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A preliminary estimate of the environmental burden of disease associated with exposure to pyrethroid insecticides and ADHD in Europe based on human biomonitoring

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Abstract

Human biomonitoring (HBM) data indicate that exposure to pyrethroids is widespread in Europe, with significantly higher exposure observed in children compared to adults. Epidemiological, toxicological, and mechanistic studies raise concerns for potential human health effects, particularly, behavioral effects such as attention deficit hyperactivity disorder (ADHD) in children at low levels of exposure. Based on an exposure-response function from a single European study and on available quality-assured and harmonized HBM data collected in France, Germany, Iceland, Switzerland, and Israel, a preliminary estimate of the environmental burden of disease for ADHD associated with pyrethroid exposure was made for individuals aged 0–19 years. The estimated annual number of prevalence-based disability-adjusted life years (DALYs) per million inhabitants were 27 DALYs for Israel, 21 DALYs for France, 12 DALYs for both Switzerland and Iceland, and 3 DALYs for Germany; while the annual ADHD cases per million inhabitants attributable to pyrethroids were 2189 for Israel, 1710 for France, 969 for Iceland, 944 for Switzerland, and 209 for Germany. Direct health costs related to ADHD ranged between 0.3 and 2.5 million EUR yearly per million inhabitants for the five countries. Additionally, a substantial number of ADHD cases, on average 18%, were associated with pyrethroid exposure. Yet, these figures should be interpreted with caution given the uncertainty of the estimation. A sensitivity analysis showed that by applying a different exposure-response function from outside the EU, the population attributable fraction decreased from an average of 18 to 7%. To ensure more robust disease burden estimates and adequate follow-up of policy measures, more HBM studies are needed, along with increased efforts to harmonize the design of epidemiological studies upfront to guarantee meta-analysis of exposure-response functions. This is particularly important for pyrethroids as evidence of potential adverse health effects is continuously emerging.

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Introduction

Pyrethroid (PYR) insecticides are a group of synthetic pesticides based on the naturally occurring compound pyrethrum or pyrethrin, extracted from the flowers of *Chrysanthemum cinerariaefolium* [1]. They are one of the most used pesticides globally, covering around 30% of the global insecticide market [2]. Well-known representatives of pyrethroids include deltamethrin, cypermethrin and permethrin. Pyrethroids are primarily used in agriculture as active substances in plant protection products (PPP) and as biocides in various domestic biocidal products. Additionally, they serve as active ingredients in several consumer products (e.g., wood products, textile) and veterinary medication (e.g., treatment of scabies or lice) [3].

The main exposure route for the general population is ingestion of pyrethroid residues from food commodities and contaminated drinking water [4]. Occupational exposure usually occurs through the dermal and inhalation route due to direct contact during pesticide applications. Inhabitants of rural areas or individuals living near treated agricultural fields may also be exposed via pesticide drifts, as well as from the evaporation of active substances and even via contaminated soil and dust particles [4].

While pyrethroid sales in the EU have increased in recent years [5], limited information exists on how this has impacted exposure trends. Human biomonitoring (HBM) programs worldwide indicate an increasing exposure to pyrethroids by measuring the internal levels of respective biomarkers of exposure; for instance, the United States Centers for Disease Control and Prevention (US CDC) reported a rise in urinary 3-phenoxybenzoic acid (3-PBA), a non-specific biomarker for several pyrethroids, from a geometric mean (GM) of 0.29 µg/L urine to 0.42 µg/L between 1999 and 2010 [6]. Similar trends were observed in the Canadian HBM program (CHMS, Canadian Health Measures Survey) with urinary 3-PBA levels in the urine of the general population having increased from a GM of 0.25 µg/L (2007) to 0.43 µg/L (2011) [7]. However, there is a lack of European data to establish clear-cut time trends. In the HBM4EU (European Human Biomonitoring Initiative; www.HBM4EU.eu) project, time pattern data on 3-PBA indicate higher urinary concentrations in recent years compared to a decade ago although studied places and age-groups may differ limiting comparability (Fig. 1). Moreover, differences in HBM data were correlated with socio-economic status (SES) and age, with higher concentrations of 3-PBA detected in children compared to adults and in individuals of lower SES [8].

The increased use of pyrethroids in agriculture can be explained by the phasing out of more notorious pesticides such as those based on organophosphate active substances. There are concerns regarding the use of pyrethroids as a growing body of epidemiological evidence

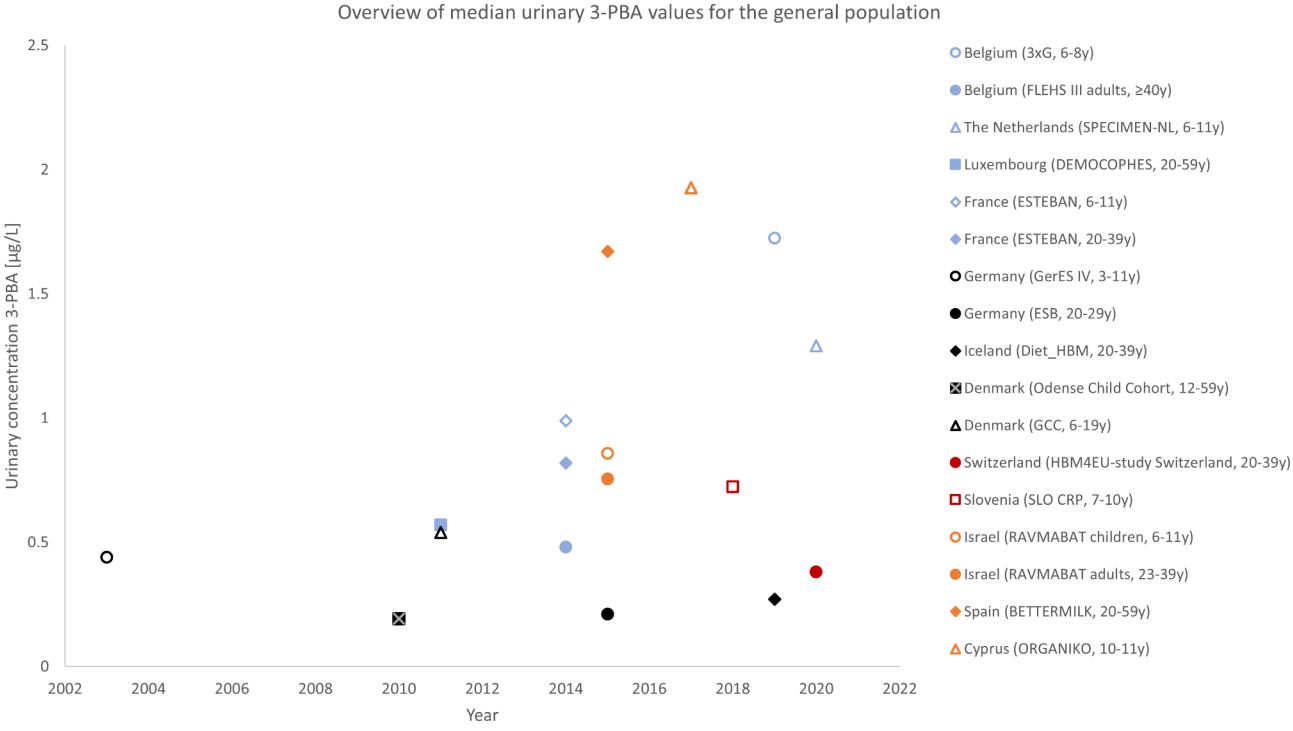

Fig. 1 Time pattern of median 3-PBA concentrations in urine for 11 European countries and Israel. Symbols with and without fill represent adult and children study populations, respectively. Results extracted from the HBM4EU dashboard (European Human Biomonitoring Dashboard | VITO HBM))

suggests that prenatal exposure to pyrethroids adversely impacts neurodevelopment in the offspring, with attention-deficit hyperactivity disorder (ADHD) and autism-spectrum disorder (ASD) often being implicated [9–11].

ADHD (ICD-10 F90) is mostly observed in children and is characterized by difficulties regarding problem-solving abilities, paying attention, and hyperactivity [12]. ADHD is estimated to affect around 5% of the world's overall population [13], accounting for approximately one million DALYs (disability-adjusted life years) for the year 2019 [14]. In Europe the prevalence of ADHD has also increased by 6% between 1990 and 2019 with unknown underlying reasons [15].

ADHD is one of the neurodevelopmental diseases with the highest heritability rates, with estimates ranging from 54 to 70% [10]. Around 10–40% of the variance regarding ADHD etiology is said to be explained by environmental, pre- or postnatal risk factors [12, 16].

In addition to epidemiological information, there is increasing evidence for neurodevelopmental effects of pyrethroids in animal toxicity studies [20]. Adverse outcome pathways (AOPs) provide mechanistic evidence suggesting that pyrethroids may affect ADHD risk, e.g., via modification of human Na^+-voltage-gated (Nav) channels, disturbance of thyroid hormones, neuroinflammation, and altered levels of brain-derived neurotrophic factor (BDNF) [10, 21, 22].

Based on epidemiological, toxicological and mechanistic data, the working group on pesticides from the HBM4EU initiative, including the European Environment Agency (EEA), evaluated the evidence for an association between behavioral effects (ADHD) in children and prenatal exposure to pyrethroids to be "strong" [4, 23]. In a recent assessment, Inserm (the French National Institute for Health and Medical Research) also found strong evidence to support a causal link between prenatal pyrethroid exposure and an increase in internalized types of behavioral disorders in children (e.g., anxiety) [24].

There is currently a scarcity of burden of disease estimates for pesticides. The aim of this study is to address this gap by making a first estimate of the burden associated with ADHD due to prenatal exposure to pyrethroids. For this risk-outcome pair, ample evidence from epidemiological, toxicological and mechanistic studies is available [10, 17–22]. This work has been carried out under the Partnership for the Assessment of Risks from Chemicals (PARC; https://www.eu-parc.eu/) and the European Topic Center on Environment and Health of the EEA (ETC HE) and builds further on HBM4EU insights. 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).

Methodology

Pyrethroid exposure

Information on harmonized urinary pyrethroid human metabolite concentrations in children and adults was gathered in the HBM4EU project. Data were retrieved from the HBM4EU dashboard (https://hbm.vito.be/eu-hbm-dashboard). Only HBM studies conducted within the HBM4EU aligned studies were included as they were subject to the same quality assurance/control (QA/QC) program, thus making their results comparable. Based on this, exposure data were available for five countries (France, Germany, Iceland, Switzerland, and Israel) with sample collection performed between 2014 and 2021. Ideally, exposure data from pregnant women or women of child-bearing age should be used given that the greatest evidence is found for prenatal exposure. However, no such data were available, instead adult exposure data were assumed to be a reliable approximation as no statistical differences for 3-PBA by sex were observed in adult data for HBM4EU.

Although multiple pyrethroid metabolites were measured in the HBM4EU studies, 3-PBA is selected for the environmental burden of disease (EBD) analysis. 3-PBA is one of the most measured and reported metabolites in epidemiological studies and comprises a nonspecific metabolite of multiple pyrethroid compounds (i.e., cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, denvalerate, permethrin and tralomethrin) [25], making it more representative of overall pyrethroid exposure compared to other metabolites. Consequently, 3-PBA concentrations in urine are taken as a surrogate measure for pyrethroid exposure.

Sampling in the HBM4EU aligned studies mainly consisted of the collection of spot or morning urine samples. Pyrethroids are readily metabolized in humans, with half-lives reported to be 6.4 to 7.6 h [26–30]. The metabolism of the specific pyrethroids consists of the parent compounds being hydrolyzed to 3-phenoxybenzyl alcohol or 3-phenoxybenzaldehyde, which are then converted to 3-PBA. Conjugation with glucuronic acid further facilitates excretion. In mammals pyrethroid esters are mostly eliminated in urine (93%) during the first 24 h [31, 32].

Adult HBM data was retrieved for the years 2014–2021. Data on concentrations of 3-PBA in urine (percentiles: P05, P10, P25, P50, P75, P90, P95), number of samples, sampling type, sample year, and country for each of the HBM studies were extracted in February 2023 (Table 1). Urinary concentrations for 3-PBA in adults varied between <LOQ (limit of quantification, 0.1 μg/L) up to 2.9 μg/L (P95 in the study of Israel) (Table 1). Relatively

Table 1 Adult urinary 3-PBA concentrations (µg/L) measured in HBM aligned studies under the HBM4EU project (2014–2021)

Country (Study)	Sampling year	Sample type	*N*	Percentiles						
				P05	P10	P25	P50	P75	P90	P95
France**	2014–2016	First morning	144	0.197	0.251	0.438	0.819	1.341	2.015	2.773
Iceland*	2019–2021	Spot	194	< LOQ	< LOQ	0.148	0.270	0.546	1.188	1.650
Switzerland*	2020	First morning	299	< LOQ	0.110	0.190	0.380	0.680	1.220	1.932
Germany*	2015–2020	24 h	180	< LOQ	< LOQ	0.128	0.210	0.363	0.544	0.770
Israel*	2015–2016	Spot	83	0.142	0.187	0.360	0.754	1.358	2.338	2.874

The studies of France (ESTEBAN), Israel (RAV-MABAT), Iceland (DIET-HBM) and Switzerland (HBM4EU) are national studies; German data are from the Environmental Specimen Bank; LOQ = 0.1 µg/L for all studies

*: Biomarker data quality assured by HBM4EU QA/QC program [33]

**: Biomarker data generated before HBM4EU but conducted according to a comparable QA/QC program [33]

Table 2 Internal adult exposure to pyrethroids stratified by education. Biomarker is 3-PBA in urine (µg/L)

Country	ISCED	*N*	P05	P10	P25	P50	P75	P90	P95
France	0–2	< 50	N.A.						
	3–4	< 50	N.A.						
	≥ 5	103	0.192	0.238	0.404	0.797	1.277	1.995	2.741
Iceland	0–2	< 50	N.A.						
	3–4	58	< LOQ	< LOQ	0.181	0.293	0.558	1.442	1.727
	≥ 5	122	< LOQ	< LOQ	0.123	0.249	0.504	1.135	1.618
Switzerland	0–2	< 50	N.A.						
	3–4	69	0.100	0.126	0.230	0.520	0.840	1.646	2.176
	≥ 5	223	< LOQ	0.110	0.180	0.350	0.650	1.098	1.476
Germany	≥ 5	180	< LOQ	< LOQ	0.128	0.210	0.363	0.544	0.770
Israel	0–2	< 50	N.A.						
	3–4	66	0.146	0.185	0.338	0.803	1.439	2.287	3.034
	≥ 5	< 50	N.A.						

N.A.: data with *N* < 50 not available due to privacy considerations (GDPR); LOQ = 0.1 µg/L for all studies; ISCED = International Standard Classification of Education

higher median concentrations were found in Israel and France compared to Iceland, Switzerland, and Germany.

Exposure data stratified by educational attainment (using the International Standard Classification of Education (ISCED)) are shown in Table 2, which shows that individuals with a lower ISCED category (0–2) are underrepresented in these studies.

Exposure-response

The starting point for selecting an exposure-response function (ERF) for the calculation of the EBD was the substance report of the HBM4EU project [4], specially referencing the peer reviewed article by Andersen et al. (2022) on exposure to pyrethroids and developmental neurotoxicity [10]. Additionally, major institutional and project websites were consulted including those of the European Food Safety Authority (EFSA), the European Environment Agency (EEA), the European Chemicals Agency (ECHA), the Agency for Toxic Substances and Disease Registry (ATSDR) and the United States Environmental Protection Agency (US EPA), to search for additional information on health effects, particularly ADHD, associated with pyrethroid exposure. Alongside this information, a literature search was performed in the scientific peer reviewed literature using PubMed (search string: ("dose-response" OR "dose-effect" OR "exposure-response" OR "exposure-effect" OR "ERF" OR "DRF" OR "odds ratio" OR "relative risk" OR "OR" OR "RR") AND "pyrethroid*" AND "ADHD"). The primary focus was to identify cohort studies with data on *in utero* exposure, as this is the most sensitive window of exposure, for which the evidence for adverse neurodevelopmental effects (e.g., ADHD) is strongest [10]. Studies on occupational exposures and animal data were excluded for the EBD calculations. Based on these search considerations, eight relevant studies were found through PubMed, of which three cohort studies, focusing on gestational exposure and ADHD, were initially retained (Table 3) (Lee et al. 2022; An et al., 2022; Dalsager et al., 2019).

Since exposure and outcome measures, ADHD assessment methods, regression model adjustment for covariates and confounders, study design, age of the individuals at examination, etc. differ considerably between epidemiological studies, performing a meta-analysis for the derivation of an ERF is not feasible [10]. Out of the selected cohort studies in Table 3, the study by Dalsager et al. (2019) was the only European study reporting an ERF for pyrethroid exposure and increasing odds of ADHD and was therefore deemed to be most relevant for the European context and for this reason was selected for the

Table 3 Overview of cohort studies reporting exposure-effect functions for prenatal pyrethroid exposure and behavioral problems in offspring

Publication; country	Maternal body burden [µg/L]*	Number and age of offspring	Exposure-effect function	Covariates in model
Dalsager et al. (2019); Denmark	P25 = 0.14 P50 = 0.21 P75 = 0.46 P95 = 1.96	948 children aged 2 to 4 years	Doubling prenatal maternal 3-PBA associated with 3% (95% CI 0% – 7%) increase in ADHD scores and 13% (95% CI 1% – 25%) higher odds of ADHD score ≥ P90 which is a predictor of later ADHD diagnosis	Creatinine, maternal education, parity, maternal age, parental psychiatric diagnosis, smoking, child age at examination, sex, preterm birth, birth weight and duration breastfeeding
Lee et al. (2022); South-Korea	GM = 0.65 P05 = 0.07 P50 = 0.77 P95 = 4.14	524 children aged 6 and 8 years	Doubling prenatal maternal 3-PBA associated with 2.7% (95% CI 0.3% – 5.2%) increase of ADHD scores (ADHD rating scores IV, ARS) at age 6 years	Maternal age at pregnancy, maternal education, family income, maternal smoking during pregnancy, diabetes mellitus during pregnancy, child's age, sex of child, BMI, birth order, delivery mode during pregnancy, premature delivery, low birth weight, breastfeeding, season of exposure and urine creatinine
An et al. (2022); South-Africa	GM = 1.113 P10 = 0.394 P50 = 1.048 P90 = 3.178	683 children aged 2 years	*In utero* log-unit increase in 3-PBA associated with increased risk of externalizing behavior (relative risk of 1.35 (95% CI 1.03–1.78) but not ADHD as defined in the article. Externalizing behavior included attention and aggressive behavior, for which attention problems are ADHD-related	Maternal education, age at delivery, risk for depression, HOME z-score, breastfeeding status at 1-year and food poverty status

*PX represents the X^{th} exposure percentile, while GM represents the geometric mean. All values reflect maternal urine 3-PBA values during pregnancy

base case EBD analysis. This study – based on the Danish Odense child cohort [37] – found that the doubling of prenatal maternal 3-PBA urinary concentration is associated with a 3% increase in ADHD scores in 2–4 year-old children and 13% higher odds of ADHD score ≥ P90 (OR of 1.13; 95% CI: 1.01–1.25), which is a predictor of later ADHD diagnosis [38]. No effect was assumed for biomarker concentrations under 0.132 µg 3-PBA/L urine [38]. The Korean Environment and Development of Children (EDC) cohort study by Lee et al. (2022) found a similar effect as the Danish study but at higher pyrethroid exposure (Table 3). This study was further used in a sensitivity analysis. A similar study performed in South-Africa by An et al. on the VHEMBE population, a population highly exposed to insecticides (e.g., DDT and pyrethroids) for malaria control, only found an association with pyrethroid exposure and externalizing behavior problems. In this study, the CBCL: 1.5-5 was used though it is not entirely clear which questions from the CBCL list were used to assess behavior problems and ADHD. Moreover, the list was not validated for the local Vhembe population, cross-cultural influences may therefore persist [36]. A study with similar positive findings on externalizing behavior and exposure to 3-PBA as the one from An et al., is the US study by Furlong et al. (2017) [39]. The study of An et al. was not considered seeing the high exposure to insecticides, including DDT which might influence findings for pyrethroids as DDT affects sodium channels [40] similarly to pyrethroids and could thus impact behavior [11, 41, 42].

DALY calculation

The EBD for ADHD attributable to pyrethroids exposure was estimated for French, Icelandic, Swiss, German, and Israeli population groups aged 0–19 years. A prevalence-based approach was used to calculate DALYs and attributable ADHD cases, therefore justifying the expansion of the window of effect compared to the age category for which the exposure-effect association was derived, assuming that prevalent cases of ADHD could have developed at an earlier age and having persisted throughout late adolescence [43]. During adulthood ADHD symptoms can become more manageable, with a fraction of the cases potentially becoming asymptomatic (33–50%) [44]; for this reason, the effect window was not expanded beyond 19 years of age.

The applied methodology follows the comparative risk assessment approach [45, 46]. In brief, data on prevalence and total non-sex-specific burden of disease for ADHD were retrieved for France, Iceland, Switzerland, Germany, and Israel from the Global Burden of Disease study by the Institute of Health Metrics and Evaluation (IHME) for the year 2021 (Tables 4 and 5) [47].

Prevalence rates for the age-group 0–19 years varied between 1.43% (Germany) and 3.37% (France) for the year 2021 (Table 4). Higher prevalence rates were observed in, e.g., Spain (6.37% in the 0–19-year category; data IHME) as well as higher exposure to pyrethroids (existing data collected under HBM4EU and derived from HBM4EU dashboard but not quality assured under HBM4EU; P50 5.91 µg 3-PBA/L). The data showed that prevalence of ADHD is <5% and the odds ratio of 1.13 (95% CI: 1.01–1.25) by Dalsager et al. (2019) was applied

Table 4 Overview of ADHD disease burden (prevalence and DALYs) for age category of 0–19 years for France, Israel, Iceland, Switzerland, and Germany. Data extracted from IHME for the year 2021

Country	Prevalence of ADHD in 2021 [%]	Prevalence of ADHD in 2021 (total cases)	DALYs (total number)
France	3.37	430,948	5286
Israel	2.97	83,891	1030
Iceland	3.27	2395	29
Switzerland	3.54	49,596	607
Germany	1.43	183,030	2244

Numbers rounded to the nearest integer

IHME data are prone to updates; thus, updated data from the 28th of June 2024 were used for all estimations

Table 5 Overview of ADHD disease burden per 10^6 inhabitants for the age category of 0–19 years for France, Israel, Iceland, Switzerland, and Germany. Numbers based on IHME data for the year 2021

Country	Prevalence of ADHD per 10^6 inhabitants	DALYs per 10^6 inhabitants
France	6491	80
Israel	8744	107
Iceland	6834	84
Switzerland	5558	68
Germany	2144	26

Numbers rounded to the nearest integer

as a proxy for the relative risk (RR) [48, 49]. Based on the relative risk and the proportion of the population exposed, the population attributable fraction (PAF) was calculated using the Levin equation [50] (Eq. 1).

$$\mathrm{PAF} = \frac{\mathrm{f} \times (\mathrm{RR} - 1)}{\mathrm{f} \times (\mathrm{RR} - 1) + 1} \quad (1)$$

In which f represents the fraction of the population exposed and RR the relative risk.

The EBD, expressed in prevalence-based DALYs, was calculated by multiplying the burden of disease (IHME 2024) with the PAF (Eq. 2). This way, the prevalence-based EBD for ADHD associated with pyrethroid exposure was calculated for the year 2021.

$$\mathrm{EBD} = \mathrm{BoD} \times \mathrm{PAF} \quad (2)$$

In which:

- PAF represents the population attributable fraction of ADHD associated with exposure to pyrethroids.
- BoD [in DALYs or total ADHD cases] represents the total burden of disease for ADHD, i.e., before consideration of any risk factor attribution.
- EBD [in DALYs or total ADHD cases] represents the environmental burden of disease for ADHD attributable to pyrethroid exposure.

Health economic analysis

Based on the estimated attributable number of ADHD cases, the direct medical costs associated with ADHD were assessed for the population of 0–19-year-olds in the targeted countries. Costs were based on the German study of Libutzki et al. (2019) and values were transferred to other countries using purchasing power parity (PPP) correction and inflation (HICP) adjustment to 2021 [51].

Libutzki et al. (2019) estimated the surplus costs incurred by individuals with ADHD compared to those without to be on average 1508 EUR (direct medical costs for all groups, for the reference year 2014); the main cost drivers are respectively hospital cost (inpatient care), psychiatrist appointment, and expenses for ADHD medication, while other factors only contributed minimally.

Based on the health costs per ADHD case (relative to individuals without ADHD) and the number of ADHD cases attributable to pyrethroid exposure (total amount of cases or per 10^6 inhabitants), the attributable health costs can be calculated as follows:

$$\text{Attributable health costs} = \text{attributable cases} \times \text{cost per case} \quad (3)$$

Disease burden and health economic estimates were not age-weighted or time-discounted. All estimations were made for the reference year 2021. Uncertainty analysis on the estimation was performed using Monte Carlo simulation (Cristal Ball, version 11.1.2.4.850) taking into account the uncertainty of the exposure-response function, the total disease burden and the population size.

Results

Table 6 shows the PAF, the EBD (measured in DALYs and in attributable ADHD cases) and the attributable health costs for France, Iceland, Switzerland, Germany and Israel based on HBM data gathered from the aligned HBM4EU studies and on exposure-effect information from Dalsager et al. (2019) (base case analysis). The population attributable fraction (PAF) varied between 10 and 26% with an average of 18%, implying that approximately 1 in 5 ADHD cases is associated with exposure to pyrethroids.

A secondary analysis was performed using the same HBM data and economic data for the five countries but using the exposure-response information from Lee et al. (2022). These results are illustrated in Table 7. In this reanalysis, the population attributable fraction varies between 1 and 12% with an average of 7%, meaning that

Table 6 Base case environmental burden of disease results (PAF, prevalence-based EBD [DALYs and attributable cases], and attributable health costs) of ADHD associated with exposure to pyrethroids based on the exposure-response information of Dalsager et al. (2019)

Country	PAF (95% CI) [%]	EBD (95% CI) [attributable cases]	EBD (95% CI) [attributable cases per 10^6 inhabitants]	EBD (95% CI) [DALYs]	EBD (95% CI) [DALYs per 10^6 inhabitants]	Attributable health costs (95% CI) [million EUR]	Attributable health costs per 10^6 inhabitants (95% CI) [million EUR]
France	26 (22–30)	113,543 (59094–170931)	1710 (890–2589)	1393 (425–2455)	21 (6–37)	156.2 (81.3–235.1)	2.4 (1.2–3.6)
Iceland	14 (5–22)	339 (95–655)	969 (273–1927)	4 (1–9)	12 (2–27)	0.6 (0.2–1.2)	1.7 (0.5–3.5)
Switzerland	17 (6–27)	8421 (2574–15143)	944 (282–1701)	103 (16–204)	12 (2–23)	17.4 (5.3–31.3)	2.0 (0.6–3.5)
Germany	10 (-4–22)	17,801 (-5757–44894)	209 (-67–522)	218 (-80–613)	3 (-1–7)	29.6 (-9.6–74.6)	0.3 (-0.1–0.9)
Israel	25 (19–30)	21,003 (11619–31569)	2189 (1188–3352)	258 (60–455)	27 (6–49)	23.8 (13.2–35.7)	2.5 (1.3–3.8)

Table 7 Sensitivity analysis environmental burden of disease results (PAF, prevalence-based EBD [DALYs and attributable cases], and attributable health costs) of ADHD associated with exposure to pyrethroids based on the dose-response information of Lee et al. (2022)

Country	PAF (95% CI)	EBD (95% CI) [attributable cases]	EBD (95% CI) [attributable cases per 10^6 inhabitants]	EBD (95% CI) [DALYs]	EBD (95% CI) [DALYs per 10^6 inhabitants]	Attributable health costs (95% CI) [million EUR]	Attributable health costs per 10^6 inhabitants (95% CI) [million EUR]
France	12 (11–13)	52,318 (28685–76314)	788 (426–1168)	642 (162–1091)	10 (3–17)	72.0 (39.5–105.0)	1.1 (0.6–1.6)
Iceland	4 (1–7)	99 (10–198)	283 (30–567)	1 (0–3)	3 (0–8)	0.2 (0.02–2.8)	0.5 (0.05–1.0)
Switzerland	6 (4–7)	2807 (1373–4503)	315 (150–518)	34 (10–60)	4 (1–7)	5.8 (2.8–9.3)	0.7 (0.3–1.0)
Germany	1 (-1–3)	2405 (-2034–6918)	28 (-24–81)	29 (-22–94)	0 (0–1)	4.0 (-3.4–11.5)	0.05 (-0.04–0.1)
Israel	12 (11–12)	9929 (5358–14002)	1035 (547–1521)	122 (33–216)	13 (4–23)	11.2 (6.1–15.8)	1.2 (0.6–1.7)

in this calculation, approximately 1 in 14 ADHD cases is associated with exposure to pyrethroids.

Discussion

Pyrethroids burden of disease

This study provides a preliminary estimate of the ADHD related disease burden attributable to pyrethroids exposure among 0–19-year-olds for France, Iceland, Switzerland, Germany, and Israel (Table 6). On average, it was found that almost 1 in 5 cases of ADHD is associated with exposure to pyrethroids. This estimate is similar to what has been found for exposure to organophosphates and ADHD [52]. The highest disease burden attributable to pyrethroids was estimated for France (1393 DALYs), followed by Israel (258 DALYs), Germany (218 DALYs), Switzerland (103 DALYs), and lastly Iceland (4 DALYs). When the disease burden attributable to pyrethroids is normalized to the population size, the highest EBD is found for Israel (27 DALYs per 10^6), followed by France (21 DALYs per 10^6), Iceland and Switzerland (both 12 DALYs per 10^6), and finally Germany (3 DALYs per 10^6). The number of ADHD cases attributable to pyrethroid exposure varied between 113,543 ADHD cases (France) and 339 (Iceland). When the attributable cases due to pyrethroids are normalized to population size, the highest burden is found for Israel (2189 ADHD cases per 10^6) and the lowest for Germany (209 ADHD cases per 10^6). The variation in EBD estimates for the five different countries is due to the difference in urinary 3-PBA concentration and the total disease burden for ADHD (only 26 DALYs per 10^6 and 2144 ADHD cases per 10^6 for Germany compared to 68–107 DALYs per 10^6 and 5558–8744 ADHD cases per 10^6 for the other four countries).

An initial health economic estimation is also provided in this study, focusing solely on the direct costs related to ADHD. Costs varied between 0.6 MEUR (Iceland) and 156.2 MEUR (France). When direct health costs are normalized to population size, the estimates range from 0.3 to 2.5 MEUR per 10^6 for the five countries. These health economic costs provide a conservative estimation as only the direct health costs of ADHD were considered. It is assumed that the economic burden would be greater if indirect medical costs and non-medical costs (e.g., lost productivity, presenteeism, absenteeism experienced by the parents of the child suffering from ADHD or experienced by individuals whose ADHD persists into adulthood) would also be considered.

The base case results discussed here are supplemented with sensitivity analysis results (Table 7). When the exposure-response information from the study of Lee (South-Korea) is applied, the average PAF decreases from 18 to 7% resulting in a lower number of attributable cases, DALYs, and costs.

Comparison of disease burden with other chemicals

The EBD for ADHD associated with pyrethroid exposure was compared with the EBD due to lead (Table 8) as this is the only environmental chemical risk factor for which the IHME has estimated the disease burden. The disease burden associated with lead was estimated for cardiovascular disease (CVD), idiopathic developmental intellectual disability (IDID), and kidney diseases by the IHME (IHME, 2024). A comparison for the age category 0–19 years was made. The estimated EBD for pyrethroids (based on the exposure-response function from Dalsager) was higher than the EBD for lead exposure for all countries (ratio EBD pyrethroids to lead of 1.02–1.37) except for Germany, where the EBD for lead was higher than that for pyrethroids (ratio EBD pyrethroids to EBD lead of 0.37).

The EBD for pyrethroids is comparable to that of lead in terms of order of magnitude (EBD ratio varying between 0.37 and 1.37 for selected countries) even though only one health outcome was selected for pyrethroids (ADHD) compared to multiple health outcomes for Pb (CVD, mental disorders, and kidney diseases). However, CVD and kidney diseases cause a low disease burden in individuals aged 0–19 years, and usually have an onset later in life. Consequently, the EBD for Pb is primarily driven by idiopathic developmental intellectual disability, a health outcome similar to ADHD in terms of disability weight (0.045 for ADHD compared to 0.043 and 0.100 for mild and moderate intellectual disability, respectively) [53]. The EBD estimates for pyrethroids and Pb for 0–19-year-olds are low when compared with the EBD for Pb for all ages (i.e., Pb-associated EBD of 103015 DALYs for all ages compared to 1031 DALYs for 0–19 years for France). This difference in EBD can be explained by a higher prevalence of CVD and kidney diseases during adulthood and higher disability weights for CVD and kidney diseases compared to ADHD or intellectual disability. The impact of neurodevelopmental disorders might be better reflected through the total associated economic cost (direct and indirect costs) related to health care expenditure, lost productivity during adulthood and psychosocial consequences among others.

When using the exposure-response information from the study of Lee, the EBD ratio of pyrethroids to lead shifts from 0.37 to 1.37 to 0.05–0.62. On average, this change in ERF information alters the disease burden of pyrethroids relative to lead by approximately a factor of three for individuals aged 0–19 years in the selected countries.

Table 8 Comparison of EBD [DALYs] between pyrethroids (for ADHD) and lead (for CVD, IDID and kidney diseases). EBD results of lead are adapted from the IHME for the year 2021. EBD estimates are for the age category 0–19 years

Country	EBD pyrethroids (95% CI) [DALYs]	EBD lead (95% CI) [DALYs]	Ratio EBD pyrethroids to EBD lead
France	1393 (425–2455)	1031 (257–2259)	1.35
Iceland	4 (1–9)	2.93 (0.5–7)	1.37
Switzerland	103 (16–204)	83 (14–198)	1.24
Germany	218 (-80–613)	585 (68–1492)	0.37
Israel	258 (60–455)	252 (63–527)	1.02

Exposure-response information from Dalsager et al. applied

Discrepancy in risk-assessment and epidemiology

In the context of risk assessment, exposure levels throughout the population are compared to toxicological reference values (TRVs). Human biomonitoring guidance values (HBM-GVs) can represent such TRVs for the general population and are defined as the concentration of a substance or its specific metabolite(s) in human biological media (e.g., urine, blood, hair) at and below which, according to current knowledge, no risk of health impairment is anticipated, and consequently no need for action is considered [54]. Recent epidemiological studies show associations between pyrethroid exposure and diagnosis of ADHD and other neurodevelopmental problems in children even at concentrations below the most stringent HBM guidance value for 3-PBA in urine (1.7 µg/L) [55, 56]. The HBM-GVs currently in place might thus not be sufficiently protective for the effects of developmental neurotoxicity [57]. This could be explained by the insensitivity of animal tests for neurotoxicity, used in this case for the derivation of HBM-GVs, regarding neurodevelopmental effects.

Inequality concerning exposure and disease burden

Reducing health inequalities is a main action point under the Zero Pollution Action Plan (ZPAP). Differences in chemical exposure as well as in vulnerability and susceptibility exist for individuals of different socio-economic status. This leads to environmental health inequalities. By getting a clearer view on exposure and disease burden differences according to SES, measures to reduce exposure can be more strongly tailored towards relevant population groups. From the limited data shown in Table 2, it can be observed that individuals with a lower education are generally more exposed to pyrethroids than those with a higher education. Additionally, individuals of more deprived backgrounds are 1.5 to 4 times more likely to suffer from ADHD compared to those from less deprived backgrounds [13].

However, a SES-specific EBD analysis could not be performed in this study due to the underrepresentation of the lower education categories in the HBM studies; because of this, aggregate exposure data were not available. Ideally, a SES-stratified EBD analysis would not only require exposure data but also ERF data and other model

parameters stratified by SES to more accurately estimate the environmental burden of disease across social groups [58]. The problem herein is that exposure-response relationships are often corrected for but not stratified by SES, with the notable exception of lead [59].

It should also be noted that the categorization used in the HBM4EU studies based on ISCED might no longer reflect the current educational tendencies seen in Europe. With education being far more accessible for Europeans at present – and with an increasing trend of individuals completing tertiary education, especially in Western and Northern European countries – having a medium education category consisting of ISCED 3–4 (i.e., high school education and post-secondary non-tertiary education) would seem outdated and/or unpractical for SES stratification [60]. A more updated categorization would be to dichotomize education into a lower (ISCED 0–4) and a higher (5–8) class. Most importantly, this would then also provide a solution to the problem encountered in the HBM4EU studies, in which the lower education category was systematically underrepresented compared to the other two categories (Table 2).

Uncertainty

A significant source of uncertainty in this EBD analysis arises from the ERF used from single studies as opposed to a more robust pooled ERF from a meta-analysis. The measured health effect considered in this ERF was the Child Behavior Checklist for ages 1.5–5 years (CBCL: 1.5-5), which provides severity scores of ADHD symptoms and requires parents or guardians to answer a questionnaire rather than using medical records or appropriate neuropsychological assessment [38]. Although the outcome of the CBCL: 1.5-5 (ADHD scores above P90) is only a predictor of future ADHD diagnosis and not an explicit clinical diagnosis, the CBCL: 1.5-5 is a well-established empirical method with high validity and reproducibility. Moreover, in the context of screening entire cohorts, assessing ADHD in a clinical setting is not feasible and would require too many resources.

To obtain a better comprehension of the uncertainty, a sensitivity analysis was performed using more conservative exposure-effect information based on the study by Lee et al. (2022). In this study, an effect similar in size to that observed in the Danish study was seen but at higher pyrethroid exposure values (median values were three times higher). Much of the uncertainty and variance in results thus depends on the exposure-response function and the reference population selected in these studies.

Another aspect of uncertainty is the fact that 3-PBA exposure data are based on a single spot or morning urine sample in most studies. Since pyrethroids are metabolized and excreted from the body within hours to days, serial urine sampling would provide a more accurate estimation of the actual exposure. However, it is generally assumed that exposure levels reach a (quasi) steady state and thus remain relatively stable in populations continuously exposed to low amounts of pyrethroids through food residues, justifying the use of single spot urine samples [34]. Also, the 3-PBA exposure data that were used, were based on the adult population from the aligned studies performed within HBM4EU, whereas exposure data for women of child-bearing age (20–40 years of age) would have been more appropriate.

The possibility of reverse causality must be acknowledged. In particular, children with ADHD may experience increased exposure due to their heightened activity levels, resulting in a greater accumulation of pyrethroid metabolites in their bodies. Nevertheless, it is anticipated that the impact of reverse causation will be less significant in cohort studies where maternal body burdens are linked to childhood health, as opposed to cross-sectional studies conducted postnatally.

Another source of uncertainty is the fact that the body burden of 3-PBA does not reflect exposure to all pyrethroids (only that of cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, denvalerate, permethrin and tralomethrin) [25]; therefore, the EBD estimates based on 3-PBA can underestimate the true disease burden linked to pyrethroids. In addition, urinary 3-PBA concentrations do not arise solely due to metabolization of pyrethroids inside the human body, but part of it can also be due to intake of naturally formed 3-PBA, which arises during the environmental breakdown of pyrethroids on crops and foodstuffs [53] and other uses of pyrethroids as indoor biocides. This implies that measured urinary levels of 3-PBA may overestimate the actual intake of the specific pyrethroids that form 3-PBA as a metabolite but at the same time underestimate the exposure to several other pyrethroids that do not form 3-PBA.

A common limitation regarding cost-of-illness studies is when the costs of comorbidities are not adequately accounted for. Failing to do so can significantly inflate the health costs that are estimated for the disease of interest. The key study of Libutzki et al. (2019), on which the health economic estimation in this study is based, did separate the costs of several comorbidities but not for ASD, of which the symptoms are known to overlap with those of ADHD. It is therefore possible that not all significant comorbidity-triggered costs are accounted for, thereby potentially inflating the total cost attributable to ADHD.

The disease burden in this analysis was estimated for the age-group of 0–19-year-olds. Since there is little data on when and to what extent exactly pyrethroids were used in Europe the last decades, the results may have been both underestimated (by excluding adults in the EBD estimation) as well as overestimated (by

extrapolating the exposure values measured in 2014–2021 to the entire time period of 2001 onwards and thus extrapolating to the age interval 0–19 years).

Finally, only ADHD was considered as a pyrethroid-related health outcome for which EBD estimates were determined. Yet pyrethroid exposure is also associated with other health outcomes such as ASD and cognitive issues [11]. Regardless of the uncertainty described above, observations already done in epidemiological, toxicological, and mechanistic studies allow for a preliminary estimation of the EBD associated with pyrethroid exposure. Also, in the framework of the precautionary principle and the widespread pyrethroid exposure, such a preliminary estimate is justifiable.

As mentioned earlier, the base case disease burden estimation made in this study was based on the findings by Dalsager et al. (2019), who found an association between prenatal pyrethroid exposure and ADHD symptoms in children aged 2–4 years. In a subsequent study of the Odense child cohort by Fage-Larsen et al. (2024), a statistically significant association was no longer found between pyrethroid exposure (both prenatally or during childhood) and ADHD symptoms at 5 years of age [61]. Several explanations are given by the authors for this weakening of association. First, the sample size in the follow-up study was significantly smaller (outcome measures available on 614 children as compared to the 948 children in the previous study), resulting in a lower statistical power. Secondly, it is a general research problem that children with behavioral problems are lost to follow-up (personal communication with study authors). A reason can be that families are more preoccupied due to the child's problems or have less resources to participate. It is also speculated that the older children get, the better they can mask ADHD symptoms compared to toddlers, making their symptoms less detectable. Finally, the exposure levels in the Odense child cohort are narrow (little variation in exposure biomarkers), possibly making it more difficult to reach statistical significance; though other factors may also contribute to the lack of statistical significance (e.g., insufficient study power, no effect, etc.).

Mechanistic evidence for pyrethroid-induced ADHD

Mechanistic data support the link between pyrethroid exposure and ADHD. Exposure to pyrethroids could elicit neurotoxic effect through the modification of Na^+-voltage-gated (Nav) channels. Deltamethrin has been shown to inactivate Nav1.6 channels, which are abundantly expressed in medium spiny neurons (MSN) of the nucleus accumbens (NAc) [21]. Dysregulation of MSN firing is thought to play a critical role in the pathophysiology of ADHD [62, 63]. Nav-channel modification could further be followed by reduced expression of BDNF (brain-derived neurotrophic factor) playing a prominent role in pre- and postnatal brain development [4, 5]. Mechanisms that could lead to reduced BDNF through pyrethroid exposure are described by Rodríguez-Carrillo et al. (2022) [22]. Crosstalk of the BDNF mechanism with neuroinflammation may take place [22]. Pro-inflammatory activity during neurological development could contribute to cognitive dysfunction [10]. Increased levels of oxidative and inflammatory markers have been shown in vitro and in animal studies [10, 64–66].

Pyrethroids have also been identified as thyroid hormone disruptors [67]. In vitro studies for example suggest that multiple pyrethroids have antagonistic effects for, e.g., T3 (triiodothyronine) induced proliferation in a pituitary cell line [68] or in a TH (thyroid hormone) receptor mediated reporter gene assay [69]. TH disturbance is further supported by multiple studies found in the literature [70–72]. T4 (thyroxine) concentrations could also be influenced through the dysregulation of the transport protein transthyretin (TTR), as was shown for permethrin [73]. The US ToxCast program indicated further moderation of the Na^+/I^--symporter (NIS) and thyroperoxidase (TPO) by several pyrethroids [10]. Other evidence from the literature points towards the identification of new molecular pathways involved in pyrethroid signaling, which could be implicated in ADHD pathobiology; these pathways include the dysregulation of Tau (tubulin associated unit) expression and GluR1 (Glutamate receptor 1). Tau is a microtubule-associated protein, known for its involvement in neurodegenerative disorders. Tau expression was found to be increased in the cerebral cortex of neonatal NMRI (Naval Medical Research Institute) male mice following cypermethrin exposure [74]. GluR1 is the predominant excitatory neurotransmitter receptors in the mammalian brain and has been shown to be necessary for hippocampal and amygdala synaptic plasticity [75]. GluR1 expression was decreased in the hippocampus while increased in the cerebral cortex of adult NMRI male mice following cypermethrin exposure [74]. ADHD phenotypes have been associated with abnormal dopamine levels in animal studies [35], possibly indicating a role of the dopaminergic system which could be influenced by pyrethroid exposure [71].

Policy relevance

In recent years, the growing awareness of the impacts that widespread reliance on chemical pesticides may have on human health and the environment has led to renewed efforts to reduce overall pesticide use and risk in Europe [23]. At the level of EU policy, the Farm to Fork Strategy adopted in 2020 as part of the European Green Deal foreshadowed a series of policy initiatives to achieve sustainable use of pesticides, with the overall aim of achieving a 50% reduction in the use and risk of chemical

pesticides and in the use of more hazardous pesticides by 2030, from a 2015–2017 baseline. A key pillar of the strategy was the legislative proposal for a Regulation on the Sustainable Use of Plant Protection Products (SUR), which sought to replace the 2009 Sustainable Use Directive (SUD) and enshrine the Farm to Fork pesticide reduction targets into EU law. However, the proposal was recently rejected by the European Parliament, and it is unlikely to be tabled again in the near future. Some of the measures contained in the SUR proposal included a general obligation for professional users of pesticides to apply the principles of Integrated Pest Management [76], the requirement for such users to be trained and independently advised on the application of pest control techniques, and the introduction of restrictions on the use of chemical pesticides in public spaces, human settlements, and ecologically sensitive areas. In certain cases, similar measures have already been implemented by some EU Member States, alongside other policy responses such as incentives for the transition to organic farming and precision agriculture and higher taxes for more hazardous pesticides [23].

Efforts to reduce overall use and risk of chemical pesticides are particularly important insofar as some adverse effects of active substances may not be predicted during the regulatory risk assessment process [77], thus raising the possibility that the replacement of banned substances by approved pesticides results in cases of 'regrettable substitution'. This phenomenon has already been described in the literature with respect to the shift in pesticide use between organophosphates and pyrethroids, although only in relation to risks for biodiversity [78]. The present study suggests that human health concerns may be linked to such a shift. From this perspective, an EU-wide requirement to monitor human exposure to priority pesticides such as pyrethroids could help identify the related trends and patterns across multiple EU countries, as well as to assess the effectiveness of policies to reduce pesticide use and risk.

In addition to addressing overall use and risk of pesticides, it is important to remember that prenatal and early postnatal life constitutes a highly vulnerable exposure windows for all chemicals and is a priority period for exposure reduction. There are some recommendations for pregnant women in place aiming to protect against different health hazards, however these are not validated by intervention studies. Therefore, implementable measures to reduce exposure to chemicals could be developed by an EU-wide expert panel and biomonitoring could be applied to test exposure reduction in this critical window. Some authors have specifically proposed the development of a global protective approach (defined as 'environmental hygiene'), which would reduce exposure of pregnant women, unborn children and infants by considering hazardous factors, adverse effects and preventive interventions as a whole rather than on a substance-by-substance basis [79].

The need for a global protective approach is also suggested by the fact that the European population is generally not exposed to one pesticide but to a mixture of pesticides and other chemicals. A recent study showed that 84% of HBM samples taken from the bodies of children and adults across five European countries contained residues of two or more pesticides [80]. Moreover, adjuvants added to the pesticide mixture also need to be covered as they may be toxic on their own, e.g., polyethoxylated tallow amine for glyphosate [81]. Given the interaction potential between pesticides and other chemicals, risk and health impact assessments should therefore focus on exposure to multiple chemicals, beyond the pesticide active substances, surfactants, and solvents but also to other chemicals.

Perspectives

Because of the paucity in literature, it is warranted to conduct future studies to more accurately determine the potential developmental neurotoxic effects of pyrethroids and the associated disease burden. In this context, cohort studies focusing on prenatal and gestational exposure to pesticides in critical exposure windows and taking multiple urine samples during pregnancy (e.g., two to three samples) followed by harmonized ADHD assessment in children are especially required for a valid meta-analysis across cohorts with different levels of exposure. In addition to this, studies focusing on geospatial variability of ADHD would also be highly valuable, especially if geospatial risk factors such as living in close proximity to agricultural fields and the influence thereof on ADHD prevalence could be investigated. Toxicity studies and mechanistic data already provide ample proof for the possibility of ADHD effects due to pyrethroids, but more harmonized epidemiological studies are needed. Currently, there is a lack of environmental burden of disease calculations related to pesticide exposure. This study aims at starting to fill this gap and develop indicators to guide policymakers by answering policy questions based on science.

Conclusion

Pyrethroid sales increased substantially during the last decade. Recent epidemiological evidence, combined with HBM data on pyrethroid exposure suggest adverse effects during neurodevelopment, and in particular ADHD development in children exposed to low levels of pyrethroids. These findings are supported by toxicity studies, in which ADHD-like behavior is seen in animals at relatively high doses, and mechanistic studies, in which pathways are proposed through which pyrethroids may

exert neurodevelopmental effects *in utero*. Estimates of the associated disease burden were lacking prior to this study.

The objective of this study was to provide an initial disease burden estimation for pyrethroids regarding ADHD for France, Germany, Switzerland, Iceland, and Israel. Only these countries were considered in this study given that only those HBM studies were conducted according to harmonized QA/QC-protocols (as part of the HBM4EU aligned studies). A first estimate was based on a single exposure-response function from a Danish study. The environmental burden of disease per million inhabitants per year was estimated to range between 209 and 2189 ADHD cases attributable to pyrethroid exposure, between 3 and 27 DALYs, and between 0.3 and 2.5 million EUR. Based on estimates for this limited set of countries, it was also calculated that on average 18% of ADHD cases were associated with exposure to pyrethroids in a specific exposure and effect window. A sensitivity analysis, applying exposure-response information collected from outside the EU, showed that the burden decreased drastically with an average PAF for the selected counties of around 7%.

Providing quantitative information on environmental pollutants and their associated health impact is crucial for evaluating the success of policies such as the EU-proposed Farm to Fork Strategy, in which a reduction in pesticide use was proposed. It is therefore essential that more QA/QC-standardized HBM studies are conducted within Europe to address pesticide exposure, data gaps in exposure (as only few HBM studies are available), and to ensure the follow-up of policy measures within the EU over time.

It is also warranted to conduct future harmonized epidemiological studies (more specifically, cohort studies focusing on prenatal exposure to pesticides, followed by harmonized diagnosis of effects during infancy), resulting in more robust and harmonized (meta-analyzed) exposure-effect functions. These studies should consider different vulnerable exposure and effect windows. In the current study, the ERF was only based on single studies. Considering the increased and widespread use of pyrethroids, reflected in higher exposures in children compared to adults, the increase of studies finding associations between pyrethroid exposure and health effects, and the results presented here, raise concerns for public health that need to be prioritized in future studies.

This study is an early attempt to estimate the potential burden of pyrethroid exposure on human health. The neurotoxicity of pyrethroids at high exposures is well established in toxicological studies, but neurodevelopmental toxicity in humans requires more research to draw firm conclusions.

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Author contributions
AP and JB conceptualized and designed the study, acquired the data, performed the calculations, interpreted the results, and drafted the manuscript. AP was the primary author in this study under the supervision of JB. All other authors provided input from the initial stage of conceptualization until the final drafting of the study, as well as critically revising the manuscript for intellectual content and approving the final version to be published. All authors are accountable for the work and integrity of this study. Finally, the corresponding author accepts full responsibility for the work presented here.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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