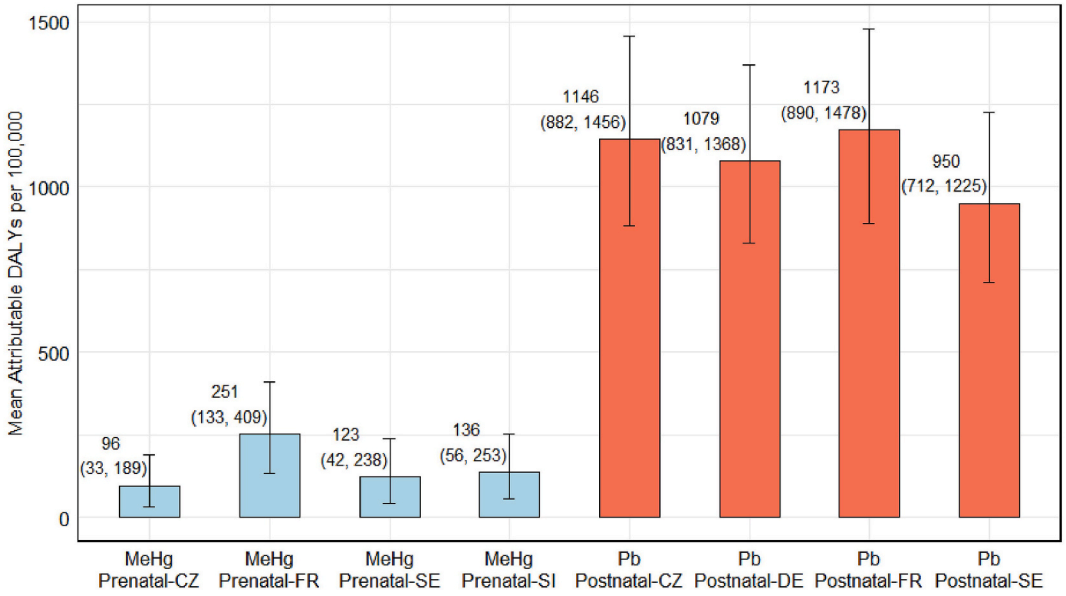

Fig. 3. Mean attributable DALY estimates per 100,000 individuals (with 95 % uncertainty interval) associated with intellectual disability for postnatal exposure to lead and prenatal exposure to methylmercury for each country. SE: Sweden, FR: France, DE: Germany, SI: Slovenia, CZ: Czech Republic.

Table 7
Monetised costs of IQ loss (in USD Purchasing Power Parity) in the five European countries included in this study due to postnatal lead and prenatal methylmercury exposure.

Country	Monetised costs (1000 USD PPP)	
	Postnatal Lead	**Prenatal Methylmercury**
Czech Republic	147,277	12,974
France	1,066,930	240,846
Germany	1,025,738	No data
Slovenia	No data	3,265
Sweden	111,339	15,336

is equivalent to method 2), except for the required matrix conversion. We obtain 1,358 (1,071, 1,658) DALYs per 100,000 using method 1), 1,367 (1,068, 1,672) DALYs per 100,000 using method 2), and 1,209 (924, 1,494) DALYs per 100,000 using the scaling factor 3). DALYs were thus lower when considering the sum of single-substance shifts compared to the total shift, and the difference between method 2) and the use of the scaling factor lies in the matrix conversion. However, it is to be noted that the uncertainty intervals around the DALY estimations overlap in all three methods: differences are thus not significant.

4. Discussion

4.1. Key novelties

In this paper, we have estimated the burden of intellectual disability linked to Pb and MeHg exposure using exposure data from five European countries. Though there are past studies that have estimated this burden, there are several novelties presented in this study.

First of all, the most recent HBM data available on the HBM4EU dashboard were used. We also used undated ERFs based on *meta*-analyses. Using a probabilistic approach, we were able to estimate the distribution of the individual IQ points lost within each studied population, separating variability and uncertainty, which is not commonly conducted in environmental burden of disease (EBD) studies. Finally, while substances are usually treated separately in EBD studies, the mixture burden calculated in this work also contributes to its novelty.

4.2. Comparison with impact assessment in the literature

We compare results of our study to previous EBD studies in order to verify that there are not differences in the magnitudes of estimates, and to try to identify sources of differences in the estimates. According to Bellinger et al. (2019), the burden of intellectual disability due to MeHg prenatal exposure for 2015 in Europe was 12 (95 % CI: 5–29) DALYs per 100,000 general population. They used blood and hair as biomarkers, and an ERF with a slope of −0.18 IQ point for each µg/g increase of maternal hair mercury concentration from Axelrad et al. (2007). In the present study, we estimated the burden within the range of 96 DALYs per 100,000 births (for Czech Republic) and 251 DALYs per 100,000 births (for France), which results in 1 to 3 DALYs per 100,000 general population. The difference can be explained by the use of different datasets, and the fact that, despite using a similar ERF, the disability weights used by Bellinger et al., are from the WHO, and about 3 times higher than those we use, from the IHME. This suggests that the choice of exposure and severity data can significantly influence results.

In the case of lead, the individual IQ points lost estimated from dietary exposure ranged between 0.83 (for Germany) and 1.31 (for Belgium) (Carrington et al., 2019), which are of similar orders of magnitude as our estimates which range from 0.36 IQ points lost, (95 % CI: 0.08–1.23) (for Sweden) to 0.47 IQ points lost (95 % CI: 0.12–1.40) (for Czech Republic). Estimated median DALYs attributable to dietary lead for the European region was 46 DALYs per 100,000 general population using the disability weights from the WHO (Carrington et al., 2019), while our estimates lie between 950 and 1173 DALYs per 100,000 births, resulting in 9 to 12 DALYs/100,000 general population using disability weights from the IHME. Differences are likely linked to both the disability weights, and more recent exposure data used in our study (2010–2023), as compared to 2012 data from EFSA for Carrington et al., The GBD estimated the total burden of idiopathic intellectual disability attributable to lead exposure at 1417, 8826 and 10,536 DALYs in Sweden, France and Germany respectively (IHME 2023), while our estimates for the incident burden are 950 (95 % CI: 713–1,226), 7,957 (95 % CI: 6,034–10,025) and 7,479 (95 % CI: 5,757–9,482) DALYs respectively for the three countries.

4.3. Mixture approach

Among the three methods proposed for the mixture burden estimation, the “Sum of shifts” methods is preferred as it enables to account for both exposure correlations and non-linearity of the ERF, followed by the “Scaling Factor” method (if matrix and windows of exposures match in order to avoid conversion factors that introduce uncertainty), and finally the “Sum of DALYs” method. The mixture approach was tested in order to account for possible correlations and the non-linear relationship between IQ loss and DALYs, and to highlight the fact that the sum of average DALYs in a population does not allow to account for these correlations. However, Pb and MeHg exposures were not correlated in the dataset used (from the French ESTEBAN study), and thus the results of the three methods were not significantly different. These conclusions could change in other case studies, and especially in the case of correlations between exposures to different substances.

Sum of burdens

Morbidity can be caused by multiple factors, hence the addition of burdens linked to separate risk factors could lead to an overestimation of real burdens. Furthermore, joint exposures can lead to enhanced or reduced potential effects. In our study, we assume independence of the toxicity of Pb and MeHg, which might not be the case in reality. For instance, (Martin et al., 2021) discuss the possibility of synergistic effects between certain metal compounds. The burden of both substances has been summed in the mixture analysis (either by summing the IQ shifts or by summing the DALYs). No interaction was considered between the two substances. Further perspectives of this study include the

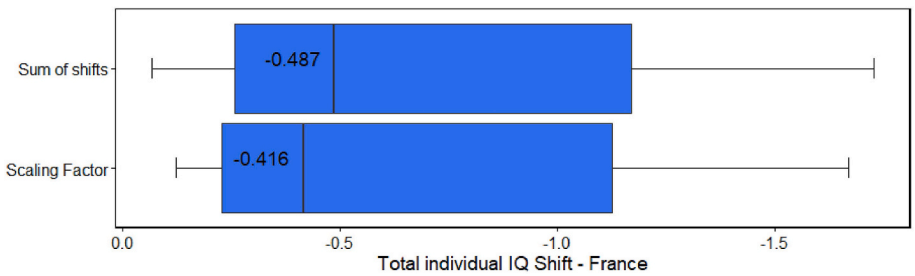

Fig. 4. Total individual IQ shift for France due to both postnatal lead and prenatal methylmercury exposure in the regular scenario, and using the scaling factor to convert methylmercury exposure to postnatal lead-equivalent exposure.

consideration of potential dependence of effects such as synergism or antagonism alongside exploring additional chemicals (e.g., manganese, cadmium or arsenic) or different chemical families with the same outcome. Concerning the conversion from IQ shift to DALY, we have also shown that non-linear relationships result in unequal results when 1) summing separate DALYs compared to 2) summing separate shifts, then calculating DALY for all studied exposures. The same would apply to non-linear exposure–response functions, especially regarding the calculation of mean burden using the two approaches. It is hence important to calculate the summary burden across all risk factors studied for each individual, then calculate the mean of the burden across individuals.

Scaling factor and Pb-equivalent exposure

In mixture risk assessment, relative potency factors (RPFs) are often used to assess risks posed by mixture components that exhibit a common mode of action (Bil et al., 2022; Martin Van den Berg et al., 2005). RPFs are derived for chemicals with the same chemical structure, such as dioxins and PFAS. However, since this paper treats two metals (MeHg and Pb) that are completely different in terms of physical and chemical properties, RPFs cannot be derived.

For the mixture assessment, there are few scaling factors identified in literature treating the Pb-MeHg mixture. Sprong et al. (2023) use prenatal endpoint-specific reference values (ESRV) from literature to obtain a scaling factor of 5, indicating a higher effect of MeHg as compared to Pb. However, in our study, we selected a postnatal estimate for Pb since it was significant and used the postnatal estimate for MeHg as well for coherence, though it wasn't significant, and hence obtained a scaling factor of 0.142. In order to test the effect of windows of exposure, we calculated the scaling factor using prenatal beta estimates from our *meta*-analysis (thus using the non-significant prenatal beta-estimate for Pb), which results in 2.6 (about 50 % lower than Sprong's).

This indicates that MeHg could be more toxic during the prenatal phase, and that the main difference between the two methodologies lies in the selected window of exposure. For instance, in animal models, the foetal brain was more vulnerable to prenatal methylmercury (Rice and Barone Jr. 2000). In epidemiological studies conducted in the Faroe islands, after adjustment for prenatal exposure no significant association was found between postnatal mercury exposure and neurodevelopment (Myers et al., 2009). In utero, methylmercury impairs neurodevelopmental processes (Antunes Dos Santos et al., 2016; Heimfarth et al., 2018), while at low postnatal exposure levels through breastfeeding or diet, as critical brain development has already taken place, neurodevelopmental impact is less important. Furthermore, mercury levels tend to decrease during the postnatal period (Z. Chen et al., 2014), emphasizing the fact that prenatal mercury has a higher effect on cognition.

An underlying hypothesis in this study is the stability of IQ points over time, which is translated through the unique disability weight applied throughout an individual's lifetime. However, since brain development continues until late adolescence, IQ also changes over this period. This could decrease the individual's disability. As a perspective, the study could integrate expected variations in IQ.

4.4. Uncertainties and limitations

The uncertainty around the beta coefficients, disability weights, and causation of effect were integrated to assess overall uncertainty of the results. However, it was not possible to quantify all sources of uncertainty.

We restricted our analyses to exposure windows showing statistically significant and biologically plausible negative associations to avoid modelling beneficial effects. In addition, selected exposure–response functions corresponded to available data. Although this approach may raise concerns about selection bias, effect sizes and their confidence intervals overlapped. The overall order of magnitude of the burden estimates is thus unlikely to differ substantially across windows.

The *meta*-analyses showed very high heterogeneity, indicating substantial variability across study results. This reflects differences in exposure ranges, population characteristics and geographical contexts. Although random-effects models were used to account for between-study variability, the resulting estimates should be interpreted with caution as their uncertainty increased. In addition, the transposability of the *meta*-analytic ERFs to European populations should be considered. However, while contributing studies included non-European populations, the biological mechanisms underlying neurotoxicity are likely consistent across regions. Moreover, exposure pathways are broadly similar. Differences in pathway contributions may exist but their impact was limited here as biomonitoring data were used.

One additional uncertainty is linked to confounding factors when considering co-exposures. Epidemiological studies frequently report single-substance exposure–response functions (Lanphear et al., 2005; European Food Safety Authority, 2012; Debes et al., 2006). Further research on possible confounding effects and building exposure–response functions that consider mixtures is needed.

In our literature review, for mercury ERF studies, a qualitative estimation of the quality of the study was considered however, no risk of bias tool or quality scoring method was used. For lead, a rapid RoB tool (Plate et al., 2024) was used as described in Sell et al. (2026, submitted). The assessment resulted in eight studies with a low RoB rating (Bauer et al., 2020; Dantzer et al., 2020; Desrochers-Couture et al., 2018; Hong et al., 2015; K.-S. Lee et al., 2021; Menezes-Filho et al., 2018; Roy et al., 2013; Schnaas et al., 2006) two with a moderate RoB (Lucchini et al., 2012, 2019) and two studies with a high RoB rating(Crump et al., 2013; Earl et al., 2016).

A linear exposure–response function is commonly used in burden-of-disease assessments because it provides a parsimonious and transparent method for translating population exposure distributions into IQ loss and intellectual disability outcomes (Carrington et al., 2019, Bellinger et al., 2019). However, for Pb, Lanphear et al., have shown that a log-linear model provided a better fit of the association (Lanphear et al., 2005, 2019). A simple sensitivity test using the loglinear estimate and an approximated linear estimate derived from Lanphear et al. (2019), applied to Pb exposures of the ESTEBAN population shows that results are lower for the loglinear model, though differences are not significant. For prenatal methylmercury exposure, epidemiological evidence from the Faroe Islands, Seychelles and New Zealand cohorts is generally consistent with an approximately linear, non-threshold relationship between maternal mercury burden and childhood IQ (Axelrad et al., 2007).

Regarding exposure levels, we used a factor of 250 for the hair-to-blood conversion of MeHg exposure, as suggested by the WHO (WHO, 1990). However, a more recent study evaluates the variability of this ratio in subgroups of the Canadian population, hence obtaining a range of 181–382 (Singh et al., 2023). This suggests that there is uncertainty related to the conversion factor used in this paper. Further investigation into this factor for the populations considered in this study would be required. Though the half-life of MeHg in blood is approximately 50 days (National Research Council (US) Committee on the Toxicological Effects of Methylmercury 2000), which means that cord blood MeHg concentrations are representative only of exposure during the last trimester of pregnancy, and hair samples are representative of exposures during the entire gestation period (Cohen et al., 2005), no clear evidence in literature suggests the preferred use of one biomarker over the other. Furthermore, according to (Grandjean et al., 1999) although the average shift in neuropsychologic performance associated with a doubling of exposure measured in cord blood is higher than for hair exposure, these differences are not large enough to justify considering one biomarker to be superior to the other: there is no *a priori* reason to suspect cord blood MeHg concentrations is a better predictor of cognitive function than maternal hair MeHg concentrations. So, studies investigating blood MeHg concentrations were not given a higher weight in the *meta*-analysis.

Regarding exposure distribution modelling, we have interpolated data from known percentiles of the exposure in the different datasets using the lognormal distribution, using an underlying assumption that exposure followed the same distribution type in all populations. However, we could not test the validity of our assumption since we did not have access to individual data except for the French ESTEBAN study.

Another exposure-related uncertainty lies in the representativeness of the HBM data. As mentioned previously, only the French ESTEBAN and the German Environmental surveys aimed at being representative of the population, while the remaining datasets were representative of specific regions. Results for these countries (Sweden, Czech Republic and Slovenia) are thus to be interpreted with caution, as they might not fully represent the variability across the whole population. The different surveys were conducted on different time frames, ranging from 2004 to 2023. The inter-country comparisons hence need to be conducted considering potential temporal trends in exposure.

Furthermore, the evaluation of intellectual development using intellectual quotient scores is a topic of debate. The World Health Organization has itself shifted from an IQ-based definition in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 WHO, 2019) to a definition based on adaptive functioning in real life contexts (ICD-11 WHO, 2025). However, this method could not be applied in the present study considering that the existing literature linking lead and methylmercury exposure to neurodevelopment are based on IQ shifts. Furthermore, we have considered a random normal distribution of IQ within all unexposed populations, using a mean of 100 and a standard deviation of 15 IQ points, while evidence suggests that IQ is not randomly distributed, and could depend on socioeconomic status (Marshall et al., 2020). However, the populations being diverse and heterogeneous, the bias that could be potentially introduced is expected to be non-differential. Furthermore, only adjusted models were considered to derive ERFs, accounting for the link between covariates, exposure and IQ. Perspectives could include the stratification of results using socioeconomic variables, for instance in the ESTEBAN dataset, and, if such information is available, considering these variables in the distribution of IQ points in the unexposed population.

Several studies have focused on the monetisation of IQ loss in the population using two main methods to evaluate the cost of one IQ point lost: the calculation of lifetime earning loss per person, and the willingness-to-pay (WTP) method. We select a recent publication by the OECD, which uses the WTP method, resulting in estimates of the same magnitude as the loss of income method (OECD, 2023). The OECD argues that the WTP method captures the individual's own evaluation of wellbeing and hence also captures differences in the attitude towards risk between individuals.

4.5. Implications in terms of public health

Different existing policy measures have allowed to reduce Pb exposures in European populations, such as the restriction of Pb use under REACH, the concentration limits in food, air, water and soil, and regulated occupational exposures. Similarly, there exist various EU environmental laws, completed by a revised regulation in 2024 (Regulation (EU) 2024/1849), prohibiting the use of Hg (on exportation, specific Hg-containing products and various industrial processes) and focusing on safer management of Hg waste. In addition, maximum concentration levels of Hg in consumed fish, water, sediment and biota and occupational settings. Despite existing efforts to reduce Pb and Hg exposure, HBM surveys and studies, including this paper, show that the matter is still of concern to public health, and that additional actions are needed to further protect populations.

For instance, old buildings could still be contaminated with Pb through paint and water piped, especially if they were constructed before the ban of Pb in paint (2003 Restriction of Hazardous Substances Directives) and the EU Drinking Water Directive (2020/2184) imposing strict limits on Pb concentrations. Another remaining considerable risk linked to Pb exposure, according to the ECHA (European Chemicals Agency), is hunting and sports shooting. Though Pb shots are banned in wetlands since 2023 (Commission Regulation (EU) 2021/57), there is still the need to extend this restriction to hunting in general and to fishing gear, in order to further reduce exposure (European Environment Agency, 2024). The revised Drinking Water directive aims at phasing out Pb contamination by 2036, which will contribute to decrease Pb exposures in the future.

For MeHg, since the main exposure source is diet (in particular seafood), there is an outstanding issue on the pros-and-cons balance of fish consumption, in particular for pregnant women and infants. Indeed, besides the potential neurotoxic effects linked to MeHg exposure, the consumption of non-predatory fish provides high-quality proteins, marine long-chain n-3 polyunsaturated fatty acids, vitamins and minerals (Byrd et al., 2021). Most EU countries currently recommend 1–2 portions of fish per week for fish with higher Hg limits and 3–4 portions for those with lower limits for the general population, and for pregnant women, the intake of smaller fish instead of large fish is recommended. A risk-balance approach is recommended to further strengthen targeted recommendations, at the national scale, due to differences in fish species consumed, especially for vulnerable populations.

Consequently, there is a need to maintain Pb and Hg human biomonitoring and EBD studies to ensure the effectiveness of public policies and assess the need for additional measures. However, as it was discussed in this study there is a lack of comparability across populations. There is hence the need for the alignment of studies in terms of exposure biomarkers, study periods, age groups and representativeness of studied populations, as well as for harmonised health-based guidance values across Europe to enhance interpretation and comparability (HBM4EU, 2022; Plass et al., 2023). It is to be noted that ongoing surveys within the Partnership for the Assessment of Risks from Chemicals (PARC) Work Package 4 were designed to be aligned.

5. Conclusion

In this study, we estimated the IQ shift and calculated the associated environmental burden of disease for Pb and MeHg, as individual substances, and as a mixture for the French ESTEBAN dataset. For the single substance analysis, we used aggregated data from HBM surveys from 5 European countries and exposure–response relationships obtained through *meta*-analyses. Pb had higher IQ shift values, and higher disease burden compared to MeHg. To our knowledge, this is the first burden of disease study that accounts for mixture effects of chemicals. In the mixture burden of disease, we demonstrated that for non-linear shift-to-DALY conversions, 1) summing separate DALYs as compared to 2) calculating the DALYs resulting from the sum of the shifts for both metals led to a higher estimate. We also derived a scaling factor for the conversion of MeHg exposure in hair as Pb-equivalent in blood, an approach that is similar to approach 2), except for the matrix conversion that introduces uncertainty, also leading to a lower estimation of the total burden. Overall, the effect of the mixture approach in our study is mostly driven by Pb exposure.

Through the integration of variability and uncertainty separately in the calculation of IQ shifts and disease burden due to lead and methylmercury, the distribution of burden within the population was captured, hence allowing to target populations at higher risk, instead of calculating only an average IQ shift. Lead exposure was associated with a loss of about 0.6 IQ points, with 2.5 % of the population experiencing cognitive reductions exceeding one IQ point. The use of exposure measured in biological samples instead of exposure modelled from dietary intake scenarios, reduces uncertainties associated with exposure modelling due to assumptions related to e.g., representativeness of chemical occurrence data and bioavailability.

Despite a decrease in blood Pb levels in Europe since the last decades, it is still relevant to monitor Pb exposure as adverse effects can occur at

lower doses (Salamanca-Fernández et al., 2025). Furthermore, Pb exposure can vary in European countries considering socio-economic factors, lifestyle behaviours, and regional industrial activities (Salamanca-Fernández et al., 2025). Regarding MeHg, European monitoring systems are in place for dietary exposure, which appears to be the main exposure source.

Our burden of disease study provides a basis for strengthening the case for preventive measures reducing Pb exposure levels. Considering the whole distribution in environmental burden of disease could be a tool for risk managers to identify specific subgroups of the population for which regulatory measures might be of interest.

CRediT authorship contribution statement

Philippe Palmont: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rachna Bhoonah:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Julien Caudeville:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Sarah Cherfan:** Writing – review & editing, Software, Methodology, Conceptualization. **Rafiqa Benchrih:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Carla Martins:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Emily Mc Vey:** Writing – review & editing. **Dietrich Plass:** Writing – review & editing. **Anthony Purece:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Sofie Theresa Thomsen:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Paulina Sell:** Writing – review & editing. **Jurgen Buekers:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Amélie Crépet:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Margaux Sanchez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rachna Bhoonah reports financial support was provided by Partnership for the Assessment of Risks from Chemicals (PARC). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2026.110446.

Data availability

Data will be made available on request.

References

Abelsohn, A.R., Sanborn, M., 2010. Lead and children. Can. Fam. Physician 56 (6), 531–555.

Al-Sulaiti, M.M., Soubra, L., Al-Ghouti, M.A., 2022. The causes and effects of mercury and methylmercury contamination in the marine environment: a review. Curr. Pollut. Rep. 8 (3), 249–272. https://doi.org/10.1007/s40726-022-00226-7.

Andersson, A., 2021. Mechanisms for log normal concentration distributions in the environment. Sci. Rep. 11 (August), 16418. https://doi.org/10.1038/s41598-021-96010-6.

ATDSR, 2020. Toxicological Profile for Lead. Agency for Toxic Substances and Disease Registry. https://doi.org/10.15620/cdc:95222.

ATSDR, 2024. Toxicological Profile for Mercury. Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. Agency for Toxic Substances and Disease Registry (US). http://www.ncbi.nlm.nih.gov/books/NBK611017/.

Axelrad, D.A., Bellinger, D.C., Ryan, L.M., Woodruff, T.J., 2007. Dose–response relationship of prenatal mercury exposure and IQ: an integrative analysis of epidemiologic data. Environ. Health Perspect. 115 (4), 609–615. https://doi.org/10.1289/ehp.9303.

Bauer, J.A., Devick, K.L., Bobb, J.F., et al., 2020. Associations of a metal mixture measured in multiple biomarkers with IQ: evidence from Italian adolescents living near ferroalloy industry. Environ. Health Perspect. 128 (9), 097002. https://doi.org/10.1289/EHP6803.

Bellinger, D.C., Devleesschauwer, B., O'Leary, K., Gibb, H.J., 2019. Global burden of intellectual disability resulting from prenatal exposure to methylmercury, 2015. Environ. Res. 170 (March), 416–421. https://doi.org/10.1016/j.envres.2018.12.042.

Berglund, M., Lind, B., Björnberg, K.A., Palm, B., Einarsson, Ö., Vahter, M., 2005. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environ. Health 4 (1), 20. https://doi.org/10.1186/1476-069X-4-20.

Bierkens, J., Buekers, J., Van Holderbeke, M., Torfs, R., 2012. Health impact assessment and monetary valuation of IQ loss in pre-school children due to lead exposure through locally produced food. Sci. Total Environ. 414 (January), 90–97. https://doi.org/10.1016/j.scitotenv.2011.10.048.

Bil W, Zeilmaker MJ, Bokkers BGH. Internal Relative Potency Factors for the Risk Assessment of Mixtures of Per- and Polyfluoroalkyl Substances (PFAS) in Human Biomonitoring. Environ Health Perspect. 2022 Jul;130(7):77005. doi: 10.1289/EHP10009. Epub 2022 Jul 26. PMID: 35881550; PMCID: PMC9320915.

Bressler, J.P., Goldstein, G.W., 1991. Mechanisms of lead neurotoxicity. Biochem. Pharmacol. 41 (4), 479–484. https://doi.org/10.1016/0006-2952(91)90617-E.

Byrd, K.A., Thilsted, S.H., Fiorella, K.J., 2021. Fish nutrient composition: a review of global data from poorly assessed inland and marine species. Public Health Nutr. 24 (3), 476–486. https://doi.org/10.1017/S1368980020003857.

Carrington, C., Devleesschauwer, B., Gibb, H.J., Michael Bolger, P., 2019. Global burden of intellectual disability resulting from dietary exposure to lead, 2015. Environ. Res. 172 (May), 420–449. https://doi.org/10.1016/j.envres.2019.02.023.

Caudeville, J., Bonnard, R., Boudet, C., Denys, S., Govaert, G., Cicolella, A., 2012. Development of a spatial stochastic multimedia exposure model to assess population exposure at a regional scale. Sci. Total Environ. 432 (August), 297–308. https://doi.org/10.1016/j.scitotenv.2012.06.001.

Chen, Z.u., Myers, R., Wei, T., et al., 2014. Placental transfer and concentrations of cadmium, mercury, lead, and selenium in mothers, newborns, and young children. J. Eposure Sci. Environ. Epidemiol. 24 (5), 537–544. https://doi.org/10.1038/jes.2014.26.

Chen, X., Zhao, L., Xiaxia, Wu., Chen, D., Yao, M., 2025. The global burden of lead exposure-related ischemic stroke: based on bayesian age-period-cohort analysis. Front. Public Health 13 (July), 1608129. https://doi.org/10.3389/fpubh.2025.1608129.

Cohen, J.T., Bellinger, D.C., Shaywitz, B.A., 2005. A quantitative analysis of prenatal methyl mercury exposure and cognitive development. Am. J. Prev. Med. 29 (4), 353–353.e24. https://doi.org/10.1016/j.amepre.2005.06.007.

Commission Regulation (EU) 2021/57, 024 OJ L (2021). http://data.europa.eu/eli/reg/2021/57/oj.

Cossa, D., Knoery, J., Bănaru, D., et al., 2022. Mediterranean mercury assessment 2022: an updated budget, health consequences, and research perspectives. Environ. Sci. Technol. 56 (7), 3840–3862. https://doi.org/10.1021/acs.est.1c03044.

Crump, K.S., Van Landingham, C., Bowers, T.S., Cahoy, D., Juhi, K., Chandalia, 2013. A statistical reevaluation of the data used in the Lanphear, et al. ( ) Pooled-analysis that related low levels of blood lead to intellectual deficits in children. Crit. Rev. Toxicol. 43 (9), 785–799. https://doi.org/10.3109/10408444.2013.832726.

Dantzer, J., Ryan, P., Yolton, K., et al., 2020. A comparison of blood and toenails as biomarkers of children's exposure to lead and their correlation with cognitive function. Sci. Total Environ. 700 (January), 134519. https://doi.org/10.1016/j.scitotenv.2019.134519.

Debes, F., Budtz-Jørgensen, E., Weihe, P., White, R.F., Grandjean, P., 2006. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicol. Teratol. 28 (3), 363–375. https://doi.org/10.1016/j.ntt.2006.02.004.

Desrochers-Couture, M., Oulhote, Y., Arbuckle, T.E., et al., 2018. Prenatal, concurrent, and sex-specific associations between blood lead concentrations and IQ in preschool canadian children. Environ. Int. 121 (December), 1235–1242. https://doi.org/10.1016/j.envint.2018.10.043.

Dos Santos, A., Alessandra, M.A., Hort, M.C., et al., 2016. Methylmercury and brain development: a review of recent literature. J. Trace Elements Med. Biol.: Organ Soc. Miner. Trace Elements (GMS) 38 (December), 99–107. https://doi.org/10.1016/j.jtemb.2016.03.001.

Earl, R., Burns, N., Nettelbeck, T., Baghurst, P., 2016. Low-level environmental lead exposure still negatively associated with children's cognitive abilities. Aust. J. Psychol. 68 (2), 98–106. https://doi.org/10.1111/ajpy.12096.

EFSA, 2010. Scientific opinion on lead in food. EFSA J. 8 (4). https://doi.org/10.2903/j.efsa.2010.1570.

European Environment Agency, 2024. "Progress in Regulating Lead (Signal)." August 28. https://www.eea.europa.eu/en/european-zero-pollution-dashboards/indicators/progress-in-regulating-lead-signal.

European Food Safety Authority, 2012. Lead dietary exposure in the european population. EFSA J. 10 (7). https://doi.org/10.2903/j.efsa.2012.2831.

Grandjean, P., Budtz-Jorgensen, E., White, R.F., et al., 1999. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. Am. J. Epidemiol. 150 (3), 301–305. https://doi.org/10.1093/oxfordjournals.aje.a010002.

Gundacker, C., Hengstschläger, M., 2012. The role of the placenta in fetal exposure to heavy metals. Wien. Med. Wochenschr. 162 (9), 201–206. https://doi.org/10.1007/s10354-012-0074-3.

Hänninen, O., Knol, A.B., Jantunen, M., et al., 2014. Environmental burden of disease in europe: assessing nine risk factors in six countries. Environ. Health Perspect. 122 (5), 439–446. https://doi.org/10.1289/ehp.1206154.

HBM4EU, 2022. Lead Substance Report. https://www.hbm4eu.eu/wp-content/uploads/2022/07/Lead_Substance-report.pdf.

Heimfarth, L., Delgado, J., Mignori, M.R., Gelain, D.P., Moreira, J.C.F., Pessoa-Pureur, R., 2018. Developmental neurotoxicity of the hippocampus following in utero exposure to methylmercury: impairment in cell signaling. Arch. Toxicol. 92 (1), 513–527. https://doi.org/10.1007/s00204-017-2042-6.

Hong, S.-B., Im, M.-H., Kim, J.-W., et al., 2015. Environmental lead exposure and attention deficit/hyperactivity disorder symptom domains in a community sample of south korean school-age children. Environ. Health Perspect. 123 (3), 271–276. https://doi.org/10.1289/ehp.1307420.

ICD-10 WHO, 2019. "International Statistical Classification of Diseases and Related Health Problems - 10th Update." https://icd.who.int/browse10/2019/en#/F70-F79.

ICD-11 WHO, 2025. "International statistical classification of diseases and related health problems mortality and morbidity statistics - 11th update." https://icd.who.int/browse/2025-01/mms/en.

Institute For Health Metrics And Evaluation, 2024. "Global Burden of Disease Study 2021 (GBD 2021) Disability Weights." Institute for Health Metrics and Evaluation. Doi: 10.6069/485B-DX41.

Jiang, H., Gao, Y., Chen, X., et al., 2024. Single-cell study unveils lead lifespan in blood cell populations follows a universal lognormal distribution with individual skewness. Anal. Chem. 96 (2), 668–675. https://doi.org/10.1021/acs.analchem.3c03441.

Kou, X., Pallejà Millán, M., Canals, J., Rivera Moreno, V., Renzetti, S., Arija, V., 2025. "Effects of prenatal exposure to multiple heavy metals on infant neurodevelopment: a multi-statistical approach." Environ. Pollut. (Barking, Essex: 1987) 367 (February): 125647. Doi: 10.1016/j.envpol.2025.125647.

Lanphear, B.P., Hornung, R., Khoury, J., et al., 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 113 (7), 894–899. https://doi.org/10.1289/ehp.7688.

Lanphear, B.P., Hornung, R., Khoury, J., et al., 2019. Erratum: 'low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 127 (9), 099001. https://doi.org/10.1289/EHP5685.

Larsen, B., Sánchez-Triana, E., 2023. Global health burden and cost of lead exposure in children and adults: a health impact and economic modelling analysis. The Lancet Planetary Health 7 (10), e831–e840. https://doi.org/10.1016/S2542-5196(23)00166-3.

Lee, K.S., Kim, K.N., Ahn, Y.D., et al., 2021. "Prenatal and postnatal exposures to four metals mixture and IQ in 6-year-old children: a prospective cohort study in South Korea." Environ. Int. 157. Scopus. Doi: 10.1016/j.envint.2021.106798.

Lee, K., Cascella, M., Marwaha, R., 2023. "Intellectual Disability." In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK547654/.

Lucchini, R.G., Zoni, S., Guazzetti, S., et al., 2012. Inverse association of intellectual function with very low blood lead but not with manganese exposure in italian adolescents. Environ. Res. 118 (October), 65–71. https://doi.org/10.1016/j.envres.2012.08.003.

Lucchini, R.G., Guazzetti, S., Renzetti, S., et al., 2019. Neurocognitive impact of metal exposure and social stressors among schoolchildren in Taranto, Italy. Environ. Health 18 (1), 67. https://doi.org/10.1186/s12940-019-0505-3.

Marshall, A.T., Betts, S., Kan, E.C., McConnell, R., Lanphear, B.P., Sowell, E.R., 2020. Association of lead-exposure risk and family income with childhood brain outcomes. Nat. Med. 26 (1), 91–97. https://doi.org/10.1038/s41591-019-0713-y.

Martin, O., Scholze, M., Ermler, S., et al., 2021. Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. Environ. Int. 146 (January), 106206. https://doi.org/10.1016/j.envint.2020.106206.

Martin Van den Berg, Linda S. Birnbaum, Michael Denison, Mike De Vito, William Farland, Mark Feeley, Heidelore Fiedler, Helen Hakansson, Annika Hanberg, Laurie Haws, Martin Rose, Stephen Safe, Dieter Schrenk, Chiharu Tohyama, Angelika Tritscher, Jouko Tuomisto, Mats Tysklind, Nigel Walker, Richard E. Peterson, The 2005 World Health Organization Reevaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-Like Compounds, Toxicol. Sci. Volume 93, Issue 2, October 2006, Pages 223–241, https://doi.org/10.1093/toxsci/kfl055.

Menezes-Filho, J.A., Carvalho, C.F., Rodrigues, J.L.G., et al., 2018. Environmental co-exposure to lead and manganese and intellectual deficit in school-aged children. Int. J. Environ. Res. Public Health 15 (11), 2418. https://doi.org/10.3390/ijerph15112418.

Merced-Nieves, F.M., Arora, M., Wright, R.O., Curtin, P., 2021. Metal mixtures and neurodevelopment: recent findings and emerging principles. Curr. Opin Toxicol. 26 (June), 28–32. https://doi.org/10.1016/j.cotox.2021.03.005.

Mhungu, F., Cheng, Y., Zhou, Z., Zhang, W., Liu, Y., 2023. Estimation of the cumulative risks from dietary exposure to cadmium, arsenic, nickel, lead and chromium in Guangzhou, China. Food Chem. Toxicol. 178 (August), 113887. https://doi.org/10.1016/j.fct.2023.113887.

Myers, G.J., Thurston, S.W., Pearson, A.T., et al., 2009. Postnatal exposure to methyl mercury from fish consumption: a review and new data from the seychelles child development study. Neurotoxicology 30 (3), 338–349. https://doi.org/10.1016/j.neuro.2009.01.005.

National Research Council (US) Committee on the Toxicological Effects of Methylmercury, 2000. Toxicological Effects of Methylmercury. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK225778/.

NTP, 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf.

OECD, 2023. Valuing the Avoidance of IQ Losses in Children: A Large Scale Multi-Country Stated Preference Approach. OECD Environment Working Papers No. 219. Vol. 219. OECD Environment Working Papers. Doi: 10.1787/71574eb4-en.

Oleko, A., Saoudi, A., Zeghnoun, A., et al., 2024. Exposure of the general French population to metals and metalloids in 2014–2016: results from the Esteban study. Environ. Res. 252 (July), 118744. https://doi.org/10.1016/j.envres.2024.118744.

Peng, X., Yang, Y., Yang, S.u., Li, L., Song, L., 2024. Recent advance of microbial mercury methylation in the environment. Appl. Microbiol. Biotechnol. 108 (1), 235. https://doi.org/10.1007/s00253-023-12967-6.

Plass, D., Kienzler, S., Bessems, J., et al., 2023. Estimating the burden of disease due to lead, PFAS, phthalates, cadmium, pyrethroids and bisphenol a using HBM4EU data – test of feasibility and first results for selected countries. (Eionet Report – ETC HE 2023/13). European Topic Centre on Human Health and the Environment. https://www.eionet.europa.eu/etcs/all-etc-reports.

Plate, K., Knüppel, S., Hornbacher, A., Greiner, M., Müller-Graf, C., 2024. Development of a tool for rapid assessment of the evidence of human observational epidemiological studies with focus on risk of bias in the context of public health and risk assessment. EFSA Supporting Publ. 21 (7), 8925E. https://doi.org/10.2903/sp.efsa.2024.EN-8925.

Ray, S., Vashishth, R., Mukherjee, A.G., Gopalakrishnan, A.V., Sabina, E.P., 2025. Mercury in the environment: biogeochemical transformation, ecological impacts, human risks, and remediation strategies. Chemosphere 381 (July), 144471. https://doi.org/10.1016/j.chemosphere.2025.144471.

Rice, D., Jr, S.B., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108 (SUPPL. 3), 511–533. https://doi.org/10.1289/ehp.00108s3511.

Rodríguez-Barranco, M., Tobías, A., Redondo, D., Molina-Portillo, E., Sánchez, M.J., 2017. Standardizing effect size from linear regression models with log-transformed variables for meta-analysis. BMC Med. Res. Method. 17 (1), 44. https://doi.org/10.1186/s12874-017-0322-8.

Roy, A., Ettinger, A.S., Howard, Hu., et al., 2013. Effect modification by transferrin C2 polymorphism on lead exposure, hemoglobin levels, and IQ. Neurotoxicology 38 (September), 17–22. https://doi.org/10.1016/j.neuro.2013.05.005.

Salamanca-Fernández, E., Peinado, F.M., Esteban-López, M., et al., 2025. Sociodemographic determinants and temporal variability of blood lead levels (2003–2019) in a pooled analysis of nine studies in four european countries. Sci. Rep. 15 (1), 34562. https://doi.org/10.1038/s41598-025-17943-w.

Santoro, N., Singer, D.M., Mulvey, B.K., et al., 2024. Neighborhood-Scale Lead (Pb) Speciation in Akron, Ohio (USA) soils: primary sources, post-deposition diagenesis, and high concentrations of labile Pb. Environ. Geochem. Health 46 (5), 164. https://doi.org/10.1007/s10653-024-01954-z.

Schnaas, L., Rothenberg, S.J., Flores, M.-F., et al., 2006. Reduced intellectual development in children with prenatal lead exposure. Environ. Health Perspect. 114 (5), 791–797. https://doi.org/10.1289/ehp.8552.

Singh, K., Blechinger, S., Pelletier, L., et al., 2023. Characterizing variability in total mercury hair: blood ratio in the general Canadian population. Environ. Res. 224 (May), 115491. https://doi.org/10.1016/j.envres.2023.115491.

Sowers, T.D., Blackmon, M.D., Wilkin, R.T., et al., 2024. Lead speciation, bioaccessibility, and sources for a contaminated subset of house dust and soils collected from similar United States residences. Environ. Sci. Technol. 58 (21), 9339–9349. https://doi.org/10.1021/acs.est.4c01594.

Sprong, C., Biesebeek, J.D.T., Chatterjee, M., et al., 2023. A case study of neurodevelopmental risks from combined exposures to lead, methyl-mercury, inorganic arsenic, polychlorinated biphenyls, polybrominated diphenyl ethers and fluoride. Int. J. Hyg. Environ. Health 251 (June), 114167. https://doi.org/10.1016/j.ijheh.2023.114167.

Stacy, C., Amélie, C., Blanche, W., et al., 2024. A plausibility database summarizing the level of evidence regarding the hazards induced by the exposome on children health. Int. J. Hyg. Environ. Health 256 (March), 114311. https://doi.org/10.1016/j.ijheh.2023.114311.

Stajnko, A., Lundh, T., Assarson, E., Krook, E.Å., Broberg, K., 2024. Lead, cadmium, and mercury blood levels in schoolchildren in southern sweden: time trends over the last decades. Chemosphere 346 (January), 140562. https://doi.org/10.1016/j.chemosphere.2023.140562.

Tebby, C., Caudeville, J., Fernandez, Y., Brochot, C., 2022. Mapping blood lead levels in french children due to environmental contamination using a modeling approach. Sci. Total Environ. 808 (February), 152149. https://doi.org/10.1016/j.scitotenv.2021.152149.

Thomsen, S.T., Jakobsen, L.S., Redondo, H.G., et al., 2022. Burden of disease of dietary exposure to four chemical contaminants in Denmark, 2019. Exposure and Health 14 (4), 871–883. https://doi.org/10.1007/s12403-022-00461-9.

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36 (August), 1–48. https://doi.org/10.18637/jss.v036.i03.

Viechtbauer, W., 2025. Metafor: Meta-Analysis Package for R. V. 4.8-0. Released January 28. https://cran.r-project.org/web/packages/metafor/index.html.

Virgolini, M.B., Aschner, M., 2021. Molecular mechanisms of lead neurotoxicity. Adv. Neurotoxicol. 5, 159–213. https://doi.org/10.1016/bs.ant.2020.11.002.

Vogel, N., Murawski, A., Schmied-Tobies, M.I.H., et al., 2021. Lead, cadmium, mercury, and chromium in urine and blood of children and adolescents in Germany – human biomonitoring results of the German environmental survey 2014–2017 (GerES V).

Int. J. Hyg. Environ. Health 237 (August), 113822. https://doi.org/10.1016/j.ijheh.2021.113822.
Vorvolakos, Th., Arseniou, S., Samakouri, M., 2016. There is no safe threshold for lead exposure: α literature review. Psychiatrike = Psychiatriki 27 (3), 204–214. https://doi.org/10.22365/jpsych.2016.273.204.
Wang, H., Mao, W.F., Jiang, D.G., Liu, S.J., Zhang, L., 2021. Cumulative risk assessment of exposure to heavy metals through aquatic products in China. Biomed. Environ. Sci.: BES 34 (8), 606–615. https://doi.org/10.3967/bes2021.084.
WHO Guideline for the Clinical Management of Exposure to Lead. 2021. 1st ed. World Health Organization.
WHO, 1990. "Methylmercury (EHC 101, 1990)." https://www.inchem.org/documents/ehc/ehc/ehc101.htm.

Further reading

Budtz-Jørgensen, E., Grandjean, P., Weihe, P., 2007. Separation of risks and benefits of seafood intake. Environ. Health Perspect. 115 (3), 323–337. https://doi.org/10.1289/ehp.9738.