A systematic review of mercury ototoxicity

Uma revisão sistemática da ototoxicidade do mercúrio

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Abstract

Mercury is neurotoxic, and numerous studies have confirmed its ototoxic effect. However, the diagnosis and follow-up of mercury exposure require understanding the pathophysiology of the chemical substance. Based on a systematic literature review, this study aimed to demonstrate whether mercury is ototoxic and to analyze its mechanism of action on the peripheral and central auditory system, in order to contribute to the diagnosis and follow-up of exposure. This was a systematic review of studies published on the effects of mercury exposure on the auditory system. The full text of the studies and their methodological quality were analyzed. The review identified 108 studies published on the theme, of which 28 met the inclusion criteria. All the articles in the analysis showed that mercury exposure is ototoxic and produces peripheral and/or central damage. Acute and long-term exposure produces irreversible damage to the central auditory system. Biomarkers were unable to predict the relationship between degree of mercury poisoning and degree of lesion in the auditory system.

Mercury; Toxicity; Hearing; Dizziness

Introduction

Environmental contamination with persistent pollutants showing toxic and cumulative effects on organisms, as in the case of mercury (Hg), has reached global proportions due to the persistence and mobility of these substances [1]. Various studies [2,3,4,5] have corroborated the Minamata findings, indicating that mercury exposure results in a series of neurotological alterations [6,7,8,9,10]. The principal complaints by patients are dizziness and hearing loss.

Each ototoxic agent has its own mode of action on the various organ systems, and diagnosis of the lesion site can vary according to time and degree of exposure. Independently, the consequences of hearing loss can be irreversible, with clinical alterations that often go undetected by neurological examination and biological markers, thus jeopardizing the quality of life of these individuals. Since mercury is known to be neurotoxic, many studies have focused only on the central auditory system. However, other studies have shown that acute or chronic exposure to mercury generates alterations in both the peripheral and/or central auditory systems [11,12,13,14].

Follow-up of ototoxicity is important for detecting hearing changes involving chemical substances, thereby suggesting new treatment strategies for the patient and phonoaudiological intervention when a disabling hearing impair-

ment occurs [15]. Murata et al. [16] demonstrated that the persistence of prolonged I-III inter-peak latencies during childhood, indicating that intrauterine mercury exposure causes irreversible neurotoxic lesions.

Interdisciplinary studies as in the case of Audiology and Clinical Toxicology are extremely rich and complex, thus justifying the current study as an important tool for organizing and summarizing similar primary studies for decision-making on therapeutic and preventive measures in the environmental and health field for populations exposed to mercury.

Based on a systematic review, the study aimed to show whether mercury is ototoxic, and if so, to elucidate its action on the peripheral and central auditory system.

Methodology

A systematic review was performed, including studies on the effects of mercury exposure on the peripheral and/or central auditory system, published from January 1966 to April 2011, the period covered by the set of selected databases.

The review of the studies focused on the following questions: "*Did the studies demonstrate that mercury is ototoxic?*", "*In the case of confirmed ototoxicity, which area was injured?*", and "*Is it possible to relate the degree of mercury poisoning or exposure time to the results of the hearing tests?*"

Inclusion and exclusion criteria

The inclusion criteria were: original articles and Master's and Doctoral theses published from 1966 to 2011 in Portuguese, English, French, or Spanish, on the acute or chronic effects of mercury on the peripheral and/or central auditory pathways in humans or laboratory animals. The study excluded review articles, editorials, case reports, and articles that related auditory alterations to noise rather than mercury exposure or auditory alterations to mercury exposure and other chemical substances concurrently.

Research strategy

The study covered the following databases: MEDLINE, from January 1966 to March 2011; LILACS, from January 1982 to March 2011; SciELO, from January 1997 to March 2011; Web of Science; and Science Direct. Electronic and manual searches were also performed for the references cited in the selected articles; in websites related to the theme, like Excerpta Medica online (EMBASE), Grey Literature, ATSDR, and SINITOX, and in thesis/dissertation databases at the University of São Paulo (USP), Oswaldo Cruz Institute/Fiocruz, and Institute of Studies in Collective Health (IESC/UFRJ). The descriptors, combined with the descriptor "*mercury*", were: "*hearing*", "*hearing loss*", "*hearing disorders*", "*dizziness*", and "*postural balance*". The search for the descriptors covered the full text and title.

All the studies selected in the database using the descriptors were classified according to the inclusion criteria through their abstracts. The full texts of the studies were analyzed and their data were keyed in to a previously established protocol containing data on the variables corresponding to the eligibility criteria for the individuals involved in the studies (age, sex, occupation), type of study (cross-sectional, cohort, case-control), exposure (chronic or acute), number of individuals in the study, presence of control groups, use of biomarkers, type of evaluation performed in the study (questionnaires, audiometry, evoked potential, cognitive tests, and others), and the conclusions' consistency with the findings. The studies were analyzed by two independent reviewers.

The studies' methodological quality was classified in a table adapted from the Cochrane Collaboration quality assessment [17] concerning the risk of bias. Eight items were analyzed: specification of inclusion criteria, presence of justification for the sample size, presence of a control group, absence of bias (selection, measurement, and loss-to-follow-up), quality of the evaluation performed to investigate the auditory pathways, exposure only to mercury, presence of biomarker, and conclusions consistent with the findings. Each of these questions was answered with *Yes*, *No,* and *Not Informed*.

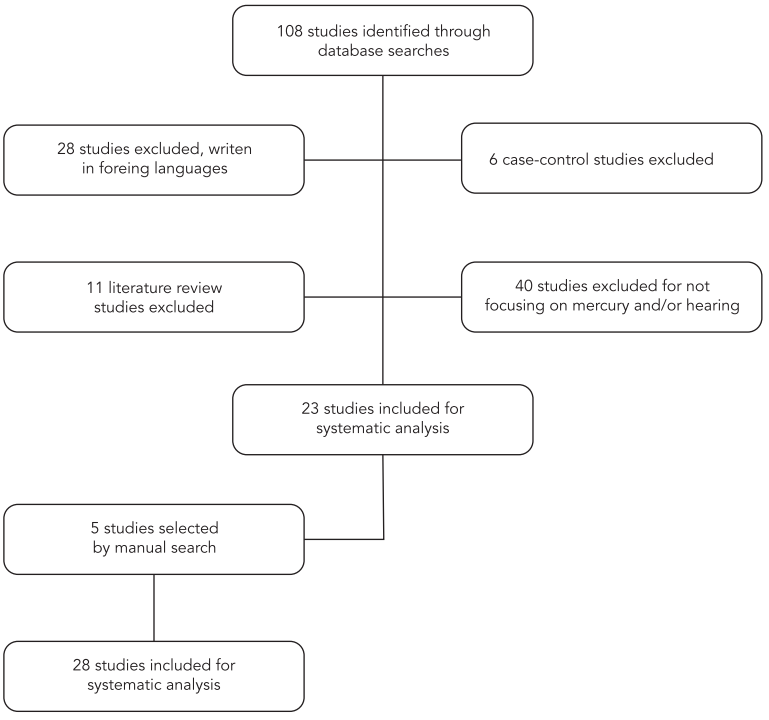
Results and discussion

The electronic database searches identified 108 articles published on the theme. Initially, based on reading the article abstracts, 85 articles were excluded because they were literature reviews, articles in foreign languages that failed to meet the inclusion criteria, case reports, and articles that were not associated with the research topic. The other 23 articles were analyzed using the full text. The manual search for references cited in the articles identified five additional articles that met the inclusion criteria (Figure 1).

The search of thesis/dissertation databases at USP, Oswaldo Cruz Institute/Fiocruz, and IESC/UFRJ identified only two Master's theses, which were not included because one investigated both

Figure 1

Description of studies found in the databases.



mercury and factory noise, while the other had already been identified in the electronic search, in the form of an original article.

Twenty-eight studies met the inclusion criteria, of which 16 had been conducted in humans (Table 1), ten in animals (Table 2), and two in *in vitro* cells (Table 3). Table 4 describes the methodological quality of the selected articles.

Among the 16 studies in humans, only two were case-controls, while the others were descriptive. Ten conducted some type of audiologic evaluation, of which five also performed the biomarker test and the other five confirmed the relationship between exposure and auditory alteration using questionnaires and/or databases. Two studies did not perform audiologic evaluations, presented data on biomarkers, and confirmed the relationship between exposure and altered hearing by means of questionnaires and/or databases. Four did not perform audiologic evaluations or biomarker tests, confirming the relationship between exposure and symptoms by means of questionnaires and/or databases. All the articles stated that mercury is ototoxic. Only one reported a relationship between exposure time or the degree of mercury poisoning and auditory alterations found in the study. Six reported that the lesion occurred in the central auditory system (five based on brainstem auditory evoked potential, or BAEP, and one on central auditory processing, or CAP), three in both the central and peripheral regions (tone audiometry with BAEP/CAP/otoneurological evaluation), one in the peripheral region (high-frequency audiometry), and six failed to report the lesion site.

In Brazil, the industrialization process generates growing amounts of waste that can lead to environmental problems if not adequately disposed of or stored. Lacerda & Marin (1997, *apud* Azevedo & Chasin [18]) estimate mercury emissions in Brazil at 116 tons/year, with various industrial sectors contributing to the emissions: chlor-alkali (10.1%), paint, electric-electronic appliances, and energy (petroleum) (< 5%), zinc, lead, and cadmium metallurgy (3.9%), iron and steel (10.4%), burning of natural plant material (7.5%), and gold mining (67.3%). Technological innovation has helped decrease the burden

Table1

Description of 16 articles on the relationship between mercury exposure and hearing in humans, selected for the systematic review.

Article	Year	N	Control group	Exposure (dose or place)	Biomarker/ Chemical substance	AE	Peripheral/ Central	Ototoxic?	Relationship time/degree of loss?
Dutra et al. [28]	2010	21	31	Worker	Urine/Hg	TA/CAP	Central	Yes	NI
Lima et al. [24]	2009	13	No	Worker	No/Hg	TA/CAP	Peripheral/ Central	Yes	NI
Choi et al. [29]	2009	42	No	Chronic/ Faroese	Hair, nails, blood/MeHg	BAEP	Central	Yes	NI
Rothwell & Boyd [30]	2008	39	No	Dentist	No/dental amalgam	HFA	Peripheral	Yes	NI
Murata et al. [16]	2004	878	No	Chronic/ Faroese	Umbilical cord, hair/ MeHg	BAEP	Central	Yes	Yes
Murata et al. [22]	2002	382 Faroese/113 Madeira	No	Faroese/ Madeira	Maternal hair/MeHg	BAEP	Central	Yes	NI
Counter et al. [25]	1998	75	34	Nambija, Ecuador	No/MeHg	TA/BAEP	Peripheral/ Central	Yes	NI
Grandjean et al. [19]	1997	917	NI	Chronic/ Faroese	Hair, umbilical cord/MeHg	BAEP	Central	Yes	NI
Uchino et al. [31]	1995	80	No	Minamata	Autopsy/ MeHg	No	NI	Yes	NI
Uchino et al. [32]	1995	77	No	Minamata	No/MeHg	No	NI	Yes	NI
Ninomiya et al. [9]	1995	NI	No	Minamata	No/MeHg	No	NI	Yes	NI
Harada [10]	1995	2,252	NI	Minamata	Hair/MeHg	No	NI	Yes	NI
Mizukoshi et al. [7]	1989	35	No	Minamata	No/MeHg	TA/OTN	Peripheral/ Central	Yes	NI
Baikir et al. [32]	1980	NI	No	Iraq	No/MeHg	NI	NI	Yes	NI
Amin-Zaki et al. [33]	1978	49	No	Iraq	No/MeHg	NI	NI	Yes	NI
Mizukoshi et al. [34]	1975	144	No	Minamata	No/MeHg	TA/BAEP/ OTN	Central	Yes	NI

AE: audiologic evaluation; BAEP: brainstem auditory evoked potential; CAP: central auditory processing; HFA: high-frequency audiometry; Hg: metallic mercury; MeHg; methyl-mercury; NI: not informed; OTN: otoneurological evaluation; TA: tone audiometry.

of contamination for workers, but it has created new risks, not only for workers but for the overall population as well. In this systematic review, only three studies assessed the conditions involved in occupational exposure.

Only two studies specified the age bracket, evaluating vulnerable populations in greater detail, such as pregnant women, newborns, children, and elderly. Importantly, mercury crosses the placenta and methyl-mercury is actively transferred to the fetus [19,20,21]. The consumption of fish contaminated with mercury leads to a series of neurotoxic effects observed in the pregnant woman, fetus, and newborn, especially when the latter is exposed during development of the central nervous system [19,22,23].

Early childhood years are critical for the development of auditory and language skills and mark the maturation of the central auditory system. No study described the consequences of hearing loss for the quality of life of these individuals. Even the two articles that reported alterations in central auditory processing did not elaborate a questionnaire or tool to assess the impact of hearing loss.

All ten studies in animals were descriptive and performed audiologic evaluations or autopsies. All reported that mercury is ototoxic.

Table 2

Description of 10 articles on the relationship between mercury exposure and hearing in animals, selected for the systematic review.

Article	Year	N	Control group	Exposure (dose or place)	Biomarker/ Chemical substance	AE	Peripheral/ Central	Ototoxic?	Relationship time/degree of loss?
Huang et al. [11]	2011	Animal	No	0.02mg/kg/ day; 7 weeks	MeHg; HgCl2	BAEP	Central	Yes	Yes
Huang et al. [12]	2008	Animal	No	10mg/kg/ day; 2-10 weeks	HgS	BAEP	Central	Yes	Yes
Huang et al. [13]	2007	Animal	No	0.05mg/kg/ day; 7 weeks	MeHg	BAEP	Central	Yes	Yes
Herr et al. [23]	2004	Animal	No	4mg/m3HgO	Hg^0	BAEP	Normal	NI	NI
Chuu et al. [14]	2001	Animal	No	0.1-1.0g/ kg/day HgS; 0.2, 2.0 and 10mg/kg/day MeHg	HgCl2; MeHg	BAEP	Central	Yes	Yes
Rice [35]	1998	5 monkeys	NI	0,10,25 or 50µg/kg/ day	MeHg	HFA	Peripheral	Yes	Yes
Rice & Gilbert [36]	1992	Monkeys	Yes	5mg/kg/ day	MeHg	HFA	Peripheral	Yes	Yes
Igarashi et al. [6]	1992	Animal	No	4mg/kg/ day, 16 days	HgCl2	Autopsy	Peripheral	Yes	NI
Wassick & Yonovitz [26]	1985	Animal	No	4 and 8mg/ kg, 3 weeks	MeHg	TA/BAEP	Peripheral/ Central	Yes	NI
Anniko & Sarkady [27]	1978	Animal	No	2.5-25mg/ kg, 1 to 49 days	HgCl2	Autopsy	Peripheral	Yes	NI

AE: audiologic evaluation; BAEP: brainstem auditory evoked potential; HFA: high-frequency audiometry; HgCl2: mercuric chloride; HgS: mercuric sulfide; MeHg: methyl mercury; NI: not informed; TA: tone audiometry.

Table 3

Description of two articles on the relationship between mercury exposure and hearing in experimental studies, selected for the systematic review.

Article	Year	N	Control group	Exposure (dose or place)	Biomarker/ Chemical substance	AE	Peripheral/ Central	Ototoxic?	Relationship between time/degree of loss?
Liang et al. [37]	2003	Cells	No	NI	HgCl2	NI	NI	Yes	NI
Gopal [38]	2003	Cells	No	NI	HgCl2	NI	NI	Yes	NI

AE: audiologic evaluation; HgCl2: mercuric chloride; NI: not informed.

Table 4

Qualitative description of studies on mercury exposure and hearing, selected for the systematic review.

Article	Inclusion criteria	Sample size	Control group	Absence of bias	Evaluation performed in study	Exposure only to mercury	Presence of biomarker	Concrete result
Huang et al. [11]	NI	NI	No	Yes	Yes	Yes	Yes	Yes
Dutra et al. [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lima et al. [24]	Yes	No	No	No	Yes	Yes	No	Yes
Choi et al. [29]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Rothwell & Boyd [30]	Yes	Yes	No	No	Yes	No	No	No
Huang et al. [12]	NI	NI	No	Yes	Yes	Yes	Yes	Yes
Huang et al. [13]	NI	NI	No	Yes	Yes	Yes	Yes	Yes
Murata et al. [16]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Herr et al. [23]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Liang et al. [37]	NI	NI	No	Yes	No	Yes	No	Yes
Gopal [38]	NI	NI	No	NI	No	Yes	No	Yes
Murata et al. [22]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Chuu et al. [14]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Rice [35]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Counter et al. [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grandjean et al. [19]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Uchino et al. [8]	No	No	No	No	No	Yes	Yes	Yes
Uchino et al. [31]	No	No	No	No	No	Yes	No	Yes
Ninomiya et al. [9]	No	No	No	No	No	Yes	No	Yes
Harada [10]	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Rice et al. [36]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Igarashi et al. [6]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Mizukoshi et al. [7]	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Wassick et al. [26]	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Baikir et al. [32]	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Amin-Zaki et al. [33]	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Anniko & Sarkady [27]	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Mizukoshi et al. [34]	Yes	Yes	No	Yes	Yes	Yes	No	Yes

NI: not informed.

Six related time of exposure or degree of mercury poisoning to auditory alterations. Four reported that the lesion occurred in the central auditory system (BAEP), one in the peripheral and central regions (audiometry and BAEP), four in the peripheral region (high-frequency audiometry), and only one found a result within normalcy, since the study's objective was to demonstrate that 4mg/m3Hg^0 was not toxic to rats, although the authors reported that mercury is ototoxic at other doses. The first studies in animals were performed to determine the pathophysiology of mercury poisoning, while the more recent studies approach issues such as the effects of mercury on animals exposed during gestation and in early life, comparing the experimental doses with those from chronic exposure in humans in contaminated areas or doses received by children, as in the case of cinnabar (a pediatric anesthetic). It would certainly be difficult to conduct a study in pregnant women, newborns, or children to evaluate the time and degree of exposure and the consequences, but excluding the fact that it is difficult to systematize a sample of this population for the factors age, time of exposure, and degree of poisoning, studies have already shown the effects of mercury in humans at these ages, and there are still occupationally and environmentally exposed populations that could help elucidate this entire picture. Such studies provide important information, for example, about the ages at which mercury exposure is more or

less aggressive to the central auditory system and the relationship between this factor and time of exposure or the exposure dose.

A study using *in vitro* cells concluded that chronic (as compared to acute) exposure presents a more toxic effect on the auditory nervous system, and that the doses used in the study were within the range of doses for human exposure. The second article analyzed the effect of mercury on the potassium currents in the external ciliated cells of the cochlea, demonstrating metabolic alterations in this system that can lead to hearing loss. Such studies are important for understanding mercury's pathophysiology in the peripheral and central auditory system, allowing therapeutic and/or preventive management.

The toxic effects of mercury on hearing have been studied for years and are still the object of investigation. This clearly demonstrates that mercury exposure is still a current problem and that its environmental liability will have consequences for many future generations. It has also been shown that the lesion occurs in both the central and peripheral auditory system, thus highlighting the need for further research in this area, assessing the consequences for the quality of life in the exposed population. The great majority of studies focused on only one type of test. In this case, the conclusions focused only on the type of procedure used for the peripheral or central evaluation of the auditory system. The use of combined procedures can increase the diagnostic precision of the lesion site, as in the case of two articles on humans [7,24,25] and one on animals [26] which performed audiometry together with BAEP or otoneurological evaluation, identifying peripheral and central alterations as the outcome.

Acute and long-term mercury exposure produces alterations in the peripheral and/or central auditory system [11,12,13,14]. Huang et al. [11,12,13] and Chuu et al. [14] suggest that the metabolic alterations in the central auditory system (Na(+)/K(+) - ATPase) may be responsible for the mechanism of the lesion. With current technological advances, new diagnostic equipment has been developed, thereby creating new fields of research and providing a better understanding of hearing. One can thus suggest further research focusing on the effect of activation of the efferent auditory system on otoacoustic emissions (suppression) that evaluate the central auditory system, together with cochlear function [27].

In all, 26 articles were published in English and two in Portuguese, while 19 investigated the biomarker.

Conclusion

All the articles analyzed here showed that mercury exposure is ototoxic, inducing peripheral and/or central hearing loss. It is a consensus in the literature that acute and long-term exposure produces irreversible damage to the central auditory system. Measuring mercury levels with biomarkers was unable to predict the relationship between the degree of mercury poisoning and the degree of damage to the auditory system.

With technological development, new fields of research have been created, but they have scarcely been explored by Clinical Toxicology. It is important to raise awareness in the overall population and define the control of exposure to chemical agents as a public health priority.

Resumo

O mercúrio é neurotóxico e muitas pesquisas confirmam sua ação ototóxica. Porém, para o diagnóstico e acompanhamento da exposição é necessário entender a fisiopatologia da substância química. O objetivo do trabalho, por meio da revisão sistemática, é evidenciar se o mercúrio é ou não ototóxico e, sendo assim, qual seria sua forma de atuação no sistema auditivo periférico e central, de forma a contribuir para o diagnóstico e acompanhamento da exposição. É uma revisão sistemática dos trabalhos publicados sobre os efeitos da exposição ao mercúrio no sistema auditivo. Analisaram-se os estudos contemplados na íntegra e também sua qualidade metodológica. A pesquisa identificou 108 artigos publicados sobre o tema, sendo que 28 se enquadraram nos critérios de inclusão. Todos os artigos analisados evidenciaram que a exposição ao mercúrio é ototóxico e induz ao dano periférico e/ou central. A exposição aguda e de longo prazo produzem danos irreversíveis ao sistema auditivo central. Os biomarcadores não puderam predizer a relação do grau de intoxicação com o grau de lesão do sistema auditivo.

Mercúrio; Toxicidade; Audição; Tontura

Collaborators

A. C. H. Hoshino, H. P. Ferreira, O. Malm, R. M. Carvallo, and V. M. Câmara contributed with the data analysis and interpretation, relevant critical revision of the intellectual content, and approval of the final version for publication.

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References

1. Dias ACL, Guimarães JRD, Malm O, Costa PAS. Mercúrio total em músculo de cação *Prionace glauca* (Linnaeus, 1758) e de espadarte *Xiphias gladius* Linnaeus, 1758, na costa sul-sudeste do Brasil e suas implicações para a saúde pública. Cad Saúde Pública 2008; 24:2063-70.
2. Mello AP, Waismann W. Exposição ocupacional ao ruído e químicos industriais e seus efeitos no sistema auditivo: revisão da literatura. Arq Int Otorrinolaringol 2004; 8(3). http://www.arquivosdeorl.org.br/conteudo/acervo_port.asp?id=285.
3. Serôdio JB. Efeitos da exposição ocupacional a produtos químicos no sistema auditivo. Niterói: Universidade Federal Fluminense; 2005.
4. Murata K, Grandjean P, Dakeishi M. Neurophysiological evidence of methylmercury neurotoxicity. Am J Ind Med 2007; 50:765-71.
5. Prasher D. Heavy metals and noise exposure: health effects. Noise Health 2009; 11:141-4.
6. Igarashi S, Koide C, Sasaki H, Nakano Y. Mercury deposition and its relationship to inner ear function in methylmercury-poisoned rats. Acta Otolaryngol 1992; 112:773-8.
7. Mizukoshi K, Watanabe Y, Kobayashi H, Nakano Y, Koide C, Inomata S, et al. Neurotological follow-up studies upon Minamata disease. Acta Otolaryngol Suppl 1989; 468:353-7.
8. Uchino M, Okajima T, Eto K, Kumamoto T, Mishima I, Ando M. Neurologic features of chronic Minamata disease (organic mercury poisoning) certified at autopsy. Intern Med 1995; 34:744-7.

9. Ninomiya T, Ohmori H, Hashimoto K, Tsuruta K, Ekino S. Expansion of methylmercury poisoning outside of Minamata: an epidemiological study on chronic methylmercury poisoning outside of Minamata. Environ Res 1995; 70:47-50.
10. Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. Crit Rev Toxicol 1995; 25:1-24.
11. Huang CF, Liu SH, Hsu CJ, Shiau SY. Neurotoxicological effects of low-dose methylmercury and mercuric chloride in developing offspring mice. Toxicol Lett 2011; 201:196-204.
12. Huang CF, Hsu CJ, Liu SH, Lin-Shiau SY. Ototoxicity induced by cinnabar (a naturally occurring HgS) in mice through oxidative stress and down-regulated Na+/K+-ATPase activities. Neurotoxicology 2008; 29:386-96.
13. Huang CF, Hsu CJ, Liu SH, Lin-Shiau SY. Neurotoxicological mechanism of methylmercury induced by low-dose and long-term exposure in mice: oxidative stress and down-regulated Na+/K+-ATPase involved. Toxicol Lett 2007; 176:188-97.
14. Chuu JJ, Hsu CJ, Lin-Shiau SY. Abnormal auditory brainstem responses for mice treated with mercurial compounds: involvement of excessive nitric oxide. Toxicology 2001; 162:11-22.
15. American Academy of Audiology. Position statement and clinical practice guidelines. Ototoxicity monitoring. http://www.audiology.org (accessed on 01/Mar/2012).
16. Murata K, Weihe PL, Budtz-Jorgensen E, Jorgensen PJ, Grandjean P. Delayed brainstem auditory evoked potential latencies in 14 year old children exposed to methylmercury. J Pediatr 2004; 144: 177-83.
17. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org.
18. Azevedo FA, Chasin AAM. Metais: gerenciamento da toxicidade. São Paulo: Editora Atheneu; 2003.
19. Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997; 19:417-28.
20. Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, et al. Effects of prenatal and postnatal methyl mercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA 1998; 280:701-7.
21. Stern AH, Smith AE. An assessment of the cord blood: maternal blood methyl mercury ratio: implications for risk assessment. Environ Health Perspect 2003; 111:1465-70.
22. Murata K, Jorgensen EB, Grandjean P. Benchmark dose calculations for methylmercury associated delays on evoked potential latencies in two cohorts of children. Risk Anal 2002; 22:465-74.
23. Herr DW, Chanda SM, Graff JE, Barone Jr. SS, Beliles RP, Morgan DL. Evaluation of sensory evoked potentials in Long Evans rats gestationally exposed to mercury (Hg0) vapor. Toxicol Sci 2004; 82:193-206.
24. Lima ERZ, Colon JC, Souza MT. Alterações auditivas em trabalhadores expostos a mercúrio. Rev CEFAC 2009; 11 Suppl 1:62-7.
25. Counter AS, Buchanan LH, Laurell G, Ortega F. Blood mercury and auditory neuro-sensory responses in children and adults in the Nambija gold mining area of Ecuador. Neurotoxicology 1998; 19:185-96.
26. Wassick KH, Yonovitz A. Methyl mercury ototoxicity in mice determined by auditory brainstem responses. Acta Otolaryngol 1985; 99:35-45.
27. Anniko M, Sarkady L. Cochlear pathology following exposure to Mercury. Acta Otolaryngol 1978; 85:213-24.
28. Dutra MDS, Monteiro MC, Câmara VM. Avaliação do processamento auditivo central em adolescentes expostos ao mercúrio metálico. Pró-Fono 2010; 22:339-44.
29. Choi AL, Weihe P, Budtz-Jørgensen E, Jørgensen PJ, Salonen JT, Tuomainen TP, et al. Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. Environ Health Perspect 2009; 117:367-72.
30. Rothwell JA, Boyd PJ. Amalgam dental fillings and hearing loss. Int J Audiol 2008; 47:770-6.
31. Uchino M, Tanaka Y, Ando Y, Yonehara T, Hara A, Mishima I, et al. Neurologic features of chronic Minamata disease (organic mercury poisoning) and incidence of complications with aging. J Environ Sci Health B Pestic Food Contam Agric Wastes 1995; 30:699-715.
32. Baikir F, Rustam H, Tikriti S, Al-Damluji SF, Shihristani H. Clinical and epidemiological aspects of methylmercury poisoning. Postgrad Med J 1980; 56:1-10.
33. Amin-Zaki L, Majeed MA, Clarkson TW, Greenwood MR. Methylmercury poisoning in Iraqi children: clinical observations over two years. BMJ 1978; 1:613-6.
34. Mizukoshi K, Nagaba M, Ohno Y, Ishikawa K, Aoyagi M, Watanabe Y, et al. Neurotological studies upon intoxication by organic Mercury compounds. ORL J Otorhinolaryngol Relat Spec 1975; 37:74-87.
35. Rice DC. Age-related increase in auditory impairment in monkeys exposed in utero plus postnatally to methylmercury. Toxicol Sci 1998; 44:191-6.
36. Rice DC, Gilbert SG. Exposure to methyl mercury from birth to adulthood impairs high-frequency hearing in monkeys. Toxicol Appl Pharmacol 1992; 115:6-10.
37. Liang GH, Järlebark L, Ulfendahl M, Moore EJ. Mercury (Hg2+) suppression of potassium currents of outer hair cells. Neurotoxicol Teratol 2003; 25:349-59.
38. Gopal KV. Neurotoxic effects of mercury on auditory cortex networks growing on microelectrode arrays: a preliminary analysis. Neurotoxicol Teratol 2003; 25:69-76.

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