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Mercury: What can we learn from the Amazon?

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ABSTRACT

Mercury is among the ten most dangerous chemicals for public health, and is a priority concern for the 128 signatory countries of the Minamata Convention. Mercury emissions to the atmosphere increased 20% between 2010 and 2015, with South America, Sub-Saharan Africa and Southeast Asia as the main contributors. Approximately 80% of the total mercury emissions in South America is from the Amazon, where the presence of the metal is ubiquitous and highly dynamic. The presence of this metal is likely increasing, with global consequences, due to events of the last two years including extensive biomass burning and deforestation, as well as mining activities and the construction of large-scale projects, such as dams. Here we present a concise profile of this mobilization, highlighting the human exposure to this metal in areas without mining history. Mercury reaches the food chain in its most toxic form, methylmercury, intoxicating human populations through the intake of contaminated fish. Amazonian populations present levels over 6 ppm of hair mercury and, according to the 175:250:5:1 ratio for methylmercury intake : mercury hair : mercury brain : mercury blood, consume 2–6 times the internationally recognized reference doses. This exposure is alarmingly higher than that of other populations worldwide. A possible biphasic behavior of the mercury-related phenomena, with consequences that may not be observed in populations with lower levels, is hypothesized, supporting the need of improving our knowledge of this type of chronic exposure. It is urgent that we address this serious public health problem in the Amazon, especially considering that human exposure may be increasing in the near future. All actions in this region carry the potential to have global repercussions.

1. Introduction: Mercury as a global pollutant

In October 2013, 92 countries signed the Minamata Convention on Mercury (www.mercuryconvention.org), an international treaty aggregating international efforts to reduce environmental contamination with mercury, and to prevent and treat cases of human intoxication with this metal. Three months later, the World Health Organization (WHO) endorsed this action, recommending the promotion of adequate healthcare to manage exposed populations, including strategies for effective risk communication, and facilitation of the exchange of epidemiological information regarding health impacts associated with mercury exposure (WHO, 2014). To date, 128 countries have signed the Convention and 119 have additionally ratified it. Brazil ratified the Convention in August 2017, but has not yet implemented a national biomonitoring program.

Why are so many countries concerned about mercury environmental contamination and human exposure? It is estimated that nearly of 19 million people worldwide are at risk of mercury exposure, representing a global public health challenge (Blacksmith Institute, 2015). According to the WHO, mercury is currently among the ten most dangerous chemicals for public health (WHO, 2017). Curiously, this metal has no known biological function. However, it is essential for our society due to its many different uses in industry and technology. Mercury has the

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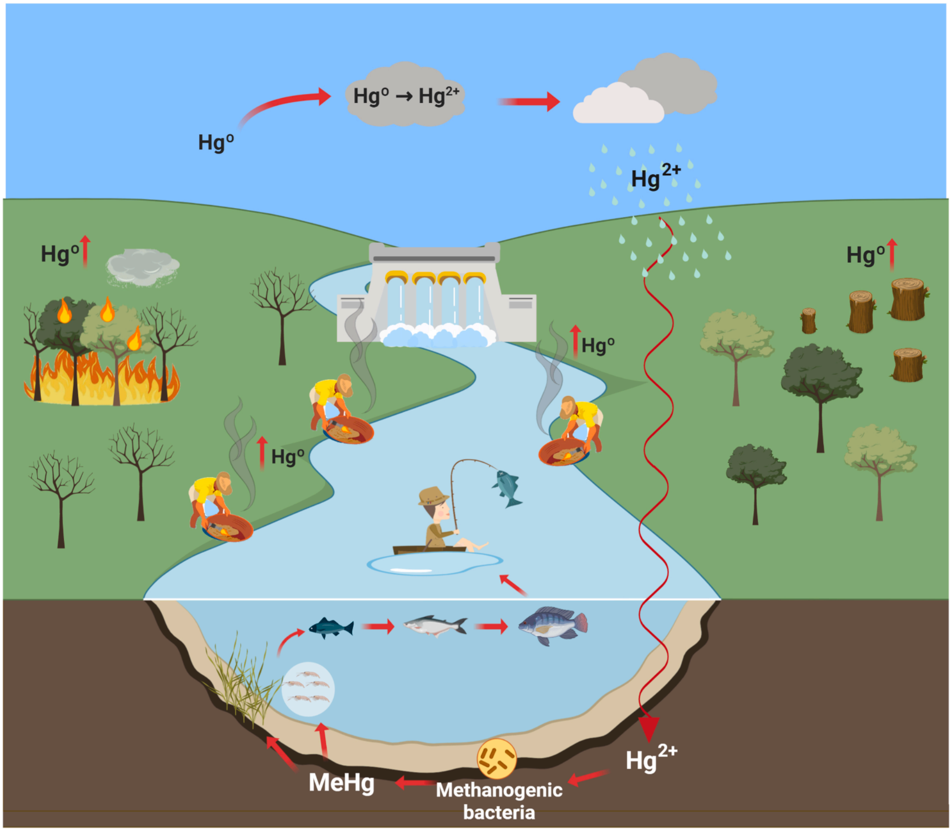


Fig. 1. Mercury dynamics in the Amazon. Artisanal small-scale mining and biomass burning are the main causes of mercury vapor (Hg^0) emission, which is transported over long distances by air. Deforestation reduces the rainforest́s capacity to remove this metal from the air, contributing to the maintenance of Hg^0 emissions. In the clouds, Hg^0 can be partially transformed into inorganic mercury (Hg^{2+}), which falls with rain, contaminating soil and water bodies. Then this Hg^{2+} is transformed into methylmercury (MeHg) by methanogenic bacteria that can exist in large quantities under favorable conditions (such as those created by dams). MeHg has a high ability to penetrate living beings, and can easily enter the food chain and reach humans through contaminated fish.

unusual property of being a good conductor of electricity in its liquid form, making it useful for hundreds of applications, including electric switches. Until recently, thermometers containing liquid mercury were common in almost every home. Yet, this liquid mercury is extremely volatile and its vapor is very toxic (Crespo-Lopez et al., 2005; WHO, 2017). To avoid dangerous residues and the possibility of children playing with mercury drops from broken thermometers, mercury thermometers have largely been replaced by mercury-free digital thermometers in many countries.

Many vulnerable populations around the world are currently facing exposure to a different form of this metal–organic mercury (mainly methylmercury, MeHg)—which is found in contaminated food. Organic forms of mercury, such as MeHg, are particularly toxic to humans because their toxicokinetic properties allow them to cross any cellular barrier. Consumed MeHg is quickly absorbed by the body, widely distributed to all tissues, and slowly eliminated (Crespo-Lopez et al., 2005, 2009). MeHg can cross tight barriers, such as the hematoencephalic and placental barriers, thus gaining easy access to the central nervous system (CNS) and fetus, respectively. Consequently, exposure to even small amounts can lead to deleterious consequences during in utero and early development (Crespo-Lopez et al., 2009; WHO, 2017).

Classically, the CNS is considered the main target organ of MeHg. Acute intoxication in humans leads to coordination and motor disturbances and progressive deterioration of visual and tactile senses, among other symptoms (Crespo-Lopez et al., 2005; WHO, 2017). This set of neurological changes is called Minamata Syndrome due to a 1956 outbreak in Minamata Bay, Japan. This episode of human intoxication, along with other outbreaks, has enabled the compilation of sufficient data for the design of various guidelines. For example, the WHO proposes a tolerable weekly intake of 1.6 μg MeHg per kilogram of body weight (b.w.) (WHO/UNEP, 2008). However, many vulnerable populations worldwide frequently consume mercury quantities well above this limit, including Amazonian riverine populations. Similar to other vulnerable communities, the Amazon also faces unsustainable economic exploitation that aggravates the problem.

Unlike isolated poisoning episodes, such as the one in Minamata Bay, these vulnerable populations have suffered chronic exposure for a very long duration, due to the characteristics of the place where they live. For example, the presence of mercury in the Amazon was first recorded in the 16th century, due to its use in gold mining, and continues to the present, mainly due to mining activities (Berzas Nevado et al., 2010; Veiga et al., 2002). In recent years, other important factors have also contributed to increasing the dynamics of mercury in the Amazonian environment. The presence of this metal is likely increasing in the Amazon, with global consequences, due to events of the last two years including extensive biomass burning and deforestation, as well as mining activities and the construction of large-scale projects, such as dams. Moreover, this contamination is of particular concern seeing the most recent data of human exposure in the Amazon. This exposure is alarmingly higher than that of other populations worldwide and recent evidences support that conclusions based on the analysis of exposed populations in developed countries or individuals with lower levels may not be consistent with what we can expect to find in Amazonian populations, making them a unique model to understand this kind of exposure.

Therefore, the objectives of this review are (1) to design the current profile of mercury mobilization in the Amazon, and (2) to contextualize the human exposure to MeHg in this region regarding to national and international guidelines and the exposure of other populations worldwide. Knowledge of the characteristics influencing the dynamics of human exposure to mercury, within the context of international guidelines, is essential for understanding the challenges faced by vulnerable populations, and will support the development of adequate prevention and intervention strategies for managing such exposure worldwide.

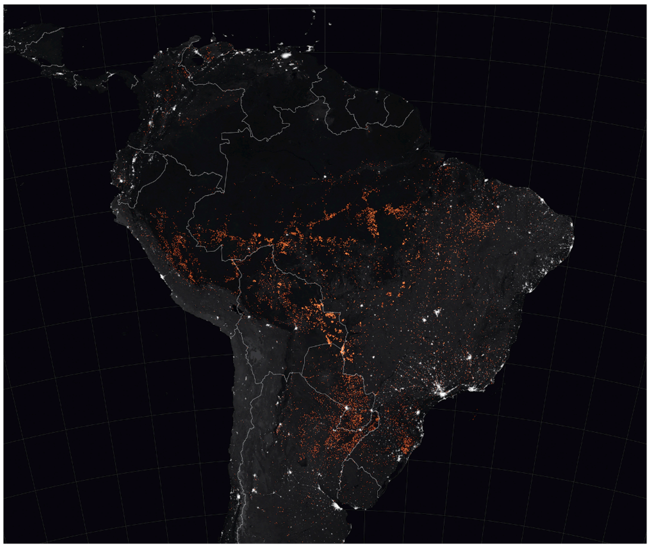


Fig. 2. Satellite image from the National American Space Agency with red indicating the points of biomass burning that were detected from August 15–22, 2019 (available at: https://earthobservatory.nasa.gov/images/145498/uptick-in-amazon-fire -activity-in-2019). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Reaching the humans: How anthropogenic actions are currently increasing the exposure

Mercury is extremely volatile, but does not disintegrate, i.e., it does not disappear over time, but rather keeps changing among different chemical forms. Mercury can be extracted from soil, travel hundreds of miles with the wind, be carried by rain, and enter the food chain with high penetration power within living beings. This means that mercury emissions into the environment are practically irreversible and difficult to contain.

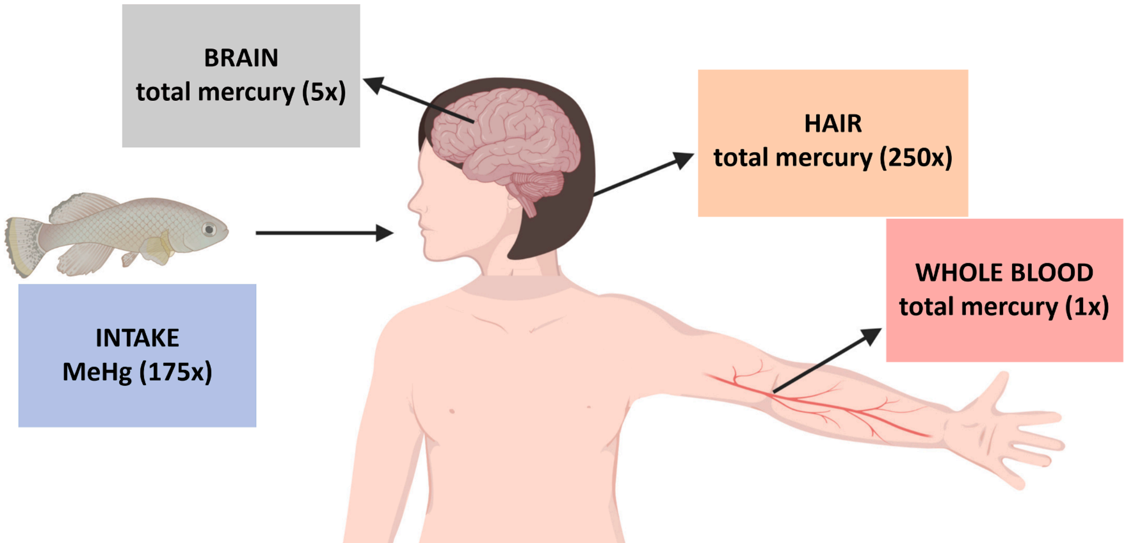
Anthropogenic emissions of mercury to the atmosphere increased approximately 20% between 2010 and 2015 (UNEP, 2019). Artisanal and small-scale gold mining (ASGM) is currently the first cause of these emissions accounting for 38% (838 tons) of the global total (Steenhuisen and Wilson, 2019; UNEP, 2019). South America is the region that contributes most to ASGM emissions worldwide, accounting for nearly half of the global ASGM emissions (Steenhuisen and Wilson, 2019; UNEP, 2019). In the Amazon, ASGM is responsible for emitting annually over 200 metric tons of mercury, which means that approximately 27% of the global ASGM emissions and 80% of total emission in South America are originated in the Amazon (Galvis, 2020). In Amazonian countries such as Guyana or Peru, mining activities are responsible for a significant deforestation and the low recovery rates of the Amazonian forest (Espejo et al., 2018; Kalamandeen et al., 2020). This problem is further aggravated by illegal mining, which has particularly intensified under the current Brazilian government. The Amazon Georeferenced Social and Environmental Information Network (AISG) reports that there are currently over 119 illegal mining settings in the State of Pará (the second largest State of the Brazilian Amazon) and about 300 settings throughout the entire Amazon (AISG, 2020). Mercury is used in ASGM activity due to its ability to amalgamate the small gold particles found in riverbeds (Fig. 1). Then the mercury and gold are usually separated by heating the amalgam, causing the evaporation of large amounts of mercury that may be transported across large distances by air before being deposited in soil, plants, and water (Fig. 1). When performed efficiently, this process requires approximately 1 kg of mercury for each kg of gold. However, ASGM often uses inefficient processes that can consume up to 50 kg of mercury for each kg of gold (WHO, 2016), thus massively increasing the amount of mercury released in the environment.

Fig. 3. Map of Brazil obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE, Brazil). Yellow lines outline the States, and black stars indicate the capitals. Red outline shows the area officially considered the Legal Amazon, including the State of Pará that is home to nearly half of the inhabitants of the North of Brazil. Also indicated are the Tapajós region (that includes the largest ASGM area in the Amazon) and Tucuruí region (home to the fifth largest hydroelectric power plant in the world). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Mercury vapor, having the predominantly chemical form of elemental mercury (Hg^0), can be transported through air over long distances, and deposited/captured in the tops and leaves of forest trees. Thus, the Amazon forest plays an essential role in removing and fixing mercury, and is considered a “sink” for atmospheric mercury (Figueiredo et al., 2018). As the largest tropical forest in the world, the Amazon possesses unparalleled potential to combat the effects of mercury emissions (Fig. 1). Unfortunately, extensive biomass burning—such as the occurrences in 2019 (Fig. 2) that drew international attention[1]—returns this mercury to the air, constituting the second greatest cause of mercury emissions in the region, after ASGM. Large mercury plumes of thousands of kilometers in size have been detected in the troposphere over South America and Africa, and biomass burning has been identified as primary [[parms resize(1),pos(50,50),size(200,200), bgcol(156)]]rce (UNEP, 2019). In fact, biomass burning is currently responsible for a higher proportion of global mercury emissions than geogenic causes such as volcanic emissions (UNEP, 2019). Moreover, deforestation reduces the capacity of the Amazon rainforest to remove mercury from the air (Fig. 1).

Unfortunately, deforestation has accelerated this year—encouraged by the current Brazilian government’s actions, including dismissal of managers in charge of inspection and a bill authorizing gold mining in indigenous and protected lands. During the first three months of 2020, a total of 796.08 km^2 of rainforest was deforested; this is an area about the size of New York City and constitutes a 51% increase compared to during the same period in 2019 (DETER-INPE, 2020). An additional 405.61 km^2 were deforested just in April 2020, which represents an increase of 63.75% when compared to April 2019. After deforestation and the removal of valuable wood, the area is usually burned during the dry season (June to October) to prepare it for the formation of immense pasture areas, in addition to the illegal appropriation of protected territory. A recent report has showed that 62% of the potentially illegal

[1] Recognized newspapers, including the New York Times, reported the significant extent of burnt areas in 2019 (see: https://www.nytimes.com/2019/12/05/world/americas/amazon-fires-bolsonaro-photos.html)



	MeHg Intake		Total Mercury		
			Hair	Brain	Whole blood
	µg/Kg per week	µg per week[1]	µg/g or ppm	µg/g or ppm	µg/ml or ppm[2]
USEPA reference dose	0.7	42	1	0.02	0.004
WHO reference dose	1.6	98	2.3	0.046	0.0092
Ratio	**175**		**250**	**5**	**1**

[1] For an adult of 60 Kg.
[2] According to the WHO, these values can reach 5 and 11.5 µg/L (or ppb) for the reference doses of the USEPA and WHO, respectively, considering that hair mercury can vary between 200 to 300 times the mercury in the blood (WHO/UNEP, 2008).

Fig. 4. Estimated total mercury burden in different tissues according to the methylmercury (MeHg) intake for fish consumers without occupational exposure. We used a 175:250:5:1 ratio for MeHg intake (in µg/kg per week):hair mercury (in ppm):brain mercury (in ppm):whole blood mercury (in ppm), in accordance with previous guidelines and data (Tables 1 and 2; NRC(2000); WHO/UNEP, 2008; Clarkson et al., 2007). The table provides the approximate content of total mercury in different tissues following consumption of the reference doses of MeHg intake established by the United States Environmental Protection Agency (US EPA) and the World Health Organization (WHO).

deforestation is promoted by the soy and beef exports to the European Union (Rajão et al., 2020). In June 2020 alone, 2,248 active fires were detected, constituting a 20% increase compared to in June 2019, as well as the highest number of fires in June since 2007 (INPE, 2020). As the second cause of mercury emissions in the Amazon, the extensive deforestation and burning detected in 2019 and 2020 would be responsible for increasing the mercury dynamics in the region, contaminating the environment and exposing living beings (including human populations) to higher mercury levels. This huge mercury emission during the last two years is likely influencing human exposure globally since mercury in the atmosphere can travel long distances.

In the atmosphere, mercury vapor is partially transformed into inorganic mercury (Hg^{2+}) when in contact with the clouds (Fig. 1). Rain transports the inorganic mercury to the soil and water, where the actions of methylating bacteria transform Hg^{2+} to MeHg (CH_3Hg), which is highly toxic to living beings (Azevedo, 2003; Beckers and Rinklebe, 2017). The bacteria-mediated methylation of mercury (i.e., addition of a radical methyl group, CH_3, to the mercury atom) is called biotransformation. These bacteria can efficiently perform mercury biotransformation in both water and sediments, extracting inorganic mercury from the soil (Azevedo, 2003; Beckers and Rinklebe, 2017). Notably, the Amazonian soil is naturally rich in mercury, including in locations without extractive history, and is thus an additional source of the metal in the environment (Wasserman et al., 2003; Siqueira et al., 2018; Galvis, 2020).

Once methylated, mercury can easily cross cell membranes and is quickly incorporated into the food chain. This process leads to biomagnification, i.e., increasing mercury accumulation in living beings with advancing trophic levels of the food chain, such that carnivorous animals contain more mercury than herbivorous animals. Thus, aquatic biota represents the main route of mercury transference from a contaminated environment to humans, especially in populations where fish are an important part of the diet (Berzas Nevado et al., 2010; Rodriguez Martin-Doimeadios et al., 2014; Alburquerque et al., 2020; Hacon et al., 2020; Ferreira da Silva and Lima, 2020).

In the Amazon, there are important ongoing anthropogenic changes that favor human exposure to mercury. Over 400 dams are currently in operation or being built in the Amazon (Winemiller et al., 2016), including some of the world's largest dams in the State of Pará (Fig. 3). The influence of dams on mercury mobilization in the environment has been repeatedly reported from different regions of the world (Bodaly et al., 2007; Gray and Hines, 2009; Johnson et al., 2015; Li et al., 2013; Forsberg et al., 2017). Increasing concentrations of mercury from sediments to suspended particulate matter and macrophytes (a main substrate for microbial activity and source of the methyl radical that it is transferred during methylation) are detected in Amazonian hydroelectric reservoirs and downstream (Kasper et al., 2014; Pestana et al., 2016, 2019). Dams also favor the processes of mercury biotransformation, accumulation and biomagnification in the food chain (Bodaly et al., 1997; Kehrig et al., 2009; Kelly et al., 1997). They can create physical–chemical conditions in the environment (e.g., regarding temperature, redox state, and degradation of submerged organic matter) that are conducive to microbial proliferation (Kelly et al., 1997; Gomes et al., 2019). A larger population of methylating bacteria in a location may be associated with more extensive mercury biotransformation, and higher amounts of MeHg passing from water and soil to living beings. Additionally, closing the ecosystem with a dam prevents large migrations of fish, which further favors mercury accumulation and biomagnification

Table 1
Reference doses of acceptable intake for methylmercury (MeHg) established by different organizations based on studies with populations presenting over 80% of mercury in hair as MeHg.

Organization	Reference dose (MeHg PTWI)[1]	MeHg quantity (PTWI × 60 kg)[6]
WHO/JECFA	3.3 μg/kg[2]	198 μg
	1.6 μg/kg[3]	96 μg
US EPA	0.7 μg/kg	42 μg
Health Canada	3.3 μg/kg[4]	198 μg
	1.4 μg/kg[5]	84 μg
FSC Japan	2.0 μg/kg	120 μg
NIPHE Netherlands	0.7 μg/kg	42 μg
ATSDR	2.1 μg/kg	126 μg
FDA	3.5 μg/kg	210 μg

Data of reference doses (MeHg PTWI) were obtained from WHO/UNEP (2008) and NRC (2000).
WHO/JECFA, World Health Organization/Joint FAO-WHO Expert Committee in Food Additives; USEPA, Environmental Protection Agency of the United States; FSC Japan, Food Safety Commission of Japan; NIPHE Netherlands, National Institute for Public Health and the Environment of the Netherlands; ASTRD, Agency for Toxic Substances and Disease Registry; and FDA, Food and Drug Administration.
[1] Provisional tolerable weekly intake (PTWI) of MeHg expressed as micrograms of MeHg per kilogram of body weight per week.
[2] In 2003.
[3] In 2007.
[4] For the general population.
[5] For pregnant women, women of childbearing age and young children.
[6] Quantity of MeHg that is acceptable weekly intake for an adult with a body weight of 60 kg.

in loco.

One of the largest dams in the Amazon is the Tucuruí Hydroelectric Power Plant (Tucuruí HPP), in the State of Pará (Fig. 3), which generates electricity for an important part of the country. Its construction remains controversial due to the lack of adequate studies regarding its environmental impact and sustainable development (Fearnside, 2001). Although no ASGM or other mercury use has been detected in this region, high mercury levels are found among inhabitants of the islands in the lake formed after closure of the dam (the Tucuruí region) (Arrifano et al., 2018d, 2018e). These mercury levels are higher than those detected in populations of regions influenced by ASGM, such as the Tapajós River basin (a main tributary of the Amazon River with the largest ASGM area) (Fig. 3) (Arrifano et al., 2018d, 2018e). Mercury in the Tucuruí region would have arrived by air and/or been extracted from the soil, with the dam-created conditions favoring its entry into the food chain. This phenomenon of increased mercury in fish and humans after impoundment without other anthropogenic source of mercury has been also detected in the region of the Balbina HPP, Western Amazon (Forsberg et al., 2017). These observations raise concerns about other projects, such as the planned Andean dams (Forsberg et al., 2017), the recently inaugurated Belo Monte HPP (the largest dam in the Amazon and the fourth largest HPP in the world, also located in the State of Pará), and the proposed Tapajós Hydroelectric Complex (a group of 5 mega-dams planned to be built in the Tapajós region). Recent data point to a possible interesting alternative consisting of hydroelectric run-of-river dams, which are smaller than conventional large-storage reservoirs and take advantage of seasonal changes in water level and flow. The Santo Antonio HPP, on the Maderia River, seems to be an example of this type of low impact dam on the mobilization of mercury (Bastos et al., 2020), although additional studies in biota and humans are needed to confirm this hypothesis. The Chief Raoni Metuktire of the Kayapó tribe from the Xingú River basin has said: "It is outside the Amazon where the problem has to be controlled, because it is the outsiders who come here with money to invest in the construction of dams, … of large things."[2].

Overall, the Amazon currently exhibits an extremely active biogeochemical cycle of mercury, which is reinforced by ASGM, deforestation/biomass burning, the relatively high mercury content in the soil, and conditions caused by large-scale projects, such as dams. All of these variables contribute to broad mobilization of mercury in the environment, creating the necessary conditions for wide dissemination of mercury throughout the entire Amazon region and probably across the planet, and favoring the introduction of large quantities of mercury into the food chain. This whole process terminates in humans, i.e., the living beings that consume the highest quantity of MeHg due to biotransformation, biomagnification, and bioaccumulation. Amazonian populations have been chronically exposed to this form of the metal, and it is likely that human exposure to MeHg will be increasing in the region in the near future based on recent anthropogenic actions. Therefore, as a starting point, it is essential to understand this human exposure in the context of internationally recognized reference doses.

3. Human exposure to MeHg in the Amazon and its global context according to the reference doses

Over 18 million people live in the region officially recognized as the "Legal Amazon" (Fig. 3), nearly half of whom are concentrated in the State of Pará (IBGE, 2019). The North region of Brazil has one of the lowest human development indexes in the country, with an average family income per capita of approximately U$35.00/month (Atlas of Human Development in Brazil, 2016). A significant portion of the population in this region permanently resides away from large cities, in remote communities with difficult access to healthcare services (Arrifano et al., 2018a). These riverine populations present a specific profile of particular eating habits, lifestyle, and racial miscegenation. Their diet includes fish as an essential element, constituting about 80% of the total protein intake (Passos et al., 2008; Berzas Nevado et al., 2010; Hacon et al., 2020). Human exposure to mercury is strongly associated to fish consumption in these populations, as well as in indigenous people (Carvalho et al., 2019; Gonzalez et al., 2019; Alcala-Orozco et al., 2019; Valdelamar-Villegas et al., 2020; Feingold et al., 2020; Hacon et al., 2020; Ferreira da Silva and Lima, 2020). Most of these communities have no large-scale industrial activities, and utilize the Amazon forest and its rivers as a key source of subsistence. Due to the scarcity and precarious conditions of highways in the region, rivers are the main means of transport for these communities. Overall, these populations have a direct relationship with the local aquatic environment—using it to transport people and products, fishing to obtain food, cooking with water from the river or from hand-dug wells, and sometimes dumping trash directly into the river due to the absence of sewage systems (Arrifano et al., 2018a). In many communities, basic services such as electricity or education are only available many kilometers away

[2] Free translation of the Chief Raoni Metuktirés statement included in: https://brasil.elpais.com/brasil/2020–07-19/cacique-raoni-voz-global-da-defesa-dos-indigenas-e-do-ambiente-e- internado-em-terapia-intensiva.html

Table 2
Studies that have been used by different organizations to establish the reference doses, and calculations regarding the relationship between MeHg intake and hair mercury level in populations in which over 80% of hair mercury is MeHg.

Organization	Based on			Critical dose/ hair mercury (B/A)	Reference dose (MeHg PTWI)[3]	Estimated hair mercury with an intake equivalent to the reference dose [MeHg PTWI/(B/A)]
	Studies	Hair mercury A	Estimated critical dose (Benchmark or LOAEL)[1] B			
WHO/JECFA	Friberg (1971)	50 ppm	35 μg/kg per week	0.7	3.3 μg/kg[4] 1.6 μg/kg[5]	4.7 ppm 2.3 ppm
US EPA	Marsh et al. (1987)	11 ppm	7.7 μg/kg per week	0.7	0.7 μg/kg	1 ppm
Health Canada	Davidson et al. (1998); Grandjean et al. (1997); Kjellstorm (1986); Kjellström et al. (1989)	10 ppm	7 μg/kg per week	0.7	3.3 μg/kg[6] 1.4 μg/kg[7]	4.7 ppm 2 ppm
FSC Japan	Not available	Not available	Not available	Not available	2.0 μg/kg	2.9 ppm
NIPHE Netherlands	Not available	Not available	Not available	Not available	0.7 μg/kg	1 ppm
ATSDR	Davidson et al. (1998)	15.3 ppm	9.1 μg/kg per week[2]	0.6[2]	2.1 μg/kg	3 ppm
FDA	Friberg (1971)	50 ppm	35 μg/kg per week	0.7	3.5 μg/kg	5 ppm

Data of studies, hair mercury (A), estimated critical dose (B) and reference doses (MeHg PTWI)of were obtained from the WHO/UNEP (2008) and NRC (2000). WHO/JECFA, World Health Organization/Joint FAO-WHO Expert Committee in Food Additives; USEPA, Environmental Protection Agency of the United States; FSC Japan, Food Safety Commission of Japan; NIPHE Netherlands, National Institute for Public Health and the Environment of the Netherlands; ASTRD, Agency for Toxic Substances and Disease Registry; and FDA, Food and Drug Administration.

1 Dose that corresponds to a specific change in an adverse response compared to the response in unexposed subjects (Benchmark dose) or to the lowest dose at which an adverse or toxic effect was detected (Lowest Observed Adverse Effect Level, LOAEL).
2 Value for the NOAEL (No Observed Adverse Effect Level).
3 Provisional Tolerable Weekly Intake (PTWI) of MeHg expressed as micrograms MeHg per kilogram of body weight per week.
4 In 2003.
5 In 2007.
6 For the general population.
7 For pregnant women, women of childbearing age, and young children.

(Arrifano et al., 2018a, 2018c). The Amazonian population shows a highest proportion of European ancestry, followed by Amerindian and then African ancestry (Arrifano et al., 2018d). Interestingly, the Amerindian ancestry was recently related to the APOE4 allele, which confers a higher genetic susceptibility to both mercury-related neurodegeneration and non-communicable diseases (NCDs) (Arrifano et al., 2018a, 2018d). The prevalence of NCDs (e.g., hypertension) can be as high as 58% of the adult population and environmental factors, such as mercury contamination, are likely main contributors to this prevalence (Arrifano et al., 2018a). Unfortunately, the health services conduct no program for biomonitoring of mercury exposure in the region, and most data on human exposure is generated by scientific research.

Many organizations worldwide have established reference doses of MeHg intake as provisional tolerable weekly intake (PTWI) for the risk of adverse health effects in humans—i.e., the maximum dose considered safe to consume in a week (Table 1). The WHO reported a PTWI of 300 μg of total mercury. Initially, they proposed that this 300 μg should include no more than approximately 200 μg MeHg, but this quantity was revised to include no more than approximately 100 μg MeHg, due to the demonstrated neurotoxicity of this metal (Table 1).

To understand this acceptable consumption in the context of intake among Amazonian riverine populations, we must look at the contamination levels in the fish that constitute the main protein in the diet of these populations. Among the most commonly consumed fish, the highest levels of mercury are found in piscivorous fish, such as "tucunaré" (*Cichla* sp.) or "dourada" (*Brachyplatystoma flavicans*) (Berzas Nevado et al., 2010; Rodriguez Martin-Doimeadios et al., 2014; Souza-Araujo et al., 2016; Lino et al., 2018, 2019; Alburquerque et al., 2020; Azevedo et al., 2021). For example, in the Tapajós River basin, piscivorous species contain an average of 0.36–0.66 μg mercury per gram of wet fish muscle (or ppm) (Rodriguez Martin-Doimeadios et al., 2014; Lino et al., 2018, 2019; Souza Azevedo et al., 2019). In contrast, mercury levels of approximately 0.03 ppm are found in non-piscivorous species such as "aracú" (*Leporinus* sp.) or "pacú" (*Mylossoma* sp.) (Rodriguez Martin-Doimeadios et al., 2014). This high difference of mercury content between piscivorous and non-piscivorous species in the region is also confirmed by the most recent data (Lino et al., 2018, 2019; Alburquerque et al., 2020). Thus, non-piscivorous fish would be more suitable for human consumption because they exhibit lower levels of contamination (Rodriguez Martin-Doimeadios et al., 2014; Souza-Araujo et al., 2016; Lino et al., 2018, 2019; Alburquerque et al., 2020; Hacon et al., 2020). Notably, with these levels of mercury, all of these species (both piscivorous and non-piscivorous) are presently released for human consumption in accordance with Brazilian legislation, which establishes maximum mercury limits of 1 and 0.5 ppm in piscivorous and non-piscivorous fish, respectively (Ministry of Health, 1998). However, is this really safe?

It has been previously reported that the riverine inhabitants of the Tapajós region eat an average of one meal per day containing 141 g of fish, half of which are piscivorous fish (Passos et al., 2008). This results in an average weekly consumption of over 340 μg of total mercury[3], which exceeds the limit recommended by the WHO. Notably, this is a very conservative approach to estimating the actual human intake of mercury since many riverine individuals in the Amazon often consume more than one meal of fish per day on many days per week, and consume higher quantities of fish than previously described (personal observations of the authors and Hacon et al., 2020). Another factor worsening the situation is the high MeHg content in these fish species (between 80 and 100%) (Berzas Nevado et al., 2010; Rodriguez Martin-Doimeadios et al., 2014; Lino et al., 2018, 2019; da Silva et al., 2020). This estimated quantity of MeHg (272 μg)[2] is nearly three times the weekly tolerable intake recommended by the WHO since 2007 (approximately 100 μg), and over six times the acceptable intake recommended by other

3 Weekly consumption of mercury from piscivorous fish: 3.5 meals per week × 141 g fish × 0.66 μg/g mercury = 321.66 μg mercury. Weekly consumption of mercury from non-piscivorous fish: 3.5 meals per week × 141 g fish × 0.03 μg/g mercury = 14.81 μg mercury. Thus, total weekly consumption of mercury: 321.66 μg + 14.81 μg = 340.52 μg mercury (with at least 80% being MeHg, i.e., 272 μg).

organizations, such as the US EPA (Table 1).

As described above, unlike the Tapajós River basin, the Tucuruí region does not have significant ASGM activity. However, studies since 1995 have demonstrated mercury contamination of water, sediments, and biota, with levels similar to or greater than those found in the Tapajós region (Aula et al., 1994; Kehrig et al., 2009; Palermo et al., 2004; Porvari, 1995; Rodriguez Martin-Doimeadios et al., 2014; Albuquerque et al., 2020). In 1995, an analysis of hair samples from fishermen and their families revealed mercury levels of 0.9–240 ppm, with an average of 65 ppm (Leino and Lodenius, 1995), which is sufficient to cause intoxication and alter neurological development. These alarming levels of human exposure have continued, with present levels even higher than those found in Amazonian populations historically influenced by ASGM (Arrifano et al., 2018d, 2018e). The available data support the hypothesis that consequences of Amazonian mercury contamination would be suffered not only in regions near ASGM areas, but throughout the entire Amazon (and perhaps globally)–especially in locations with conditions favoring mercury dynamics (e.g., burning/deforested areas and dams).

In agreement with the high mercury intake in the Amazon, recent systematic reviews demonstrate that some of the highest levels of human exposure to mercury occur in South America, especially among the Amazonian riverine populations (Basu et al., 2018; Sharma et al., 2019). Although mercury levels in blood have globally declined since the 1960s (Sharma et al., 2019), mercury emissions to the atmosphere from anthropogenic sources have recently increased (Steenhuisen and Wilson, 2019; UNEP, 2019), and anthropogenic actions in the Amazon over the last two years are likely mobilizing mercury worldwide and increasing its bioavailability to humans. Moreover, the latter systematic review (Sharma et al., 2019) did not include studies analyzing mercury levels in hair. This is an important limitation to generating a clear picture of human exposure since many exposed populations around the world are vulnerable and/or remote/isolated, making hair the most suitable biomarker for analyzing MeHg exposure due to its stability and simple conservation under precarious conditions and the non-invasive collection. In fact, hair and urine are currently considered the most suitable and cost-effective biomarkers to monitor mercury, particularly in resource-limited settings (UNEP, 2019). Therefore, excluding studies that use hair as the biomarker of exposure may create a bias favoring studies of more developed regions (having better conditions for sample collection and conservation) and underrepresenting remote/isolated populations.

According to the WHO, human hair is a very good biomarker for MeHg exposure and is more stable than blood (WHO/UNEP, 2008). Mercury levels in blood change over time, peaking at between 4 and 14 h after exposure, and then being cleared (WHO/UNEP, 2008). In contrast, MeHg deposited in the hair remains stable for a long time. Growing about 1 cm per month, hair provides a historical record of MeHg exposure, with quantitation of the mercury content in one centimeter corresponding to the approximately exposure over one month. This provides a more reliable measure of exposure that the analysis at a moment of the day provided by blood mercury measurement.

Despite the advantages of this biomarker and its importance for vulnerable populations, no organization has recommended limits for the mercury content in hair (or other human samples). Available recommendations include the acceptable weekly levels of MeHg intake based on different studies of outbreaks in which the mercury content in the population has been quantified and the critical dose estimated (Tables 1 and 2). However, the reference doses of acceptable intake can be converted to measurements of hair content. Hair mercury content is generally directly proportional to MeHg intake, and estimations can be calculated with reasonable confidence. For example, the WHO reports that a weekly intake of 0.7 μg/kg b.w. will lead to hair mercury concentrations of approximately 1 ppm (WHO/UNEP, 2008). Interesting information can be obtained by analyzing the relationships between hair mercury quantities and the estimated weekly intake values in the studies used for establishing references doses (Table 2). Based on the data analyzed by organizations to generate current recommendations, a factor of 0.7 for weekly MeHg intake/hair mercury (B/A) can be generally observed (Table 2). This is the same factor assumed by the WHO/UNEP for fish consumers in whom over 80% of the mercury in hair is MeHg, as shown above (i.e., 0.7 μg/kg b.w./1 ppm). This factor seems to be approximately constant up to 50 ppm of mercury in hair (Table 2). Therefore, the references doses of weekly acceptable MeHg intake established by the US EPA and WHO are approximately equivalent to 1 and 2.3 ppm of mercury in hair, respectively (Table 2). This is an important insight because the 0.7:1 ratio for MeHg intake:hair mercury enables estimation of intake from quantification of total mercury in hair and vice versa.

Interestingly, hair mercury is also proportional to mercury concentrations in other tissues. For example, MeHg in hair is approximately 250 times higher than in whole blood, and 50 times higher than in the brain (Clarkson et al., 2007). These proportions are generally preserved for total mercury when MeHg is the main form of exposure (e.g., for fish consumers in whom over 80% of the total mercury in hair is MeHg) (WHO/UNEP, 2008). Considering the above 0.7:1 ratio for MeHg intake: mercury hair, we can deduce a ratio of 175:250:5:1 for intake:hair:brain: blood (Fig. 4). Therefore, a person consuming the WHO PTWI of MeHg will present a brain burden of approximately 0.05 ppm of mercury (according to the 35:50:1 ratio of MeHg intake:mercury hair:mercury brain). Surpassing these thresholds does not necessarily mean that the human brain will be damaged, but as the WHO warns, the magnitude, frequency, and duration of exceeding the reference levels will likely increase any risk (WHO/UNEP, 2008).

Many populations around the world, including populations in Europe and North America, usually present hair and blood mercury levels below these values (Basu et al., 2018; Sharma et al., 2019). In fact, current cohorts in these regions, such as ALSPAC or REGARDS, register extremely low levels of mercury, which may explain the lack of association with harmful consequences in these populations (Chen et al., 2018; Hibbeln et al., 2018). However, the situation in the Amazon is alarmingly different. A recent systematic review demonstrated that Brazilian Amazon populations present mean hair mercury levels of over 6 μg/g (Santos Serrao de Castro and de Oliveira Lima, 2018). Interestingly, this is also confirmed by the calculated MeHg intake of 272 μg for an adult of 60 kg (based on mercury content in Amazonian fish and the weekly intake of fish by Amazonian populations, see footnote 3). According to the 175:250:5:1 ratio, this intake may lead to approximately 6.5 ppm of total mercury in hair[4], a level very similar to that described by the systematic review (Santos Serrao de Castro and de Oliveira Lima, 2018), and potentially equivalent to a mean brain burden of 0.13 ppm. Epidemiological data confirm our previous conclusion that Amazonian populations may be consuming approximately two to six times the tolerable MeHg intakes recommended elsewhere. Recent data confirm typical symptoms of Minamata Disease, currently detectable in Amazonian communities and associated with high levels of exposure, such as color vision and visual perimeter deficits (Lacerda et al., 2020), emotional and motor perturbances (paresthesia, tremor, insomnia and anxiety) (Costa et al., 2017), and somatosensory deficits (altered tactile and vibration sensations, and two-point discrimination impairments) (Khoury et al., 2015). The outcomes detected in Amazonian children in the last five years (deficits in neurodevelopment and psychomotor performance, visual alterations, memory deficits, processing and reasoning impairments and oxidative stress) are of particular concern (Marques et al., 2015; Marques et al., 2016a, 2016b; 2016c;; dos Santos Freitas

[4] 272 μg of weekly MeHg intake x 60 kg of body weight = 4.53 μg/kg of weekly MeHg intake; according to the ratio 175:250:5:1 for weekly MeHg intake:hair mercury:brain mercury:blood mercury, this intake is equivalent to 6.5 ppm in hair (4.53 μg/kg x 250 / 175), 0.13 ppm in brain (4.53 μg/kg x 5 / 175), and 0.026 ppm in blood (4.53 μg/kg x 5 / 175).

et al., 2018; Feitosa-Santana et al., 2018; Carvalho et al., 2019; Reuben et al., 2020; Santos-Lima et al., 2020). All these findings, in addition to above-described likelihood that human exposure to mercury could be increasing in the region, raises many concerns and shows a clear need for immediate intervention in the Amazonian populations.

In a recent systematic review, Hu and colleagues revealed the importance of understanding the exact context of mercury exposure in the pursuit of investigating potential associations with adverse effects (Hu et al., 2018). They analyzed data from over 55,000 participants in a total of 29 studies, conducted in 17 different countries, looking for a possible association between human exposure to mercury and increased blood pressure. This relationship has been controversial for many years, with some studies supporting an association and others supporting the lack of association. Based on their dose–response meta-analysis, Hu and colleagues concluded that there is a non-linear association between mercury levels and hypertension prevalence. They found no association for mercury exposure below 2 ppm in hair (equivalent to approximately 8 ppb or μg/L in blood according to the aforementioned ratio). However, higher exposure was associated with a 59% increase in the odds ratio for hypertension. Since hypertension is a recognized risk factor for stroke and metabolic syndrome, among others conditions, it is not improbable that there may be a non-linear relationship between mercury exposure and the prevalence of these diseases. Additional studies are needed to answer this question. Meanwhile, it is highly important that new studies clearly describe the exact values of mercury content detected in individuals (preferably in both the abstract and the main text), avoid subjective classifications (such as “relatively low levels” or “low-to-moderate exposure”) and discuss the exposure within the context of international recommendations.

This apparent biphasic behavior with low and high mercury exposure has been also demonstrated in terms of the influence of genetic susceptibility to neurodegeneration. A recent study conducted in the Amazon reported the prevalence of allele E4 of apolipoprotein E (APOE4) linked to the Amerindian origin of the Amazonian riverine population and higher than that described globally (Arrifano et al., 2018d). The APOE4 genotype plays a main role in neurodegenerative disease development, and may potentiate mercury-induced damage, sharing diverse mechanisms of cellular toxicity with the metal (Arrifano et al., 2018b). The study performed in the Amazon also provides the first demonstration that APOE4 carriers accumulate more mercury with high exposure levels (above 10 ppm of hair mercury)—an effect that is not detected with hair mercury levels below 10 ppm. Therefore, APOE4 may exert a kinetic influence on mercury accumulation, with a biphasic behavior, and represent an important biomarker for future prevention strategies in public health (Arrifano et al., 2018d).

All of these data support the importance of increasing our knowledge about higher mercury exposure. Mercury has been present in the Amazon for centuries, and Amazonian individuals are frequently exposed throughout their lifetime. Due to their close relationship with the environment, they are intimately associated with any environmental changes. Unlike other contaminated locations around the world, the situation in the Amazon is not an outbreak that will end over time. Mercury will remain in the Amazon, and its presence is probably increasing at this time. Consequently, the Amazonian population is one of the few populations in the world that allows investigation of continued chronic exposure to higher doses of mercury. While there is presently no intervention action, they provide a unique model of study to understand all aspects of long-term mercury exposure in humans.

4. Conclusions

What can we learn from the Amazon? South America, Sub-Saharan Africa, and Southeast Asia are presently the main regions responsible for mercury emissions worldwide (Steenhuisen and Wilson, 2019; UNEP, 2019). In this context, the Amazon plays a central role in combating mercury contamination and exposure. All actions (beneficial or deleterious) in this region carry the potential to have global repercussions.

ASGM is responsible for approximately 68% of the mercury emissions to air in the Southern Hemisphere (Steenhuisen and Wilson, 2019). ASGM is also the predominant cause of mercury emissions in the Amazon. Moreover, in contrast to the global trend of falling mercury imports, this region registered an 28.5% increase in total mercury imports from 2008 to 2015 (Galvis, 2020), highlighting the economic importance of this activity for the region. Thus, improving the inefficient processes currently used in ASGM could dramatically reduce the emissions of this metal.

Other factors have also become important in recent years. The Amazon is the largest rainforest in the world, and acts as a “sink” for mercury emissions (Figueiredo et al., 2018). The extensive deforestation and biomass burning detected during the last two years have broken historical records. As the second greatest source of mercury emissions in the Amazon, this deforestation and biomass burning is likely responsible for increasing the mercury dynamics in the region, contaminating the environment, and exposing the living beings (including human populations) to higher levels of the metal. Moreover, this huge emission will probably influence human exposure globally since mercury can travel long distances in the atmosphere. Efforts must be multiplied to urgently reduce both deforestation and biomass burning. Reforestation actions could also be recommended, as long as they are conducted with respect for the Amazonian ecosystem.

Mercury dynamics and introduction into the food chain are also favorited by large-scale projects in the Amazon, such as dams. There are currently over 400 dams in operation or being built in the Amazon (Winemiller et al., 2016), including some of the largest in the world. Studies in the Amazon have taught us that these projects could have effects as deleterious as those of ASGM for populations under their influence—concentrating the metal in the environment and favoring its biotransformation and biomagnification through the food chain.

The idiosyncratic characteristics of the Amazonian population make them highly influenced by changes in the environment. The indigenous philosopher Ailton Krenak has said “I don’t see Earth and humanity. Everything is nature.” (Krenak, 2019). Fish consumption is the main pathway of human exposure to mercury in the Amazon. Although Brazilian law establishes limits on the mercury content in fish for human consumption, human populations still present high levels of the metal (over 6 ppm in hair). Studies in Amazonian populations reveal the current high levels of exposure in these communities, which are far above the levels presented by some European and USA populations, and above the recommendations of different organizations and guidelines. Considering that some evidence supports a possible biphasic behavior of mercury-related phenomena, with consequences that may not be observed in individuals with lower levels, it is essential to improve our knowledge of what is happening to Amazonian populations, as a unique model to understand this kind of exposure.

All of these data, in addition to the recent events that are likely increasing human exposure, support the need for a national program of biomonitoring and expanding the technical capacity of mercury quantification in environmental and human samples in the region. Brazil is one of the countries with the highest levels of mercury contamination and exposed people in the world. However, Brazilian law presently recognizes no reference dose or threshold of intake or hair mercury, only limits of the mercury content in individual fish for human consumption. This action is clearly insufficient when considered with respect to the exposure of Amazonian populations in the global context of internationally recognized reference doses.

Here exists a critical need for biomonitoring and intervention actions in these populations, as well as the legal establishment of reference doses that may indicate the need for clinical intervention. Such actions could potentially revert the present situation of underreporting, and limit as much as possible the potential increase of human exposure in the near future. Brazil, as a signatory to the Minamata Convention since

2013, should be committed to combat the environmental contamination and exposure to mercury. This issue is urgent, especially considering the present scenario of events that increase mercury dynamics in the Amazonian environment. The Amazonian populations await the fulfillment of this promise made to the world.

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Declaration of Competing Interest

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

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