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Review

Human neurotoxicity of mercury in the Amazon: A scoping review with insights and critical considerations

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ABSTRACT

Human exposure to mercury is a major public health concern, causing neurological outcomes such as motor and visual impairment and learning disabilities. Currently, human exposure in the Amazon is among the highest in the world. A recent systematic review (doi:10.1016/j.jtemb.2018.12.001), however, highlighted the lack of high-quality studies on mercury-associated neurotoxicity. There is, therefore, a need to improve research and much to still learn about how exposure correlates with disease. In this review, we discuss studies evaluating the associations between neurological disturbances and mercury body burden in Amazonian populations, to generate recommendations for future studies. A systematic search was performed during July 2020, in Pubmed/Medline, SCOPUS and SCIELO databases with the terms (mercury*) and (Amazon*). Four inclusion criteria were used: original article (1), with Amazonian populations (2), quantifying exposure (mercury levels) (3), and evaluating neurological outcomes (4). The extracted data included characteristics (as year or origin of authorship) and details of the research (as locations and type of participants or mercury levels and neurological assessments). Thirty-four studies, most concentrated within three main river basins (Tapajós, Tocantins, and Madeira) and related to environmental exposure, were found. Mercury body burden was two to ten times higher than recommended and main neurological findings were cognitive, vision, motor, somatosensory and emotional deficits. Important insights are described that support novel approaches to researching mercury exposure and intoxication, as well as prevention and intervention strategies. As a signatory country to the Minamata Convention, Brazil has the opportunity to play a central role in improving human health and leading the research on mercury intoxication.

1. Introduction

According to the World Health Organization (WHO), mercury is listed as one of the top ten chemicals of major public health concern (WHO, 2017). International efforts have been added to the Minamata Convention on Mercury (UNEP, 2020), a global treaty to protect human health and the environment from the adverse effects of mercury. Among other 127 signatory countries, Brazil ratified this treaty in August 2017, but so far, no national program of mercury surveillance has been undertaken.

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Mercury is found naturally in soils and released into the atmosphere and hydrosphere by anthropogenic actions, such as biomass burning, artisanal small-scale gold mining (ASGM), fossil fuel combustion and dam construction (Arrifano et al., 2018; Berzas Nevado et al., 2010; Crespo-Lopez et al., 2021; UNEP, 2019). Mercury-enriched soils can be found in various regions of the world, for example, in central Spain and Northern Brazil (Crespo-Lopez et al., 2005). Mercury is largely used in several industrial and technological applications such as dental amalgams and gold extraction activities, among others (WHO, 2008), and the majority of these applications are due to the ability of mercury to bind to other metals.

In the Amazon, ASGM is the main contributor to elevated mercury in the environment (Berzas Nevado et al., 2010; Crespo-Lopez et al., 2021). The extraction of gold from ores using the amalgamation process (where mercury is employed to separate gold from impurities), combined with deforestation and the construction of dams, cause serious environmental impacts living in the region, increasing the accumulation of mercury in Amazonian soils and rivers (Berzas Nevado et al., 2010; Arrifano et al., 2018e; Crespo-Lopez et al., 2021). During ASGM, gold-mercury amalgams are heated to separate the gold particles, and consequently mercury vapor (Hg^0) is emitted into the environment (Crespo-Lopez et al., 2005, 2021; Berzas Nevado et al., 2010). Subsequent oxidation and bacterial methylation can then produce organic compounds of mercury, primarily methylmercury (MeHg). MeHg easily enter the food chain, which results in the contamination of fish that constitute the main part of the Amazonian riverine populations' diet (Berzas Nevado et al., 2010; Rodriguez Martin-Doimeadios et al., 2014; Crespo-Lopez et al., 2021). This is especially aggravated by the constructions of large-scale projects such as hydroelectric power plans. These dams create physical-chemical conditions in the environment (such as degradation of submerged organic matter and redox state) that favors microbial proliferation and increase bacterial methylation of mercury, in addition to prevent the large migrations of piscivorous fish which further increase bioconcentration and biomagnification *in loco* (reviewed by Crespo-Lopez et al., 2021).

Both Hg^0 and MeHg can easily cross biological barriers, such as placenta and blood-brain, and can be distributed widely throughout the body (ATSDR, 1999; WHO, 2008). The consequences of human exposure include a variety of effects, such as neurotoxicity, nephrotoxicity, genotoxicity and cardiovascular disturbances, among others (Berzas Nevado et al., 2009; Crespo-Lopez et al., 2009, 2011, 2016; Genchi et al., 2017; Leocádio et al., 2020; Silva et al., 2020; WHO, 2008), however, the main target organ for mercury toxicity is the Central Nervous System (CNS). Mercury binds to sulfhydryl groups of cysteine and mimics methionine that is actively transported to the other side of the blood-brain barrier. In the brain, mercury is deposited in various areas leading to different neurological dysfunctions, which is dependent on the damaged region. Inside the CNS cells, mechanisms such as oxidative stress, neuronal death, mitochondrial damage, release of excitatory aminoacids and changes in the proteomic expression, among others, occur after mercury exposure (do Nascimento et al., 2008; Bittencourt et al., 2019; Santana et al., 2019). Pre-clinical studies have demonstrated that these molecular and cellular changes in the brain are closely associated with neurological disorders such as memory loss, learning disabilities and impaired motor function (Belém-Filho et al., 2018; Bittencourt et al., 2019; do Nascimento et al., 2008; Oliveira et al., 2018; Santana et al., 2019).

The seminal recording of mercury intoxication occurred in the Bay of Minamata (Japan) in the 1950s, where thousands of people consumed contaminated fish and this exposure was linked with severe neurological disorders that lead to coma and eventually death (National Research Council, 2000). Since then, the set of neurological outcomes caused by mercury intoxication has been termed Minamata Syndrome. According to the WHO, this syndrome can include neurobehavioral defects related to neuronal loss, eventually leading to death (WHO, 2008). The most common clinical signs observed in adults were paraesthesia, ataxia, sensory disturbances, tremors, impaired hearing, constriction of the visual field and difficulty in walking (National Research Council, 2000; WHO, 2008). The developing CNS is particularly sensitive to mercury exposure and the impact on infants and young children must be considered as a public health priority (National Research Council, 2000; WHO, 2008; Ceccatelli et al., 2013).

Surprisingly, a recent systematic review found low or very low levels of evidence supporting an association between MeHg exposure and the occurrence of neurological outcomes (Puty et al., 2019). However, the review only analyzed studies with adults that included control groups, a quality requirement that limited the analysis to six studies. Moreover, only two papers of the selected six research studies quantified mercury exposure in the individuals. It is noteworthy that one of those final two selected studies that accomplished all the quality exigencies of the systematic review, was performed in the Amazonian region, and it demonstrated the association of mercury exposure with neurological disturbances (Khoury et al., 2015).

Many studies have confirmed that chronic exposure to high levels of mercury occur in Amazonian populations and recent reviews have recorded this as some of the highest levels of human exposure in the world (Basu et al., 2018; Castro and Lima, 2018; Sharma et al., 2019; Crespo-Lopez et al., 2021). The high prevalence of non-communicable diseases, such as hypertension or diabetes, has already been demonstrated in the Amazonian riverine population, as well as elevated genetic susceptibility to neurodegeneration (Arrifano et al., 2018a, 2018d). Unfortunately in Brazil, unlike for cardiovascular disorders, there is no national program of biomonitoring of non-communicable diseases related to neurotoxicity or exposure to mercury and reporting depends on the analysis of scientific research.

The geographical inaccessibility and the precarious conditions of the Amazonian region and widespread mercury contamination mean that epidemiological studies do not frequently include a control group and, consequently, many research studies were not considered in the recent review (Puty et al., 2019). With this in consideration, there is a need to enhance the quality of epidemiological studies to investigate the neurological outcomes associated with elevated mercury levels in Amazonian populations. Furthermore, recommendations are required to guide researchers on how best to collect useful information to support future studies and generate recommendations to the populations of the Amazonian region most impacted by mercury intoxication.

2. Search strategy

The present scoping review followed the PRISMA guideline (Tricco et al., 2018). A systematic search was performed during July 2020 in PubMed/Medline, SCOPUS and SCIELO databases with the terms (mercury*) and (Amazon*) queried in the title, abstract and keywords fields (Fig. 1). No restriction on language or year of publication was applied. Articles were selected based on four inclusion criteria according with the aim: original article (1), with Amazonian populations (2), quantifying exposure (mercury levels) (3), and evaluating neurological outcomes (4). When the title and abstract were vague enough to doubt whether the criteria were met, the complete article was reviewed. This selection was performed at least by two different co-authors and revised by a third one to ensure that the criteria were met. Duplicate records between the different databases were then excluded. Finally, the list of references of the selected studies were also checked for additional studies. Only one of the latter studies was not included because the main text was not available. The extracted data included characteristics (year, origin of authorship, type of reader access, type of indication of locations) and details of the research (locations and type of participants, sample size, type of exposure and marker, mean/median levels of total mercury, proportion of MeHg -if available-, neurological assessments and findings).

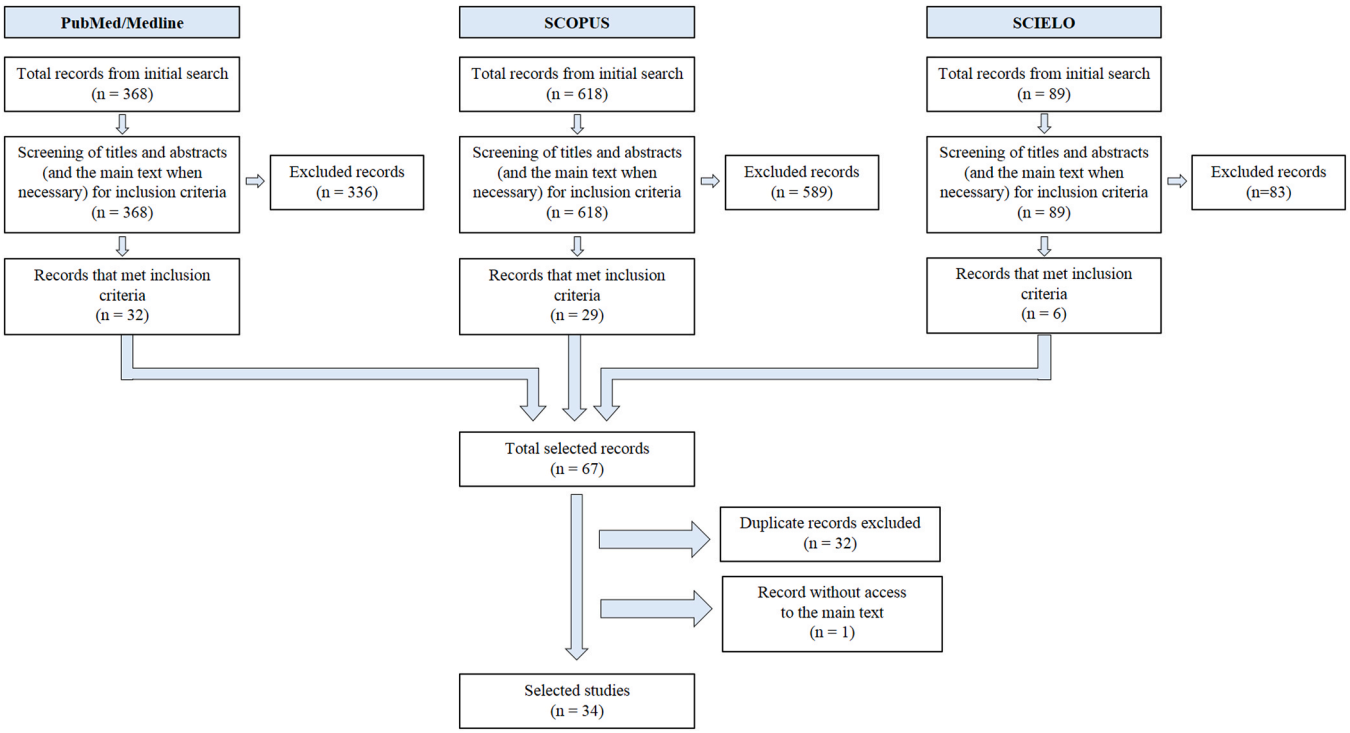

Fig. 1. Flowchart of the search strategy carried out in this scoping review.

3. Features of the studies on mercury-related neurological outcomes in the Amazon

In addition to Japan, where Minamata Syndrome was first described, the Amazon is a region where studies have been conducted analyzing the association between mercury exposure and neurological disorders. Surprisingly, there are no studies before the 1990s that systematically analyzed human neurotoxicity associated with mercury exposure in the Amazon and include both the quantification of mercury and neurological outcomes evaluation. The first record of this association is from 1996 (Lebel et al., 1996), although the full article is unavailable online. This fact is poignant, considering that the Amazonian population has been exposed to mercury for at least 40 years (Berzas Nevado et al., 2010), and human exposure to the metal was demonstrated before 1900s (Branches et al., 1993). Fortunately, research on human neurotoxicity associated with mercury increased since the 1990s (Fig. 2). However, since 2006 we observe a relatively constant number of 10 studies each five years (Fig. 2). This is clearly insufficient considering the Amazonian region, where monitoring needs to be captured by long term studies that require significant resources and investment in community monitoring.

Less than half of the studies were published in open access journals (Table 1, references with an asterisk). The scientific popularization of the research results may increase the impact of these publications and the access of local health services and education/research institutes from underdeveloped and developing countries located in the Amazon. This also can facilitate the inclusion of published data in general surveillance systems such as SINAN in Brazil, as recently proposed (Castro and Lima, 2018), and can stimulate the notification of exposed cases by health professionals (at present, case reporting is voluntary in Brazil and particularly low in the Amazon, as demonstrated elsewhere) (Castro and Lima, 2019). Currently, Brazil does not have a monitoring program for human exposure to mercury and the epidemiology of the Amazonian population is largely dependent on research from the scientific community. Therefore, "sustainable" research (i.e. accessible and useful for both the local health services and participating communities) would be

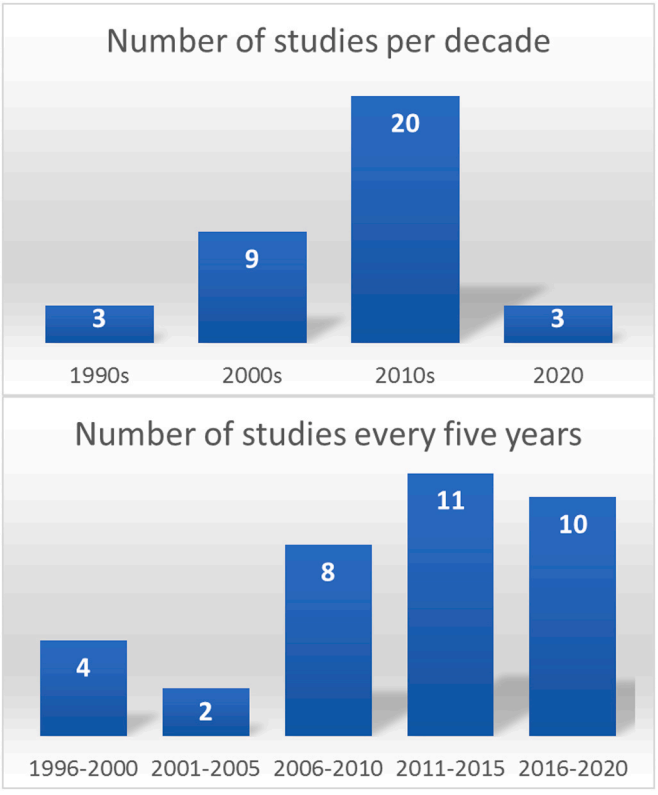

Fig. 2. Number of studies published until July 2020, grouped per decade (above) and every five years (below), related to human neurotoxicity associated with mercury exposure in Amazonian populations. The individual studies are detailed in Tables 1, 2 and 3. Note: one study in 1996, which full article was unavailable online (see Fig. 1), was included here but excluded in other tables and figures.

Table 1
Features of the studies performed in the Amazon identifying the possible association of neurological disorders with mercury exposure. Open access manuscripts are indicated with an asterisk (*).

Study	Authorships	N	Location (Country/River basin)	Showed by
(Lebel et al., 1998)	Brazil/Canada	91	Brazil/Tapajós	Coordinates
(Grandjean et al., 1999)*	Brazil/Denmark/USA/UK	351	Brazil/Tapajós	Map
(Dolbec et al., 2000)*	Brazil/Canada	68	Brazil/Tapajós	Coordinates
(Harada et al., 2001)	Brazil/Japan	50	Brazil/Tapajós	Map
(Tavares et al., 2005)*	Brazil	209	Brazil/Cuiabá	–
(Corbett et al., 2007)	Brazil	235	Brazil/Tocantins	–
(Marques et al., 2007)*	Brazil	200	Brazil/Madeira	–
(Rodrigues et al., 2007)*	Brazil	28	Brazil/Tapajós	–
(da Costa et al., 2008)	Brazil	93	Brazil/Not described	–
(Fonseca et al., 2008)	Brazil	70	Brazil/Madeira	Map
(Chevrier et al., 2009)	France/USA/Denmark	395	Brazil/Tapajós French Guiana/Maroni	–
(Benefice et al., 2010)*	Bolivia/Lao	173	Bolivia/Beni	–
(Marques et al., 2010)*	Brazil	249	Brazil/Madeira	Map
(Fillion et al., 2011a)*	Brazil/Canada	243	Brazil/Tapajós	Map
(Fillion et al., 2011b)	Brazil/Canada	31	Brazil/Tapajós	Map
(Dorea et al., 2012)*	Brazil	281	Brazil/Madeira	–
(Fillion et al., 2013)	Brazil/Canada	228	Brazil/Tapajós	Map
(Khoury et al., 2013)*	Brazil	157	Brazil/Tapajós Brazil/Tocantins	Coordinates
(Cardoso et al., 2014)*	Brazil	41	Brazil/Madeira	–
(Marques et al., 2014)	Brazil	96	Brazil/Madeira	–
(Peplow and Augustine, 2014)	USA	22	Suriname/Tapanahoni	Map
(Marques et al., 2015)	Brazil	294	Brazil/Madeira	–
(Hoshino et al., 2015)*	Brazil	58	Brazil/Purus	–
(Khoury et al., 2015)*	Brazil	157	Brazil/Tapajós Brazil/Tocantins	Map
(Marques et al., 2016a)	Brazil	690	Brazil/Madeira	Map
(Marques et al., 2016b)	Brazil	1139	Brazil/Madeira	–
(Marques et al., 2016c)	Brazil	365	Brazil/Madeira	–
(Costa et al., 2017)*	Brazil	144	Brazil/Tapajós	Coordinates
(Arrifano et al., 2018c)	Brazil	224	Brazil/Tapajós Brazil/Tocantins	Map
(Dos Santos Freitas et al., 2018)	Brazil	174	Brazil/Tapajós Brazil/Tocantins	Map
(Feitosa-Santana et al., 2018)	Brazil	78	Brazil/Madeira	Map
(Lacerda et al., 2020)*	Brazil	44	Brazil/Tapajós Brazil/Tocantins	Map
(Reuben et al., 2020)	Peru/USA	164	Peru/Madeira	Map
(Santos-Lima et al., 2020)	Brazil/Peru	263	Brazil/Madeira	Map

recommended in the Amazonian region, where data on the health of populations at risk would be freely available.

Brazilian scientific community is especially sensitive to the problem of the possible neurological consequences associated to mercury in the Amazon, as shown by the origin of the authorships (Table 1). International collaboration would, however, enhance research capacity and stimulate dialogue within the broader international scientific community.

The Amazon region in South America is greater than 5 million km^2 (larger than the size of the Western United States), much of the land is challenging to access and the geography is relatively unknown for the majority of the population outside of the Amazon. The lack of clear maps and geographical coordinates detailing where research has occurred is apparent in many of the reviewed papers (Table 1) and this would be an important recommendation for futures studies.

To date, most of the documented research was performed in the Brazilian Amazon, with only four studies outside of this country, in Peru, Bolivia, Suriname and French Guiana (Table 1 and Fig. 3). This is expected, as the majority of the Amazon is within Brazil and it is here where most of the anthropogenic mercury can be found (Crespo-Lopez et al., 2021). Most of the studies is concentrated within three main river basins belonging to large tributaries of the Amazon River: Tapajós River, Tocantins River, and Madeira River (Fig. 3).

The largest area of ASGM and one of the oldest is located in the Tapajós basin and its riverine population is the most studied to date in the Amazon (Table 1) (Berzas Nevado et al., 2010; Crespo-Lopez et al., 2021). In this region, the most recent data in environmental samples show levels of total mercury as high as 23.84 ng/L in water, 157 ng/g and 155 ng/g in dry weight of suspended particulate matter and sediments, respectively, 316 ng/g in plankton and 1.172 μg/g in wet weight of muscles of piscivorous fish (Rodriguez Martin-Doimeadios et al., 2014; Lino et al., 2018, 2019; Souza Azevedo et al., 2019). More than 80% of total mercury in fish was MeHg and piscivorous species (especially *Cichla* sp.) presented significantly higher levels than non-piscivorous (Rodriguez Martin-Doimeadios et al., 2014; Lino et al., 2018; Souza Azevedo et al., 2019; Lino et al., 2019).

In the Tocantins Basin, there are no occurrences of ASGM but it has the world's fifth largest dam, the Tucuruí Hydroelectric Power Plant (HPP). Since its completion in 1984, multiple papers cite elevated mercury exposure in surrounding populations, which is attributed to the increase in metal concentration in the food chain from water stagnation and altered flow regimes (Leino and Lodenius, 1995; Arrifano et al., 2018c, 2018d, 2018e). Mercury in water and sediments presented values of 12.7 ± 8.4 ng/L and 12–37 ng/g, respectively (Aula et al., 1995; Kehrig et al., 2009). Also, floating plants such as *Eichhornia crassipes* or *Scirpus cubensis* showed levels of mercury as high as 0.075 ± 0.038 μg/g (Aula et al., 1995). As observed in the Tapajós basin, in the Tocantins basin, herbivorous fish such as *Anostomidae* sp. and *Prochilodus nigricans* presented lower mercury levels (0.06–0.22 μg/g) than those (0.41–2.2 μg/g) of omnivorous or

Table 2
Mercury exposure (body burden) in Amazonian populations tested for neurological outcomes.

Population	Type of Exposure	N	Exposure marker	Total mercury (mean or median)	MeHg (%)	Basin[n]	Study
Adults	Environmental	91	Hair	23.9/14.3/12.6 μg/g[b]	72.2–93.6	T	(Lebel et al., 1998)
		68	Hair	9.0 μg/g	94.4	T	(Dolbec et al., 2000)
			Blood	27.0 μg/g			
		50	Hair	23.6 μg/g	-	T	(Harada et al., 2001)
		173	Hair	5.5 μg/g	-	B	(Benefice et al., 2010)
		31	Hair	16.9/11.3/7.8 μg/g[c]	-	T	(Fillion et al., 2011b)
		243	Hair	14.4 μg/g	-	T	(Fillion et al., 2011a)
			Blood	51.6 μg/L			
			Plasma	8.0 μg/L			
		228	Hair	14.4 μg/g	-	T	(Fillion et al., 2013)
		157	Hair	8.6/9.1 μg/g[d]	-	T/To	(Khoury et al., 2013)
		41	Hair	13.5/12.1 μg/g[e]	-	M	(Cardoso et al., 2014)
		22	Hair	24.0/14.0 μg/g[f]	-	Ta	(Peplow and Augustine, 2014)
		58[a]	Hair	10.9 μg/g	-	P	(Hoshino et al., 2015)
		157	Hair	8.8 μg/g	-	T/To	(Khoury et al., 2015)
		144	Hair	9.1 μg/g	-	T	(Costa et al., 2017)
		224	Hair	4.1 μg/g	71–97	T/To	(Arrifano et al., 2018c)
		10	Hair	~20 μg/g	-	T	(Lacerda et al., 2020)
	Occupational	235	Hair	<10 μg/g	-	To	(Corbett et al., 2007)
			Urine	40.2 μg/L			
		28	Hair	14-47 μg/g	-	T	(Rodrigues et al., 2007)
			Urine	400 μg/L			
		93	Urine	415.6 μg/L	-	?	(da Costa et al., 2008)
		34	Hair	~1.2 μg/g	-	To	(Lacerda et al., 2020)
Children	Environmental	351	Hair	11.0 μg/g	-	T	(Grandjean et al., 1999)
		209	Hair	5.3 μg/g	-	C	(Tavares et al., 2005)
		200	Hair	5.4/1.5/1.8 μg/g[g]	-	M	(Marques et al., 2007)
		70	Hair	18.4 μg/g	-	M	(Fonseca et al., 2008)
		395	Hair	9.8 μg/g	-	T/Ma	(Chevrier et al., 2009)
		249	Hair	4.3 μg/g	-	M	(Marques et al., 2010)
		281	Hair	3.9/1.8/3.8 μg/g[h]	-	M	(Dorea et al., 2012)
		96	Hair	2.0/3.0/4.8 μg/g[i]	-	M	(Marques et al., 2014)
		690	Hair	2.7/4.1 μg/g[j]	-	M	(Marques et al., 2016a)
		294	Hair	0.8/1.0/1.9 μg/g[i]	-	M	(Marques et al., 2015)
		1139	Hair	4.9/12.0/9.9 μg/g[k]	-	M	(Marques et al., 2016b)
		365	Hair	7.13/4.59 μg/g[l]	-	M	(Marques et al., 2016c)
		174	Hair	4.98 μg/g	-	T/To	(Dos Santos Freitas et al., 2018)
		78	Hair	18.4/26.0 μg/g[m]	-	M	(Feitosa-Santana et al., 2018)
		164	Hair	2.0 μg/g	-	M	(Reuben et al., 2020)
		263	Hair	2.0 μg/g	-	M	(Santos-Lima et al., 2020)

[a] Including adults and children.
[b] Values are for fishermen/other men/women, respectively.
[c] Values in 1995/2000/2006, respectively.
[d] For the inhabitants of Barreiras/São Luiz do Tapajós, respectively.
[e] For individuals with and without tinnitus.
[f] In 2008/2012, respectively.
[g] For mothers and babies (newborns and at 6 months), respectively.
[h] For the inhabitants of Itapuã/Bom Futuro/Porto Velho, respectively.
[i] For newborns, at 6 months and at 24 months, respectively.
[j] For babies with 6 and 24 months of breastfeeding, respectively.
[k] For 6-months babies grouping according to: a) mothers with <3 μg/g of hair mercury and <25 μg/g of ethylmercury, b) mothers with >3 μg/g of hair mercury and >25 μg/g of ethylmercury, and c) other mothers.
[l] For 5-years children with birth delivery at home or at the hospital, respectively.
[m] For the groups that performed the D15d and FM100 tests, respectively.
[n] Basin (B=Beni; C=Cuiabá; M=Madeira; Ma=Maroni; P=Purus; T=Tapajós; Ta=Tapanahoni; To=Tocantins; ?=not described).

piscivorous fish such as *Cichla* sp. (Kehrig et al., 2008, 2009; Rodriguez Martin-Doimeadios et al., 2014).

Currently, 413 dams are operational or being built in the Amazon, and 334 additional dams are planned/proposed (Winemiller et al., 2016). Most of these dams are located in the basins of Tocantins, Tapajós and Madeira Rivers, and are expected contribute to increased metal content in the food chain. The Tapajos Hydroelectric complex is especially concerning since a group of 5 mega-dams is planned in the Tapajós basin, which is one of the most contaminated regions of the Amazon (Crespo-Lopez et al., 2021).

In the Madeira basin, for example, we can find both ASGM areas and mega-dams (such as the Santo Antônio HPP) that may contribute to environmental contamination and human exposure. The most recent data show levels of mercury as high as 46.06 ng/L and 2625 ng/g in water and suspended particulate matter, respectively (Bastos et al., 2020). The highest levels are found in piscivorous fish such as *Brachyplatystoma filamentosum*, the most consumed fish by the riverine population of the Madeira River, that currently presents 0.378 ± 0.009 and 0.617 ± 0.011 μg/g of mercury in muscle and liver tissues, respectively (Queiroz et al., 2019).

It is unknown whether human exposure to mercury in regions of the Amazon, other than the Tapajós, Madeira and Tocantins basins, may be causing neurological disorders. Multiple studies have demonstrated high exposure in populations residing within the basins of the Negro and

Table 3
Neurological assessments and main findings in the studies of the Amazonian populations reporting the association with mercury exposure.

Population	Type of Exposure	Study	Neurological assessments	Neurological findings associated with high mercury levels
Adults	Environmental	(Lebel et al., 1998)	Motor and visual battery; clinical examination	Near visual contrast sensitivity and manual dexterity dysfunction
		(Dolbec et al., 2000)	Psychomotor and motor tests (Santa Ana manual dexterity test, Grooved Pegboard Fine motor test, finger tapping test, dynamometry for grip and pinch strength)	Dexterity and motor speed impairments
		(Harada et al., 2001)	Clinical examination (sensory, balance, memory, motor, visual tests and insomnia)	General deficits such as numbness, imbalance, memory impairment, motor disturbance, hearing impairments, tremor among others
		(Benefice et al., 2010)	Clinical examination (motricity and somato-sensory disturbances)	Paresthesia, static and dynamic imbalance, poor motor coordination and reduction in visual field
		(Fillion et al., 2011a)	Clinical examination (Allen Chart, Tumbling E Chart)	Visual acuity deficits
		(Fillion et al., 2011b)	Neurofunctional battery (Allen Chart, Tumbling E Snellen Chart, Lanthony D-15 desaturated test, Santa Ana dexterity test and grip strength)	Color vision and visual acuity deficits
		(Fillion et al., 2013)	Clinical examination (Allen Chart, Vistech VCTS 6000 charts and Lanthony D-15 desaturated test)	Contrast sensitivity and color vision deficits
		(Khoury et al., 2013)	Clinical examination (motricity and somato-sensory tests, static and dynamic balance and motor coordination)	Balance and gait impairments and motor coordination deficits
		(Cardoso et al., 2014)	Clinical examination and Tinnitus Handicap Inventory	No correlation between tinnitus and mercury exposure
		(Peplow and Augustine, 2014)	Index of neurological integrity, Drawing test and Copying test	Cognitive and motor deficits (glove-and-stocking type sensory disturbance, tremor, numbness and two-point discrimination deficit)
		(Hoshino et al., 2015)	Clinical examination (auditory system)	None
		(Khoury et al., 2015)	Somatosensory tests (tactile sensation threshold, vibration sensation duration and two-point discrimination threshold)	Somatosensory deficits (tactile sensation, vibration sensation and two-point discrimination impairments)
		(Costa et al., 2017)	Clinical examination (depression, anxiety, sleep quality, paresthesia, muscular strength, balance and tremors)	Emotional and motor deficits (insomnia, anxiety, paresthesia and tremor)
		(Arrifano et al., 2018c)	Quantitation of mRNA S100B levels in blood and questionnaire of symptoms	Increased levels of mRNA S100B
		(Lacerda et al., 2020)	Visual tests (Foster perimeter and Farnsworth-Munsel tests)	Color vision and visual perimeters deficits
	Occupational	(Corbett et al., 2007)	Epidemiological and medical questionnaire	Paresthesia, fatigue, irritability, insomnia, memory loss, visual field constriction, hearing loss, tremor, knee-heel test deficit and walking impairment
		(Rodrigues et al., 2007)	Visual tests (Mullen`s paradigm, Farnsworth-Munsell test and Mollon-Reffin test)	Contrast sensitivity deficits and color vision impairment
		(da Costa et al., 2008)	Retinal and cortical electrophysiology	Low transient pattern electroretinogram amplitudes and delayed transient pattern visual evoked potential
		(Lacerda et al., 2020)	Visual tests (Foster perimeter and Farnsworth-Munsel tests)	Color vision and visual perimeters deficits
Children	Environmental	(Grandjean et al., 1999)	Motor performance, attention, memory and visual tests (finger-tapping task, Santa Ana form board, Wechsler Intelligence Scale for Children-III, Stanford-Binet Intelligence Scale, coping test, and bead memory test)	Motor, attention and visual deficits in exposed children
		(Tavares et al., 2005)	Neurological battery (balance, sensory and motor tests)	Inconclusive
		(Marques et al., 2007)	Neurodevelopmental examination (Gesell Developmental Schedules)	Inconclusive
		(Fonseca et al., 2008)	Cognitive battery (Wechsler Intelligence Scale for Children-III and Human Figure Drawings)	Deficits in Wechsler Intelligence Scale for Children-III performance
		(Chevrier et al., 2009)	Stanford-Binet Copying Test	Reduced score on the drawing task (Increased errors of rotation, simplification, and perseveration in the drawings)
		(Marques et al., 2010)	Neurodevelopmental examination (Gesell Developmental Schedules)	Deficits in motor and language development
		(Dorea et al., 2012)	Neurodevelopmental examination (Gesell Developmental Schedules)	Lower breastfeeding score
		(Marques et al., 2015)	Bayley Scales of Infant Development (mental development index, psychomotor development index, and age of walking and talking)	Neurodevelopment deficits in children living in mining present sex differences with boys having lower Bayley scores at 6 months
		(Marques et al., 2014)	Cognitive battery (Bayley mental development index, psychomotor development index, and age of walking and talking)	Impaired mental development and motor deficits
		(Marques et al., 2016a)	Clinical examination and neurodevelopmental test (age of walking and talking and Bayley Scale of Infant Development)	Decreased mental development index and psychomotor development index
		(Marques et al., 2016b)	Clinical examination and neurodevelopmental test (age of walking and talking and Bayley Scale of Infant Development)	Neurodevelopmental and psychomotor Deficits
		(Marques et al., 2016c)	Bayley Scale of Infant Development and Stanford-Binet intelligence tests	None
			Visual test (Lanthony Desaturated D-15 test)	Color vision deficit

(*continued on next page*)

Table 3 (*continued*)

Population	Type of Exposure	Study	Neurological assessments	Neurological findings associated with high mercury levels
		(Dos Santos Freitas et al., 2018)		
		(Feitosa-Santana et al., 2018)	Visual tests (D15d and FM100 color vision tests)	Color vision deficit
		(Reuben et al., 2020)	Visual-motor and cognitive tests (Beery-VMI developmental test, and Batería-III Woodcock-Munhoz)	Visual-motor integration deficits, working memory deficits, verbal comprehension deficits, auditory processing and reasoning impairment
		(Santos-Lima et al., 2020)	Neuropsychological tests (intelligence -WASI-, working memory -Corsi Block-Tapping Task and Digit Span-, verbal fluency -Word Generation/NEPSY II-, inhibitory control -Inhibition Errors/NEPSY II-, shifting -Trail Making test- and manual motor dexterity -Grooved PegBoard test-)	Verbal and visuospatial working memory deficits

Fig. 3. Map of South America with the Brazilian States (yellow lines), capital locations (black stars) and the main tributaries of the Amazon River basin (blue lines). The red points indicate the locations where studies in Table 1 were carried out. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Xingú Rivers (Fig. 3) (Vasconcellos et al., 1994; Barbosa et al., 1998; Castro and Lima, 2018), but possible neurological outcomes associated with this exposure were not analyzed. Moreover, the Belo Monte HPP, the largest dam in the Amazon and the fourth largest HPP in the world, was recently constructed on the Xingú River and there is no monitoring of human exposure. There is, therefore, a very real and urgent need to expand the research on possible neurological consequences of human exposure to mercury in the Amazon.

The mean sample size in the studies is 209 ± 37 individuals (presented as mean ±SEM) with no appreciable difference over time (Table 1). This reduced size may be reflect the size of many Amazonian communities and the difficulties in reaching these remote/isolated populations (Arrifano et al., 2018a, 2018c). There is not, however, a sufficiently comprehensive cross-sectional or longitudinal clinical study in the Amazon (with a high number of participants from different geographical regions), as in Europe or in North America with cohorts such as ALSPAC or REGARDS (Chen et al., 2018; Hibbeln et al., 2018). This type of study is critical as exposure in this region is chronic (Berzas Nevado et al., 2010; Crespo-Lopez et al., 2021). Larger epidemiological studies can help dispel excessive underreporting of cases in the region and provide monitoring even in regions where access to health services is very difficult. Without this information, it is not possible to develop prevention strategies and early identification of individuals at risk.

4. Analyzing the results of the studies on mercury-related neurological outcomes in the Amazon

4.1. Type of exposure, methodological issues and contextualized levels

From the literature, two main types of exposure can be observed: individuals occupationally exposed by ASGM activities and populations living at the contaminated environment (Table 2). In the first case, all individuals were miners from ASGM areas exposed to inhalation of metallic mercury (Hg^0) vapor during the burning of the gold-mercury amalgam (Table 2). About 80% of the inhaled mercury is rapidly absorbed in the lungs and widely distributed (ATSDR, 1999; WHO, 2008). Once inside the tissues, the Hg^0 is largely oxidized to inorganic mercury (Hg^{2+}) that is retained due to its polarity. Over time, Hg^{2+} is eliminated from the body by excretion in the urine, and this is a biomarker that can be quantified. Hair is not commonly used as a biomarker for Hg^{2+} exposure because of the low proportion deposited in this tissue as compared to the quantity that was inhaled and absorbed by the body (WHO, 2008). Hence, all the studies recorded, except one, analyzing occupationally-exposed individuals used urine as the main exposure biomarker (Table 2).

Studies detailing associations between neurological outcomes and occupational exposure in the Amazon are relatively scarce (Tables 1–3) and although most present total mercury levels in urine, these levels are related to the total volume of urine (μg/L). The WHO guidelines recommend expressing mercury levels as μg/g of creatinine found in urine (WHO, 2008). Creatinine is a product of the degradation of creatine, and its elimination from the body is relatively constant with a normal kidney functioning. Quantitation of creatinine is necessary to adjust changes in the urine volume due to water intake and kidney function, among other confounding factors that could influence the mercury concentration. The mercury content in the urine of non-exposed individuals rarely exceed 5 μg/g creatinine and the maximum mercury concentration recommended for occupationally-exposed individuals was set at 50 μg/g of creatinine by the WHO (WHO, 2008). Future studies involving occupationally-exposed individuals in the Amazon should prioritize the quantitation of creatinine to accurately determine mercury levels within the body and hence exposure.

In addition to occupational exposure from ASGM activities, the most widespread form of exposure in Amazonian populations is due to environmental contamination (Crespo-Lopez et al., 2021; and Table 2). In this case, the main pathway of human exposure is intake of contaminated food, particularly piscivorous fish (Berzas Nevado et al., 2010; Rodriguez Martin-Doimeadios et al., 2014; Crespo-Lopez et al., 2021). MeHg is the main mercury compound in contaminated food in the Amazon, and it can account for more than 80% of the total mercury content in the exposed individual. After ingestion, MeHg is rapidly absorbed in the gastrointestinal tract and the main target organ is the CNS (Clarkson et al., 2007; WHO, 2008). Regarding the literature on environmentally-exposed humans, hair is utilized as the main exposure biomarker (Table 2). According to the WHO, human hair is a reliable biomarker for MeHg exposure, with the added benefit that the mercury concentrations remain stable for long periods of time (WHO, 2008). Moreover, mercury levels recorded in hair are directly proportional to the concentration of metal in the brain with a ratio hair:brain of 50:1 approximately (Clarkson et al., 2007; Crespo-Lopez et al., 2021). In our review, only one group additionally evaluated the mercury content in the blood and plasma of the participants (Table 2). In blood, mercury levels change over time, with peak levels occurring around 4–14 h after exposure and subsequent clearance (WHO, 2008). The measurement of hair as a mercury biomarker is more reliable than that of a moment of the day provided by blood mercury. In addition, hair-sampling is non-invasive and the preferred biomarker for vulnerable individuals such as children (Table 2). With respects to demographics, most of the research on adult exposure has been carried out in the Tapajós Basin; however, the neurological alterations associated with exposure in children have been predominantly studied in the Madeira Basin (Table 2). This bias supports the urgent need for further studies regarding the neurological alterations associated with MeHg exposure, both in adults within the Madeira Basin and children within the Tapajós Basin.

Further recommendations for future studies would include quantifying MeHg in addition to total mercury. Although the proportion of MeHg is typically very high (above 80%) when contaminated fish is the predominant mechanism of human exposure, it is, nonetheless, important to confirm that the neurological changes are positively associated with this molecule. Pre-clinical and clinical studies have already demonstrated that other mercury compounds such as Hg^{2+} or Hg^0 can cause neurological damage (Corbett et al., 2007; Rodrigues et al., 2007; Aragao et al., 2018; da Costa et al., 2008; Teixeira et al., 2018). Unfortunately, the species of mercury is not frequently stated in the studies from the Amazonian region (Table 2). Moreover, to improve transparency, it is recommended to avoid presenting total mercury data as MeHg when no speciation is available (as observed, for example, in Fonseca et al., 2008; Feitosa-Santana et al., 2018).

In the case of the Amazonian communities living downstream garimpos (mining areas) and presenting more than 80% as MeHg in hair (an indicative of environmental exposure through contaminated food intake), the levels of mercury can be compared with international guidelines (Crespo-Lopez et al., 2021). Both United States Environmental Protection Agency (US EPA) and the WHO established provisional tolerable weekly intakes (PTWI) of 0.7 and 1.6 μg/Kg of MeHg, respectively, for fish consumers (National Research Council, 2000; WHO, 2008). These values equate to approximately 1–2.3 μg/g of hair mercury and 4–9.2 μg/L of blood mercury (Clarkson et al., 2007; WHO, 2008; Crespo-Lopez et al., 2021). A recent systematic review showed levels of mercury in the populations from Europe and North America below these values, with medians of 1 μg/L and 0.79 μg/L for blood mercury, respectively, and 0.3 μg/g for hair mercury in Europe (Basu et al., 2018). In fact, current cohorts in these regions such as ALSPAC or REGARDS, usually register very low levels of mercury and therefore do not indicate association with deleterious consequences (Chen et al., 2018; Hibbeln et al., 2018). This is not the case in the Amazon (Table 2) where all adult populations tested for neurological outcomes had mercury levels two to ten times higher than both WHO and US EPA PTWIs (National Research Council, 2000; WHO, 2008). These results are confirmed by a recent systematic review that reported populations of the Brazilian Amazon had mean levels of hair mercury above 6 μg/g (Castro and Lima, 2018). Based on data from a European cohort (the German Environmental Survey; GerES), two human biomonitoring thresholds (HBM) were proposed for children and women of childbearing age (Schulz et al., 2011). The upper threshold (HBM-II) of 15 μg/L total mercury in the blood, approximately equivalent to 3.75 μg/g of hair mercury according to the ratio 250:1 for hair:blood (in μg/g and μg/ml, respectively; Crespo-Lopez et al., 2021), is the level of mercury above which there is an increased risk; thus, designated as a threshold for intervention. In this review, all the studies with children revealed relatively high mean levels of hair mercury and a significant proportion of children exceeded the HBM-II limits (Table 2). This profoundly supports the need of urgent intervention strategies to protect the health of this vulnerable population. Another recommendation is to ensure that the authors accurately classify the epidemiological studies highlighting possible associations between mercury exposure and deleterious health effects to avoid vague and subjective classifications, such as “relatively low levels” or “low-to-moderate exposure”. Studies must be adequately contextualized, including mercury concentrations in both the Abstract and main text, with discussion of the exposure levels relative to the international guidelines.

4.2. Main neurological problems associated with mercury exposure in the Amazon and future recommendations

Considering the relatively high levels of mercury exposure and the widespread contamination in the Amazon, it is not surprising that only five studies (out of 34 studies in total) failed to find associations with neurological outcomes (Table 3). Furthermore, as described by the authors, it is not possible to conclude that there were no deleterious consequences due to study limitations such as small sample size or age of the participants, among other factors. Moreover, the diversity of the experimental designs, type of analysis, and missing or misleading information may make it difficult the comparison between studies. We recommend that future studies be standardized, adopting international guidelines for epidemiological studies such as STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (EQUATOR Network, 2019), with the inclusion of a simple checklist to ensure that all necessary information is included in the manuscript.

Despite the wide range of studies, most clearly demonstrated the significant association between neurological disorders and mercury levels that were tested in different biological systems. The most important neuropathological findings associated with mercury intoxication are cognitive, vision, motor, somatosensory and emotional deficits (Table 3). Among vision deficits, color vision, acuity and low contrast sensitivity seem to be the most impacted outcomes (Lebel et al., 1998; Fillion et al., 2013; Dos Santos Freitas et al., 2018; Feitosa-Santana et al., 2018; Lacerda et al., 2020). Motor deficits were revealed as disorders in dexterity, strength, speed and balance (Lebel et al., 1998; Grandjean et al., 1999; Dolbec et al., 2000; Harada et al., 2001). Studies investigating effects of mercury intoxication in children, even when exposure was pre-natal, demonstrated neurodevelopmental and motor disturbances such as delayed milestone achievements (for example, age of first walking and talking), language issues and low mental and psychomotor indices (Grandjean et al., 1999; Harada et al., 2001; Marques et al., 2007; Fonseca et al., 2008; Santos-Lima et al., 2020). Although mercury exposure was significantly associated with neurological problems, simple correlations between these two variables were not always obvious. It is important to note, however, that exposure markers may change over time, where values are dynamic and depend on several factors, such as the period of time after exposure when the measurements were performed. Conversely, damage to the CNS is uni-directional, especially in older individuals, and it eventually triggers neurodegeneration. In chronically exposed populations such as those of the Amazon, it would not be unusual to find individuals, especially adults, displaying neurological damage with low levels of mercury, after possible past episodes of high exposure. Thus, for chronically exposed populations, continuous (annual at least) biomonitoring of exposure is highly recommended to capture the long-term exposure rates, particularly in individuals presenting neurological problems but with low mercury exposure levels.

Although the scientific literature shows an association between mercury contamination and neurological problems, standardization of the testing and analysis of the data is required for direct comparison. The research studies in the Amazon had differing protocols, for example methodologies of monitoring mercury exposure, clinical protocols and neurological tests, which makes it challenging to infer “safe” exposure threshold levels or determine the correct protocol to survey possible effects of neurotoxicity at different stages. Selecting the most appropriate test to determine neurological effects is critical to reach meaningful conclusions (Chen et al., 2000), which include the detection of early neurological performance indicators by physicians (de Jager et al., 2002). This is exemplified where inconclusive associations between mercury exposure and neurodevelopment effects in children were attributed to the inaccurate testing methods in riverine populations of the Amazon (Tavares et al., 2005). There are numerous neurological tests, commonly employed, such as Cambridge Neuropsychological Test Battery (CANTAB) and Mini Mental State Examination (MMSE), suitable for populations and research studies that may require very low instruction level, cultural sensitivity and dynamic interfacing between participants and researches/health workers to hold attention and interest (Bertolucci et al., 1994; de Macedo et al., 2015; Green et al., 2019).

A novel approach to avoid subjective evaluations and to detect the early changes caused by mercury exposure is the use of biomarkers in blood or saliva. Only two studies have evaluated markers that intimately linked neural damage and neurodegeneration in the Amazonian populations exposed to mercury (Arrifano et al., 2018c, 2018d). The first showed the increase of S100B mRNA levels in blood associated with mercury exposure (Arrifano et al., Arrifano et al., 2018c). The S100B protein is a well-established biomarker used to detect brain damage and it is a strong candidate biomarker for mercury-related neurotoxicity in humans (Yardan et al., 2011; Yilmaz et al., 2014). Accurate measurement of proteins is, however, challenging in isolated/remote populations as samples need to be immediately frozen to ensure stability. Our group has used a method to quantify circulating mRNA as an alternative to the S100B protein, where samples can be stored at room temperature with a RNA stabilizing reagent for 24 h, allowing time to transport the samples to adequate storage (Arrifano et al., 2018c). The second study analyzed the genetic susceptibility to neurodegeneration in 794 individuals of Tapajós and Tocantins basins by genotyping the apolipoprotein E (APOE) (Arrifano et al., 2018d). APOE4 genotype is the strongest genetic risk factor for Alzheimer’s disease, and seems to potentiate the damage caused by mercury as the diverse mechanisms of cellular toxicity are analogous (Arrifano et al., 2018b). Additionally, the study from the Amazon demonstrated, for the first time, that APOE4-carriers accumulate more mercury and this was an important biomarker for future prevention strategies of public health (Arrifano et al., 2018d). Although the association between biomarkers of mercury neurotoxicity and neurological outcomes is in debate, a combination of biomarkers for exposure, intoxication and genetic susceptibility could provide additional support for the screening and early identification of high-risk individuals.

5. Conclusions

Mercury in the Amazon is ubiquitous and it presents a major human health hazard (Crespo-Lopez et al., 2021). Mercury exposure in humans is typically either occupational (by ASGM) or environmental (from ingestion of contaminated fish). Through these two different routes, humans are exposed to elemental mercury or MeHg, respectively. Recent systematic reviews report that Amazonian populations present one of the highest levels of mercury exposure in the world (Basu et al., 2018; Castro and Lima, 2018; Sharma et al., 2019). However, according to a previous systematic analysis (Puty et al., 2019), only one study in the Amazon (Khoury et al., 2015) includes all the requirements of a quality research study, such as the inclusion of a control group and mercury quantification to accurately define exposure, to confidently demonstrate the association between mercury exposure and neurological alterations. To improve future research, this review analyzed the main attributes of previously reported studies from the Amazon that evaluated both mercury exposure and neurological changes, and the following conclusions and recommendations are made:

- The average production of approximately two studies per year in the last fifteen years (as shown by our results) is insufficient to properly monitor a region as extensive as the Amazon. A higher investment (national and international) in research is essential to build a database and confidently highlight the problem.
- Only four studies were carried out outside Brazil, revealing the importance of expanding the research in countries bordering the Amazonian region.
- There is a need for a scientific popularization of the research to disseminate data to a wider audience, especially those who are directly affected, such as the riverine communities of the Amazon.

- Brazilian scientists clearly leader this endeavor, but international collaboration would enhance dialogue and recognition within the international scientific community.
- Within the research studies, the inclusion of the exact geographical location of the populations (with specific coordinates) must be included to plot the full extent of the problem.
- All Amazonian populations identified "at risk" need to be evaluated for neurological outcomes. Areas where high exposure is demonstrated in populations living at the Negro River basin (reviewed by (Castro and Lima, 2018)), have not, for example, been fully evaluated to elucidate the presence or extent of neurological damage. Also, the impacts of the Belo Monte HPP on the Xingú River, an anthropogenic alteration of the environment that known to cause mercury accumulation, have not been studied. This highlights the very real and urgent need of biomonitoring to capture exposure and prevent poor public health.
- Future studies on occupationally-exposed populations in the Amazon should prioritize the quantitation of creatinine to normalize urine mercury, and ensure comparison can be drawn with other pre-existing data.
- Further investigation is urgently required to detect the possible neurological problems associated with MeHg exposure in both adults of the Madeira Basin and children of the Tapajós Basin.
- The quantification of MeHg in human samples is recommended in addition to total mercury. As recently proposed (Castro and Lima, 2018), increasing the technical capacity in the Amazonian region is essential to support future studies.
- It is vitally important that epidemiological studies contain absolutely concentrations to justify associations between mercury exposure and deleterious effects on human health. Subjective classifications should be avoided, and studies must be properly contextualized, with the values of mercury concentrations in both the Abstract and main text and discussion of the exposure level compared with international guidelines.
- Future studies must be normalized to enable direct comparisons between locations and age groups, among others and we recommend adopting international guidelines for epidemiological studies such as STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) to divulgate the results.
- Neurological problems have been associated with mercury exposure in the Amazonian populations, and these manifest as visual (deficits in color vision, acuity and low contrast sensitivity) and motor (disturbances in dexterity, strength, speed and balance) deficits. In exposed children, delayed milestone achievements (age of walking and talking), language problems and low mental and psychomotor indices are associated with mercury exposure.
- Amazonian populations are chronically exposed to mercury and exposure levels can vary according to the frequency of intake/inhalation and rate of individual elimination of the metal. However, CNS damage, especially in adults, is cumulative. Therefore, analysis of the association with neurological outcomes would be more appropriate with multiple measurements to capture the individual's exposure over time.
- Selection of appropriate neurological test to define the neurological effects is critical. Neuropsychological batteries such as the Cambridge Neuropsychological Test Battery (CANTAB) and the Mini Mental State Examination (MMSE) are recommended.
- A novel approach is the development of biomarkers in the blood or saliva to indicate mercury-related neurotoxicity, which can be employed for the early detection of individuals at risk. Biomarkers such as APOE genotyping, for genetic susceptibility to neurodegeneration, and RNA expression of S100B, for neural damage, have been successfully tested in these populations.

As a signatory country to the Minamata Convention, Brazil has the opportunity to play a central role in leading the research into human exposure to mercury, especially in the Amazon. We call upon the Government to implement fundamental actions such as: (1) a national program for the surveillance of human exposure and epidemiology, (2) increase the technical capacity in the Amazonian region, for quantification and speciation of mercury and (3) raise national and international investment in research on the consequences of the chronic exposure in the Amazon, among others. This review provides useful strategies to improve the quality of future research and to support prevention and intervention approaches improving public health in vulnerable populations such as the Amazonian riverine population.

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Credit authorship contribution statement

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Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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