# Human mercury exposure and adverse health effects in the Amazon: a review

## Exposição humana ao mercúrio e efeitos adversos à saúde na Amazônia: uma revisão

Carlos J. S. Passos [1]
Donna Mergler [2]

## Abstract

[1] Faculdade de Ciências
Farmacêuticas de Ribeirão
Preto, Universidade de São
Paulo, Ribeirão Preto, Brasil.
[2] Centre Interdisciplinaire de
Recherches sur la Biologie,
la Santí, la Societé, et
l'Environnement, Montréal,
Canada.

**Correspondence**
C. J. S. Passos
Departamento de Análises
Clínicas, Toxicológicas e
Bromatológicas, Faculdade
de Ciências Farmacêuticas de
Ribeirão Preto, Universidade
de São Paulo.
Via do Café s/n, FCFRP, sala
085A-A, Ribeirão Preto, SP
14049-903, Brasil.
cjpassos@fcfrp.usp.br

*This paper examines issues of human mercury (Hg) exposure and adverse health effects throughout the Amazon region. An extensive review was conducted using bibliographic indexes as well as secondary sources. There are several sources of Hg (mining, deforestation, reservoirs), and exposure takes place through inhalation or from fish consumption. There is a wide range of exposure, with mean hair-Hg levels above 15µg/g in several Amazonian communities, placing them among the highest reported levels in the world today. Dietary Hg intake has been estimated in the vicinity of 1-2µg/kg/day, considerably higher than the USEPA RfD of 0.1µg/kg/day or the World Health Organization recommendation of 0.23µg/kg/day. Neurobehavioral deficits and, in some cases, clinical signs have been reported both for adults and children in relation to Hg exposure in several Amazonian countries. There is also some evidence of cytogenetic damage, immune alterations, and cardiovascular toxicity. Since fish provide a highly nutritious food source, there is an urgent need to find realistic and feasible solutions that will reduce exposure and toxic risk, while maintaining healthy traditional dietary habits and preserving this unique biodiversity.*

*Mercury Poisoning; Environmental Exposure; Amazonian Ecosystem*

## Introduction

Mercury (Hg) contamination of the large Amazon Basin has been the subject of much concern over the last two decades. In 1979, a major "gold rush" began in the Brazilian Amazon, which, over time, brought several hundred thousand persons (*garimpeiros*) to the region searching for riches [1]. A health study conducted from 1986 to 1991 showed elevated urinary and blood Hg concentrations in miners with signs and symptoms of Hg intoxication [2]. World attention focused on the plight of miners and those exposed to vapors from gold refining [1,2,3]. Biogeochemical studies showed that these uncontrolled gold-mining activities released thousands of tons of Hg into the environment, and increased levels of this metal were reported in water, sediments, and fish [3,4]. Gold mining became synonymous with Hg pollution [5]. In the Amazon, the bioaccumulation and biomagnification of methyl-Hg in fish, as well as the link between fish consumption and elevated hair-Hg levels were made in the early 1990s [4]. Flooded forests and macrophyte mats are specific features of many areas of the Amazon and constitute important links between Hg inputs from natural and anthropogenic sources and methyl-Hg exposure of local populations through fish ingestion [6]. Seasonal inundation of rivers and their floodplains seems to govern the production and bioavailability of methyl-Hg to food webs [7].

As data accumulated on elevated levels of Hg in fish and human populations, even among those living far away from gold-mining activities, other primary Hg sources were proposed. Veiga et al. [8] estimated that forest fires and biomass burning could make an important contribution to the environmental Hg burden. Subsequent studies on the distribution and partition of total Hg in waters of the Tapajós River in Brazil showed that Hg content in the water column was influenced by the amount of particulate matter, independently from upstream gold-mining activities [9]. Pioneering studies in the Tapajós region further showed that Amazonian soils constitute major natural Hg reservoirs that release substantial amounts of the metal into the aquatic ecosystems through soil erosion and leaching resulting from deforestation practices, such as "slash and burn" agriculture and/or cattle raising [10,11,12,13]. Since then, a growing number of publications has corroborated the role of deforestation and soil erosion as a major source of Hg release into the waterways, and hence to fishing resources and human fish-eating communities [14,15,16,17,18]. Deforestation and soil erosion resulting from gold-mining activities as well as Hg releases from abandoned mining sites constitute additional sources of Hg to the environment [19]. Because of the multiple sources and continuing environmental degradation leading to elevated Hg in the food web, human Hg exposure is prevalent in numerous mining and fish-eating populations in many regions of the large Amazonian territory.

Much of our knowledge of environmental methyl-Hg clinical toxicity is strongly linked to the disasters that occurred over 40 years ago in Minamata and Niigata, Japan, as well as in Iraq [20,21], where high levels of methyl-Hg exposure caused death and neurological damage to thousands, who were exposed directly or *in utero*. These events were recently reviewed elsewhere [22,23]. Over the last decade, international public health concerns on the toxicological risks of methyl-Hg have focused almost exclusively on developmental neurotoxicity associated with prenatal exposure [24,25]. The findings of large prospective birth cohort studies have formed the basis for recent risk assessments and revision of reference doses proposed by national and international bodies [24,25]. However, in most of the Amazon region, little has been done to protect mining and fish-eating communities and Hg exposure remains elevated [26,27].

The purpose of this paper is to examine the scientific literature on human Hg exposure and adverse health effects in the Amazon, with a view to understanding the implications for intervention, risk management, and environmental health in this developing region.

## Methods

A computerized database search of MEDLINE, LILACS, SciELO, and Scopus was conducted using the following search terms: mercury, methylmercury, environmental exposure, fish consumption, occupational exposure, gold mining, deforestation, hair mercury, blood mercury, urinary mercury, toenail mercury, risk assessment, health effects, neurotoxic, immunotoxic, cardiovascular, genotoxic, diet, nutritional factors, selenium, fruit consumption, intervention, and Amazon. In addition, secondary reference searching and hand-searching were used to identify relevant primary studies and reviews dealing with biogeochemical and ecotoxicological issues, human exposure, health risk assessment and communication, human health effects, as well as dietary/nutritional studies and interventions to reduce exposure and toxicity.

In our survey of the literature, we included peer-reviewed documents, as well as published reports by international organizations dealing with policy and research programs to reduce the adverse ecological and human health impacts of Hg pollution. The bibliographic research covered articles and reports written in English, Portuguese, Spanish, and French.

In all, we examined 24 primary studies covering the anthropogenic and natural sources of Hg into the environment and related ecotoxicological issues. Fifty-four studies addressed questions relating to human exposure in mining, riparian, indigenous, and urban populations, while only eight studies assessed health risk and communication. Human health outcomes were examined in 34 studies, and a limited amount of work was retrieved on community-based interventions and dietary, nutritional, and genetic factors that could influence Hg exposures in the Amazon. For the sake of comparison, 42 primary studies and review papers as well as authoritative sources analyzing Hg issues around the globe are also included in the present report.

## Results and discussion

### Mercury exposure in the Amazon Basin

Hair-Hg is generally considered to be a good indicator of Hg exposure through fish consumption [22,25], and many studies in the Amazon have examined hair-Hg concentrations in occupational

settings at gold-mining and refining sites (see Da Silva [28] for location of the most important sites) and for environmental exposures in urban and remote riparian and indigenous settlements. Table 1 provides a chronological summary by country for studies conducted in several Amazon watersheds and cities. The first published assessment of hair-Hg levels was made in gold miners and dates back to 1988 in the Brazilian literature [29], while Malm et al. [4] published the first evaluation in remote riparian villagers, for communities along the Madeira River. Around the same time, Boischio & Barbosa [30] reported that of 311 hair samples analyzed in the Madeira River area, 51% had Hg levels over 10µg/g, with wide inter-individual variations and concentrations as high as 303µg/g. To our knowledge, Malm et al. [4] published the first report that recognized fish consumption as the exposure route for communities not living in the vicinity of gold-mining sites. Since those initial studies, consistently elevated hair-Hg levels have been reported in different watersheds of the Brazilian Amazon Basin. In 1995, Olivero et al. [31] reported elevated hair-Hg levels in a mixed population living in a mining area of the Colombian Amazon, with fishermen showing higher levels than miners, and in 1998 a study in French Guiana, another Amazonian country, likewise revealed elevated Hg levels in fish consumers of different ethnic groups [32]. Elevated hair-Hg concentrations have since been reported for the Amazonian areas of Bolivia, Ecuador, and Suriname [33,34,35,36].

Among fish consumers, riparian communities present the highest degree of exposure, with mean hair-Hg as high as 38.6 ± 14.4µg/g [37] and 65 ± 58µg/g [38]. Overall, urban fish-consumers are the least exposed, presenting mean hair-Hg levels of 2.4µg/g [39], 2µg/g [40], and 1.9µg/g [34]. However, a recent pilot study in two municipalities of the Negro River in the Brazilian Amazon (São Gabriel da Cachoeira and Barcelos) showed mean hair-Hg levels of 13µg/g and 9.7µg/g, with upper values as high as 81.3µg/g [41].

Some studies have provided information on the percentage of methyl-Hg in hair samples (Table 1). Methyl-Hg is generally above 70%, but a few studies show wider variations. In three pregnant women from French Guiana with exceptionally elevated hair-Hg (88µg/g, 420µg/g, and 530µg/g), speciation of Hg showed that it was mainly inorganic Hg; the authors suggested that this probably resulted from direct exposure to metallic Hg in the household [32]. Indeed, pregnant women constitute a group deserving particular attention since Hg crosses the placenta to the fetus, and methyl-Hg is actively transferred [42,43,44].

In the Amazonian mining communities, urinary Hg, considered the most valid bioindicator for exposure from inhalation of elemental Hg vapors [22], has been assessed in several studies. In this region, gold-Hg amalgam burning has contributed to substantial Hg exposure, with urinary Hg values ranging from 0.2 to 663µg/L in adults [2,45,46,47,48,49], while in children concentrations from 26 to 159µg/L [35,50] have been reported. More recently, and consistent with recent findings in other areas of the world [51,52,53,54,55], fish-eating has been associated with relatively elevated urinary Hg in non-occupationally exposed populations in the Brazilian Amazon. Passos et al. [56] reported urinary Hg levels above 10µg/L for almost 20% of a population with no evidence of exposure from Hg vapors; in that study, elevated urinary Hg was associated with consumption of carnivorous fish.

## Mercury sources, fishing resources, and bioindicators of exposure

Identification of Hg sources is particularly important for mitigation, and elevated Hg levels in Amazonian communities probably reflect a multiplicity of sources releasing Hg into the environment and fishing resources. While in some areas of Colombia, Suriname, and Venezuela, Hg from gold mining most likely predominates over deforestation and/or hydroelectric damns [31,36,57], in other regions, such as Peru, it is difficult to ascertain whether fish-Hg contamination is attributable to mining or other causes [58], and in countries like Brazil, Ecuador, and Bolivia there seems to be an interplay of various sources [17,18,26,33,59,60] that contribute synergistically to environmental and aquatic biota contamination, as recently proposed in the French Guiana Amazon [19].

The recent study in the Negro River, cited above, provides an interesting illustration of possible multiple sources. While the authors point to gold mining in the Upper Negro River (Colombian Amazon) as the probable source, recent biogeochemical studies have shown the important impact of naturally occurring Hg in this basin [14,61,62], concluding that Hg leaching from soils constitutes the largest regional reservoir of this metal [14]. These findings are supported by studies analyzing environmental determinants of Hg levels in fish as well as dietary human exposure, all of which indicate that fish and human Hg levels in the Negro River Basin are strongly influenced by naturally high background Hg levels [37,63,64]. However, it is difficult to ascertain the true source of exposure (which may not be unique) for each community, and the variation in results from

Table 1

Reported hair-Hg levels in fish-eating groups in the Amazon Basin.

| Location | Population | Age (years) | n | Total hair-Hg (μg/g) Mean ± SD | Range | %MeHg (Range) | Reference |
|---|---|---|---|---|---|---|---|
| Brazil | | | | | | | |
| Madeira River | Riparian | - | 713 | 15.2 ± 9.6 | 6-150 | - | Bastos et al. [26] |
| Tapajós River | Riparian | < 15 to 65 | 69 | ≅ 15 ± NA | - | - | Pinheiro et al. [27] |
| Madeira River | Riparian | - | 241 | 17.2 ± NA | NA-303 * | ** | Boischio & Barbosa [30] |
| Xingu Park | Indigenous | - | 27 | 18.5 ± 5.9 | 6.9-34 | - | Vasconcelos et al. [154] |
| Cuniã Lake Reserve | Riparian | - | 75 | 8.7 ± NA | NA-31.9 | 70-80 | Barbosa et al. [45] |
| Fresco River | Indigenous | - | 419 | 8.0 ± NA | - | - | Barbosa et al. [45] |
| Tapajós River | Riparian | - | 101 | 21 ± NA | 4.7-151 | 85-91 | Malm et al. [65] |
| Santarém City | Urban | - | 10 | 2.7 ± NA | - | - | Malm et al. [65] |
| Gurupi goldfield | Riparian | - | 10 | - | 0.2-15 | - | Palheta & Taylor [46] |
| Negro River | Riparian | - | 101 | 38.6 ± 14.4 | - | - | Eve et al. [37] |
| Teles Pires and Juruena Rivers | Indigenous | - | 55 | 34.2 ± NA | 10 to > 50 | 87.2 *** | Barbosa et al. [66] |
| Yanomami Indians | Indigenous | - | 14 | 3.3 ± 1.2 * | 1.5-6.0 * | 58-97 | Kehrig et al. [67] |
| Tapajós and Madeira Rivers | Riparian | - | 82 | 16.7 ± 7.3 * | 1.0-59.4 * | 8.7-100 | Kehrig et al. [67] |
| Tapajós River | Riparian | ≥ 15 | 96 | 12.9 # | 0-145 | 73-94 | Lebel et al. [68] |
| Fresco River | Indigenous | < 2 to 45 | 28 | 8.1 ± 3.2 | 0.8-13.7 | - | Barbosa et al. [155] |
| Madeira River | Riparian | < 2 to 45 | 98 | 14.1 ± 10.7 | 2.6-94.7 | - | Boischio & Cernichiari [156] |
| Madeira River | Riparian | 0.1-32 | 28 | - | 4.0-84.4 | 84-90 | Barbosa et al. [155] |
| Pracuúba Lake | Riparian | - | 15 | 16.7 ± NA | - | - | Guimarães et al. [75] |
| Alta Floresta City | Urban | 14-45 | 75 | 1.1 ± 1.17 | 0.1-8.2 | - | Hacon et al. [70] |
| Tapajós River | Riparian | - | - | 17 ± 8.5 | 2.9-71.5 | - | Pinheiro et al. [71] |
| Xingu Park | Indigenous | - | - | 13.6 ± 4.7 | 4.3-32.8 * | - | Vasconcelos et al. [118] |
| Negro River | Riparian | < 15 to 40 | 76 | 21.4 ± 12.7 | 1.7-59 | 34-100 | Barbosa et al. [157] |
| Tapajós River | Riparian | 12-68 | 36 | 12.5 # | 2.9-27 | - | Dolbec et al. [72] |
| Rio Branco City | Urban | 0 to > 60 | 2,318 | 2.4 ± 3.9 | 0.8-72.7 | - | Santos et al. [39] |
| Tapajós River | Riparian | < 1 | - | 12 ± NA | 9.6-14.6 | - | Boischio et al. [158] |
| Santarém City | Urban | 17-25 | 44 | 2.0 ± 1.8 | 0.08-15.2 | - | Passos et al. [40] |
| Pakaanóva Indians | Indigenous | 0.5-90 | 910 | 8.4 ± 6.4 | 0.5-83.9 | - | Santos et al. [73] |
| Tapajós River | Indigenous | < 10 | 203 | 8.1 ± 5.2 | - | - | Dórea et al. [159] |
| Negro River | Urban | - | 399 | 11.4 ± NA | 0.1-83.1 | - | Santos et al. [41] |
| Tapajós and Tocantins Rivers | Riparian | 0.1-12 | 168 | 5.1 ## | 0.4-53.8 | - | Pinheiro et al. [160] |
| French Guiana | | | | | | | |
| Maroni and Oyapock Rivers | Indigenous | < 15 to 80 | 156 | 5.4 ## | 0.2-530 | - | Cordier et al. [32] |
| Maroni River | Indigenous | 23 *** | 235 | 11.4 ± 4.2 | 1.9-27.2 | - | Fréry et al. [76] |
| Bolivia | | | | | | | |
| Beni River | Indigenous | - | 80 | 9.8 ± NA | 4.3-19.5 | - | Maurice-Bourgoin et al. [33] |
| Colombia | | | | | | | |
| San Jorge River | Riparian | 15-65 | 94 | 4.9 ± 0.55 | 0.5-40 | - | Olivero et al. [31] |
| Ecuador | | | | | | | |
| Napo River Valley | Urban | - | 46 | 1.9 ± NA | 0.03-10 | - | Webb et al. [34] |
| Napo River Valley | Indigenous | - | 54 | 7.0 ± NA | 1.5-13.6 | - | Webb et al. [34] |
| Nambija mining area | Indigenous | 0-14 | 80 | 6.0 ± 17.5 | 1.0-135 | - | Counter et al. [35] |

NA: not available.

* Hair MeHg;

** Authors indicate that 70% of a sub-sample had > 80% MeHg;

*** Arithmetic mean;

# Median;

## Geometric mean.

communities in the Negro River basin might depend upon where sampling was performed.

No matter what the environmental source, fish-eating practices are the most important predictor of Hg exposure in most areas of the Amazon, explaining a substantial proportion of the variation of total and methyl-Hg concentrations in both blood and hair. Based on these bioindicators, as well as Hg measurements in fish tissue, many studies in the Amazon have associated Hg exposure with fish consumption [4,26,27,32,33,37,39,45,46,65,66,67,68,69,70,71,72,73,74], especially for members of fishing families [75,76,77]. These studies support the universal observation that fish consumption constitutes the most important source of Hg exposure worldwide [22,25]. What distinguishes communities in the Amazon from many others around the world is that for an important proportion of this population, fish is the dietary mainstay and many eat fish at least once a day [68,72].

Studies on Hg in fish have noted a sizeable variation in concentrations among a large number of species, ranging from 0.01 up to 3.77µg/g, depending on the feeding habits and location [26,33,65,68,69]. There are, however, few studies of Hg speciation in fish from the Amazon region. Notable exceptions are Kehrig et al. [69] and Maurice-Bourgoin et al. [33] who respectively reported methyl-Hg fractions above 95% and varying from 73% to 98% of the total Hg in fish from the Balbina Reservoir and the Madeira River areas. Recent studies of total fish-Hg concentrations in the Amazon have also stressed the particular influence of annual flooding [64,78] and the role of fish species' food regimes [79,80] on the bioaccumulation patterns in the different ecosystems.

Investigators who examined the strength of associations between fish consumption frequency and hair-Hg concentrations [31,38,40,68,72] have shown correlation coefficients ranging from 0.2 to 0.89, depending on the frequency of fish intake as well as the fish species consumed. In addition, significant seasonal differences in hair-Hg levels have been reported for villages on the Tapajós River [68,72], where water levels can vary by around six meters between the rainy and dry seasons, affecting fish habitats and the availability of specific fish species. In contrast, no seasonal variations were observed for communities in the Andean Amazon [34], although the local habits of fish consumption as well as the different fish-eating patterns among communities were important determinants of exposure.

### Risk assessment studies

Given the elevated levels of exposure, some researchers have attempted to estimate the rates of Hg intake for purposes of health risk assessment. Table 2 lists studies that measured daily fish and Hg intake rates in different settings. Large amounts of fish are consumed throughout the Amazon; average daily intake in one area was around 340g/day and reached up to more than 600g/day in periods of abundance [76]. For many in the Amazonian watershed, fish constitutes the dietary mainstay, with intake depending on cultural practices and seasonal availability of this food. Different investigators have estimated the health risks of Hg exposure using predictive models.

Kehrig et al. [69] estimated that the population living near the Balbina Reservoir ingested 35.2µg of methyl-Hg during the whole year, while Fréry et al. [76], who performed extensive calculations using data from fish-Hg concentrations as well as amounts and frequency of fish consumed by each household, estimated Hg intake between 40 and 60µg/day. Others have presented estimates in µg/kg/day. These Hg intake rates, presented in Table 2, range from 0 to more than 4µg/kg/day, largely exceeding the exposure limit for Hg intake of 0.23µg/kg/day, recently revised by the World Health Organization (WHO) [24].

Hacon et al. [77] and Boischio & Henshel [81] also estimated potential health risks, using hazard quotients (HQ) based on the ratio of the estimated dose rate to the selected reference dose. If HQ is less than one, there is no anticipated risk of adverse effects, while there is a possibility of such risks in sensitive groups if it is equal to or greater than one [77]. Using a reference dose of 0.3µg/kg/day, these studies showed that the highest hazard quotients were observed for the riparian populations of the Madeira River [77,81].

### Human health studies

Over the last decade a number of human health studies have been carried out in different Amazonian communities. We identified 34 studies, of which the majority was conducted in the Brazilian Amazon (82%). Sixty-three percent focused on adult populations, while 24% examined children and 12% surveyed both adults and children. All of the studies used cross-sectional designs. Neurotoxic outcomes were the most extensively examined: 36% attempted to identify clinical neurological signs of Hg intoxication, while 42% tested the hypothesis of long-term low-dose exposure as a risk factor for neurobehavioral deficits at the population level. The remaining 12% included cytogenetic damage and more recent emerging evidence on immune and cardiovascular effects.

Table 2

Summary of risk assessment studies in Amazonian settings.

| Location | Setting | Fish intake | Total population | Hg intake Women | Children | Mean hazard quotient | Reference |
|---|---|---|---|---|---|---|---|
| Madeira River | Riparian | 200g/day | 2.2µg/kg/day | 1.2µg/kg/day * | 6.4µg/kg/day ** | Women: 0.02; children: 21 | Boischio & Henshel [81] |
| Tartarugalzinho River | Riparian | 200g/day | 1.6µg/kg/day | - | - | - | Bidone et al. [161] |
| Alta Floresta City | Urban | General population: 8g/day; children: 5g/day; fisher families: 110g/day | Fisher families: 2.2µg/kg/day | - | Fisher families: 3.5µg/kg/day | General population: 1.4; fisher families: 8.6 | Hacon et al. [77] |
| Barbina Reservoir village | Riparian | 110g/day | 35.2µg/y | - | - | - | Kehrig et al. [69] |
| Madeira River | Riparian | 243g/day | 2.6µg/kg/day | - | - | - | Boischio & Henshel [128] |
| Upper Maroni River | Indigenous | 163.1g/day | 40-60µg/day | 41.4µg/day | 17.5µg/day | - | Fréry et al. [76] |
| Northern Mato Grosso State Municipalities | Urban | - | 0.01-3.9µg/kg/day | - | - | - | Hacon et al. [162] |
| Tapajós River | Riparian | 141g/meal | 0-4.3µg/kg/day | - | - | - | Passos et al. [122] |

* 15-48 years old;

** < 5 years old.

• **Neurotoxic effects**

Table 3 summarizes the results of studies that examined associations between exposure and neurofunctional deficits in fish-eating communities. The first studies showing neurotoxic effects in adults below 50µg/g hair-Hg were conducted in the Amazon. In these studies, significant dose-effect associations were reported for motor, visual, and/or cognitive functions [82,83,84,85,86]. Two studies of children identified deficits in attention and visuo-spatial performance, as well as poorer leg coordination [87,88], whereas two other studies in children did not detect effects [89,90]. These latter negative studies examined riparian and urban children respectively, with substantially lower levels of exposure compared to other Amazonian communities; both used different neurobehavioral and statistical approaches from previous investigations, which makes it difficult to compare their findings with the others. On the other hand, the positive findings in the Amazon child studies are consistent with other investigations conducted around the world, such as the prospective cohort studies in the Faeroe Islands and New Zealand [91,92,93] and cross-sectional investigations in the Canadian Arctic and Japan [94,95].

In the Amazon region, Hg exposure has been inversely associated with hearing threshold as well as auditory brainstem evoked responses in both children and adults living in the Nambija gold mining area of Ecuador [96,97]. Although the study population lived in a mining area, the authors suggest that these persons may be at neurological risk not only from elemental Hg vapors inhaled during amalgam burning, but also from Hg exposure through consumption of foods with elevated Hg. In another study conducted in the Brazilian Amazon, auditory deficits were not observed for children and adolescents exposed through fish consumption [98]. It is difficult to determine whether differences in exposure (inorganic Hg vapors vs. dietary methyl-Hg) are the underlying reason for the inconsistencies.

Other investigators have used clinical methods including neurological examinations to identify typical symptoms of methyl-Hg poisoning (e.g. glove- and-stocking-type sensory disorder, visual field constriction, tremor, and cognitive disorders such as difficulty in concentrating and recent memory losses). We identified seven clinical cross-sectional studies of fish-eating communities, of which two reported neurological deficits related to Hg exposure, includ-

Table 3

Summary of neurobehavioral outcomes examined in relation to hair-Hg levels in Amazonian fish-eating communities.

|  | Adult population | | | | | Child population | | | |
|  | Lebel et al. [82] | Lebel et al. [83] | Dolbec et al. [84] | Yokoo et al. [85] | Silveira et al. [86] | Grandjean et al. [87] | Cordier et al. [88] | Tavares et al. [89] | Marques et al. [90] |
|---|---|---|---|---|---|---|---|---|---|
| Hair Hg (µg/g) | 14 * | ≅ 13 ** | 11 ± 6 *** | 4 ± 2 *** | 0.6-72 # | 11 * | 10.2 * | 5 ± 3 *** | 1.81 ** |
| Color vision | ↓ ## | ↓ | - | - | ↓ ## | - | - | - | - |
| Near visual contrast sensitivity | ↓ | ↓ ## | - | - | ↓ ## | - | - | - | - |
| Grip strength | ↓ | ↓ | - | - | - | - | - | - | - |
| Muscular fatigue | ↑ | ↑ | - | - | - | - | - | - | - |
| Visual field | ↓ | ↓ ## | - | - | - | | - | - | - |
| Manual dexterity | ↓ ## | ↓ ## | ↓ ## | - | - | ↓ ## | - | - | - |
| Fine motricity | - | - | ↓ ## | ↓ ## | - | ↓ ## | ↓ | - | - |
| Logical memory | - | - | - | ↓ ## | - | - | - | - | - |
| Digit span | - | - | - | ↓ ## | - | ↓ ## | ↓ ## | - | - |
| Easy learning | - | - | - | ↓ ## | - | - | - | - | - |
| Concentration | - | - | - | ↓ ## | - | - | - | - | - |
| Visuospatial functions | - | - | - | - | - | ↓ ## | ↓ ## | - | - |
| Leg coordination | - | - | - | - | - | - | ↓ ## | - | - |
| Static balance | - | - | - | - | - | - | - | NS | - |
| Dynamic balance | - | - | - | - | - | - | - | NS | - |
| Appendicular coordination | - | - | - | - | - | - | - | NS | - |
| Motor persistence | - | - | - | - | - | - | - | NS | - |
| Trunk-limb coordination | - | - | - | - | - | - | - | NS | - |
| Sensory perception | - | - | - | - | - | - | - | NS | - |
| Gesell developmental schedules | - | - | - | - | - | - | - | - | NS |

NS: non-significant.

* Geometric mean;

** Median;

*** Arithmetic mean and standard deviation;

# Range;

## Statistically significant.

ing sensory and balance disturbances, tremor, hyperreflexia, dysarthria [99,100]. In addition, the study by Lebel et al. [83] on fish-eaters from the Tapajós Basin included a neurological examination showing that although participants had normal results on most items, those with higher hair-Hg levels presented a significantly high prevalence of disorganized movements on the Branches Alternate Movement Task (BAMT) as well as restricted visual fields. The BAMT, which requires the individual to perform coordinated hand-knee movements, continually passing one arm over the other as rapidly as possible [83], was developed by Dr. Fernando Branches, a physician and pioneer in Hg neurotoxicity in the Brazilian Amazon [2,65,83]. Impaired BAMT performance has also been observed in connection with low Hg exposures through fish consumption as well as with occupational exposures in Italian cohorts [101,102]. The results of the clinical investigations of Amazonian communities provide supplementary evidence of Hg neurotoxicity, despite the non-specific nature of several signs.

• **Non-neurological outcomes**

Only one study has reported cytogenetic damage (decreased mitotic index and increased frequency of polyploid cells) related to hair-Hg levels in a fish-eating community on the Tapajós River [103]. In a follow-up of this population, five years later, after a 40% decrease in hair-Hg levels, the same cytogenetic endpoints no longer displayed significant associations with hair-Hg. The authors suggest that this is consistent with reduced biological impact resulting from the decrease in Hg exposure [104]. However, there is a lack of evidence in the literature concerning the association of both organic and inorganic Hg with cytogenetic outcomes, and more studies are needed to con-

firm these relations with early biomarkers of cytogenetic damage.

Some recent studies have focused on possible immune outcomes associated with Hg exposure. One epidemiological study reported that even if no relation was observed between bioindicators of Hg exposure and prevalent malaria, the odds ratio for reporting past malaria infection was four times higher for those also reporting a history of working with inorganic Hg [105]. Further investigation of the relationship between Hg exposure and prevalent malaria in the Amazon has produced consistent results in terms of Hg-induced effects on biomarkers of autoimmunity. One study reports on immune changes indicative of autoimmune dysfunction in environmentally exposed villagers [106], and another investigation shows that positive serum antinuclear antibodies are more frequently observed in riparian fish-eaters than in low fish consumers from an urban area [107]. The experimental and human evidence of possible inorganic Hg-induced immunological alterations [108] are particularly important in the Amazon, since these traditional populations (riparian and indigenous) are concomitantly exposed to vector-borne diseases such as malaria and Chagas infection.

Only two studies have analyzed cardiovascular outcomes in relation to Hg in the Amazon; one examined four indigenous villages [109] and the other surveyed six riparian communities on the Tapajós [110]. Dórea et al. [109] reported that while no significant differences in body mass index were observed between villages, there was a trend towards a lower increase in blood pressure with age among the higher fish consumers. On the other hand, Fillion et al. [110] showed blood pressure directly and significantly associated with total hair-Hg levels, and no association between fish consumption and blood pressure. A multi-center case-control study among men 70 years old or younger from eight European countries and Israel showed toenail-Hg levels directly associated with the risk of myocardial infarction, while an inverse association was observed with adipose-tissue docosahexaenoic acid (DHA) [111]. Although it is difficult to compare this study to the ones on cardiovascular outcomes in the Amazon, given the higher levels of exposure in many Amazonian communities as compared to North American and European cohorts [111,112], and because of possible toxicokinetic interactions promoted by traditional diet [113,114,115], future epidemiological studies should attempt to include a wider range of cardiovascular endpoints and further examine the possible influence of dietary and genetic factors.

## The role of dietary and nutritional factors

In the Seychelles Islands cohort study of childhood neurodevelopment, some results suggest beneficial outcomes correlated with Hg levels during pregnancy, which was interpreted as a possible protective effect of fish-borne nutrients [42], although no specific nutrient was identified. There is a growing interest in candidate nutrients that could protect against Hg absorption and/or toxicity [116].

Because of protective effects observed in a certain number of animal studies, selenium (Se) has received the most attention as a potential protector against Hg toxicity in populations consuming seafood [117]. A few studies have analyzed blood and/or hair-Se concentrations among fish-eating communities in areas of the Brazilian Amazon [118,119,120,121]. While most are in the normal range, Lemire et al. [121] reported elevated blood-Se concentrations for a group of persons in one village, suggesting that there may be wide variations throughout the region. There are some reports [118,119,121] of positive relations between bioindicators of Se and Hg, suggesting that fish may constitute a source of dietary Se. Although the authors of these studies point out that Se may play a role with respect to Hg toxicity, no investigation has been carried out so far.

Recent studies by Passos et al. [113,114,115,122] show that the strong relationship between fish consumption and Hg exposure is significantly modified by fruit consumption, which may indicate possible toxicokinetic interactions promoted by fruit intake [122]. Despite general recognition of the antioxidant properties of many nutrients contained in fruits [123], including Amazonian fruits [124,125,126,127], this food has received little attention as a dietary factor with potential to counteract Hg exposure and/or toxicity. And yet, fruit gathering and consumption are repeatedly reported by many studies addressing Hg issues in traditional communities of the Amazon [26,33,37,128,129,130]. Fruit is a particularly important component of riparian and indigenous diets, contrary to the diet of communities occupationally exposed in the mining areas [131]. Notwithstanding the encouraging and promising results concerning the role of fruits on Hg exposure, the studies conducted so far have not examined the possible physiological events that may be involved in the interactions between fruit nutrients and Hg absorption, and the potential protective effect of fruit intake with respect to toxicological outcomes also remains to be demonstrated.

## Methodological challenges

Exposure and health studies in the Amazon are methodologically challenging. Villages are often located in remote areas, with few or no health facilities and often with little or no electricity. There is a high prevalence of tropical diseases, such as malaria and different intestinal parasites. Recruitment of study participants can be difficult due to cultural and religious beliefs within the communities and/or mistrust of outsiders. Educational level is low. Study designs need to consider these factors in determining sampling strategies for bioindicators of exposure, questionnaire design for comprehension, face validity and inclusion of potential covariates, validation and administration, and testing procedures (particularly for neurobehavioral testing). Information, such as medical history that can only be collected from individual reporting, may suffer from differences in understanding, and validation against medical records is not possible in the absence of health facilities.

To date, all of the Amazonian studies have used cross-sectional designs, with most of them based on convenience samples due to the difficulties associated with random sampling strategies in these areas. However, since Hg exposure is not obvious and the effects are often not physically evident, selection bias with respect to Hg exposure and effects is probably not a major problem. Moreover, relations are consistent between fish consumption and/or proximity or involvement of gold-mining activities and the appropriate bioindicators of Hg exposure. In the neurobehavioral and neurological studies, persons with a history of disease unrelated to Hg exposure that might affect test outcomes, such as stroke, loss of consciousness over a long period, birth trauma (for studies in children), and others were excluded from most investigations either *a priori* or *post hoc* [82,83,84,85,87,88].

Hair has been the most extensively used bioindicator for Hg exposure in the Amazon region, and when hair and blood were both assessed, they have been shown to be highly correlated [84,115]. Hair sampling is particularly appropriate for studies in remote areas of the Amazon because it can be easily preserved and transported. However, in gold-burning areas and in the season when brush and forest are burned during farming (traditional "slash-and-burn" practices), there may be external Hg contamination. In the Amazon, toenails have not been used as a bioindicator for exposure. Although toenail-Hg has been correlated with hair and urine Hg levels [55], the related period of exposure is not known. Moreover, this bioindicator might not be appropriate for the Amazon setting, because in many areas people go barefoot or wear sandals, and soil-Hg may constitute a source of external contamination. For the studies reviewed here, hair-Hg was the most widely used bioindicator of exposure (76%), followed by blood (21%) and urinary Hg concentrations (12%).

For neurobehavioral and neurological outcomes, different tests and examinations have been used in the different studies. However, there is a commonality of effects observed in the adult studies, with motor coordination and visuo-motor performance showing the most consistent associations with Hg exposure [82,83,84,85,86]. The cultural appropriateness of the tests used in these studies has been criticized [100], but the expected variation in results with age and schooling tend to indicate that the tests were understood and performed in a similar way to other populations. In studies of children, a wide range of tests has been used and thought to be culturally appropriate for children living in these settings [87,88]. While this may not necessarily be the case, it should be noted that in studies that examined similar domains to those shown to be associated with Hg in other areas of the world, there were similar associations with bioindicators of Hg exposure [87,88]. One of the issues that none of these studies can answer is the relative contribution of intrauterine and current exposure to the observed relations.

In analyzing results, most studies that examined the relations between bioindicators of exposure and effects took age and schooling into account (where relevant); other factors such as smoking, alcohol consumption, malaria, working in gold-mining areas, and others identified through regression analyses have been included in the multiple regression models for the adult studies [82,83,84,85,86]. For the children's studies, potential covariates have been examined in some studies; these include maternal education, illness during childhood, parity, maternal age at delivery, maternal education, household income, illness during pregnancy, and duration of breastfeeding [88]. Some studies have included basic clinical examinations, which provide an indication of health status [83,88,89,90,97,99,100,105,106,109]. In studies which cover several villages, educational level may reflect different realities since it is very dependent on the local system and teachers, although place of birth or residence, which can reflect different exposures and/or different socioeconomic and cultural situations, have been included in some of the studies [87,88,110]. Despite the inclusion of a wide range of potential covariates in several studies, certain covariates (most notably dietary factors) may not have been iden-

tified or assessed, and were thus not included in the regression models.

Recent studies have underscored the benefits of fish nutrients as possible confounders and/or modifiers of relations between Hg exposure and health effects. Indeed, fish-borne nutrients such as DHA, iodine, iron, and choline have been considered potential modifiers of the effects of methyl-Hg on child outcomes in the Seychelles' studies [116]. Possible toxicokinetic interactions promoted by fruit intake, not only in Amazonian but most probably for other fish-eating populations where fruit is an important component of diet, might also constitute an effect modifier [113,114,115,122] and should be taken into account in future studies. To our knowledge, there is no published data on fatty acid levels in fish or humans in the Amazonian region, and this information would be useful for further investigations.

### Interventions

There has been some debate in the Amazon as to what (if anything) should be done about Hg exposures through fish consumption. Some researchers have suggested that "normal" safe values, higher than those proposed by WHO, could be established in the Amazon [130], while others have claimed that despite the high Hg concentrations, daily consumption of large amounts of fish does not necessarily pose a health hazard [132,133]. A contrasting opinion was expressed even in the early 1990s, when some authors recommended community-based interventions for both the occupational settings [2] and the environmental context [37]. Considering the potential for Hg-induced deleterious health effects, these latter authors indicated that environmental biomonitoring would be pointless if not directed at clear action, and suggested that any approach seeking solutions to the high exposure problem should include a major educational component.

Most mitigation attempts have been undertaken to reduce the use of Hg in gold-mining activities. In recent years, national and international organizations have made efforts to introduce cleaner artisanal gold mining and extraction technologies in many developing countries [134]. These initiatives center on capacity- and awareness-building about the links of small-scale gold-mining practices to human and ecosystem health [135]. Initial results from these activities in terms of reduction of Hg use and emissions through the adoption of homemade solutions have recently been reported in Africa [136].

In the Amazon, during the early 1990s, major projects proposed alternative techniques to reduce Hg use and exposure in gold-mining ac-

tivities [137,138], but the results on the efficiency of these interventions are not available. There are ongoing educational and capacity-building efforts in Brazil, Venezuela, Ecuador, and French Guiana [19,139], but there are no reports on their success in reducing human exposure. These initiatives have encountered several barriers to change, the most important and challenging one being poverty; lack of resources and political support are also cited [140]. Hilson et al. [141] have pointed out that despite extensive research conducted over the past 15-20 years in Latin America and in Africa, most of the investigations have failed to identify appropriate mitigation measures, and education strategies have at best been marginally effective due to socioeconomic and poor living conditions in mining areas. The historical data in the present review clearly and sadly shows that despite many years of research, Hg exposure remains elevated throughout the Amazon region, corroborating the conclusions by Hilson et al. [141].

To date, there has been little effort linked to the mitigation of Hg contamination through reduction in soil erosion, although there are current attempts to reforest areas in the Upper Tapajós region (Brazil), where gold mining was extensive and many studies have been carried out [142]. However, the increasing pressure to "develop" the Amazon through extensive exploitation of its natural resources and, more particularly, the recent push of the agricultural frontier, constitute a further barrier to reduction of deforestation and soil erosion [143,144].

A few efforts have addressed the question of fish-eating practices [19,128,145], although in general there has been little focus on this issue possibly due to lack of political interest and the difficult trade-offs in public health regarding the reduction of toxic exposures through fish consumption. Indeed, these trade-offs have been the subject of much international debate over the last years because of the nutritional benefits from fish consumption [146,147,148,149]. Modifying fish-eating habits through the use of fish advisories has constituted the most popular approach to reduce exposures and health risks in North America, Europe, and Japan, even if many policymakers consider such an approach an unfortunate and interim public health necessity [150]. In the Amazon, debate has been raging on the appropriateness of intervention [122,132,133] not only because fish is a very important dietary mainstay, but also because according to some authors [132,133] priority should rather be given to the high prevalence of other general health problems such as tropical diseases and intestinal parasites. Because of regional and seasonal variations in fish-Hg lev-

els, as well as intercommunity differences in fish portions, Passos et al. [122] discuss the suitability of using fish advisories as a policy intervention in the Amazonian context and suggest that a risk management strategy that focuses solely on limiting the overall number of fish meals might unnecessarily deprive these populations of this important food source. Similar to the authors of studies in French Guiana [76], these authors [122] encourage close collaboration with local populations, public health authorities, and scientists to develop concrete recommendations and adopt measures to reduce the environmental sources of exposure. In the short term, and due to the high biodiversity of fish and fruit in the Amazon, dietary Hg exposures in the environment may be reduced through changes in fish-eating practices without necessarily limiting fish consumption frequency [122,145].

One such intervention was carried out in a village on the Tapajós River in Brazil. The investigators used a participatory strategy based on capacity building, aimed at maintaining fish consumption but shifting towards less contaminated fish species [145]. Through community involvement and education based on posters showing the status of Hg contamination in relation to fish species, villagers continued to eat the same quantity of fish, but decreased the proportion of carnivores, which resulted in a reduction in hair-Hg levels of close to 40%. An interesting aspect explored in this process was the role of community participation to achieve exposure reduction [145]; using a social communication network analysis, these authors observed that participation was associated with awareness of the critical information that led to changing dietary habits towards the preferential consumption of the less contaminated fish species.

## New perspectives provided by the Amazonian research

The studies performed in the Amazon have added important information to our knowledge on Hg sources, exposure, and effects. In this region, like elsewhere, Hg pollution is coming from multiple anthropogenic and natural sources, and the degree of contamination of the fishing resources is further influenced by the dynamics of the regional and local ecosystems. It was here that the first reports were made of dose-related neurofunctional deficits in adult humans chronically exposed to low doses of Hg, below limits recommended by national and international bodies [151]. These effects were observed at exposure levels below the benchmark dose level (BMDL) for

blood-Hg (58µg/L) that was used to calculate the U.S. Environmental Protection Agency (EPA) reference dose [25], as well as the BMDL for hair-Hg (14µg/g) used to determine the recently revised WHO reference dose [24]. Other health outcomes (cardiovascular, cytogenetic, and immunological) require more investigation.

The studies in the Amazon region have further advanced our knowledge on the relations between fish consumption, Hg intake, and exposure. Villagers' interest and participation in the studies, particularly women [145], made it possible to examine the relations between diet and Hg exposure and demonstrate that fruit consumption modulates the relation between Hg intake and bioindicators of exposure. Further studies need to examine the underlying mechanisms. Investigations of the possible effects of elevated levels of Se, reported in this region, may provide some answers to the frequently asked questions about whether Se can influence Hg toxicity.

Despite the many remaining gaps, a picture of a complex situation, reflecting the biodiversity of the region, is emerging. In these populations that are already challenged by poor living and sanitary conditions, a high prevalence of tropical diseases and limited access to health care, further assault to physiological functions through exposure to Hg increases their vulnerability. Mitigation efforts in mining activities have hopefully reduced direct exposure of many miners and their families, but for the moment this is not reflected in a reduction of Hg concentrations in fish or humans. Deforestation remains extensive, among other reasons because of the encroachment of the agricultural frontier. In most Amazonian countries, public health authorities have not provided guidelines on fish consumption, possibly in part due to the importance of the nutritional value of fish and the consideration that the health effects of Hg are less severe than those of other health problems.

Could and/or should Hg reduction become a priority in the Amazon region? If one makes a long list of priorities, because of the multitude of environmental, social, and health problems, it might not be very near the top. But if one adopts an ecosystem approach that examines how it fits into current concerns over deforestation, environmental degradation from mining, social and economic development of the region, and improvement of human health, Hg reduction could be included as an outcome of research and intervention programs on many levels. To achieve this, we need to identify the social, political, and economic factors underlying deforestation and small-scale gold-mining operations [143,144,152], as well as the socio-cultural factors that influence

regional agricultural and forestry practices and diet [18,128,153]. We need to increase our understanding of the biogeochemical issues that will allow for control of the sources that contribute to the release of Hg into the aquatic ecosystems and increase our knowledge of the factors that influence Hg absorption and toxicity.

Finally, because of the ongoing severity of the problem, on a short-term basis we could take advantage of the high biodiversity of fish and fruits readily available in these ecosystems, by coupling traditional knowledge and cultural practices to scientific information on Hg transmission from fish to humans and the factors that influence this relationship. The use of this information within a public health program could provide the means for modifying dietary habits and reduce Hg exposures, while maintaining the health benefits of a diet rich in fish intake.

## Resumo

*Este artigo examina questões sobre exposição humana ao mercúrio (Hg) e seus efeitos adversos à saúde na Amazônia, com base em extensa revisão da literatura. Diferentes bioindicadores revelam uma ampla faixa de exposição, com teores médios de Hg em cabelo acima de 15µg/g em diversas comunidades amazônicas, situando-as dentre as mais expostas no mundo atualmente. Taxas de ingestão diária de Hg foram estimadas em alguns estudos e situam-se entre 1-2µg/kg/dia, consideravelmente acima das doses de referência estabelecidas pela USEPA (0,1µg/kg/dia) ou pela OMS (0,23µg/kg/dia). Déficits neurocomportamentais e, em alguns casos, sinais clínicos relacionados à exposição mercurial têm sido relatados tanto em adultos quanto em crianças de diversos países amazônicos. Há também evidências de dano citogenético, mudanças imunológicas e toxicidade cardiovascular. Visto que peixe é altamente nutritivo e há diversas fontes de Hg nesta região, existe uma necessidade urgente de encontrar soluções realistas e viáveis capazes de reduzir os níveis de exposição e de risco tóxico, ao mesmo tempo mantendo os hábitos alimentares tradicionais, preservando a biodiversidade píscea e frutífera e melhorando a saúde das populações desfavorecidas e afetadas.*

*Intoxicação por Mercúrio; Exposição Ambiental; Ecossistema Amazônico*

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