temperature precollection, GC separation and CV AFS detection. *Talanta* 1994;41:371-9.
24. Liang L, Horvat M, Bloom NS. Simultaneous determination of methyl and inorganic mercury in biological samples. *Clin Chem* 1994;40:602-7.
25. Frankenburg WK, Dodds JB. The Denver Developmental Screening Test. *J Pediatr* 1967;70:181–91.
26. Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. *JAMA* 1998;280:701-7.
27. 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.

Mercury in dental amalgam: a risk analysis

Maths Berlin MD, PhD.
Professor emeritus of Environmental Health, University of Lund, Sweden.

Correspondence to Professor Maths Berlin, Box 2081, 18202 Danderyd, Sweden. E-mail maths.berlin@ofa.ki.se

Abstract

Mercury is a highly potent cell toxin with effects on human and animal nervous systems. Mercury vapour released from dental amalgam is the predominant source of mercury in the human adult and foetal central nervous system in populations of developed countries. Only in small populations with high consumption of methyl mercury containing fish can the contribution from fish consumption reach or surpass that of amalgam fillings. The most severe health risk is that of interference with foetal and child brain development. This effect of mercury vapour exposure has been demonstrated in animal experiments on monkeys and rats and in nerve cell cultures at nanomolar concentrations. The effect is also supported by epidemiological studies on women occupationally exposed to mercury vapour during pregnancy. However, there is no data permitting an assessment of dose-response relations for this effect in humans. In epidemiological studies on populations with occupational exposure to mercury vapour, subclinical effects on kidneys, the immune system, thyroid function, and CNS function have been observed at an exposure level equal to the upper range of the exposure range seen in amalgam bearers and measured as urine excretion rate of inorganic mercury. The cell toxic effect of mercury is likely to be based on the ability of mercury to modify protein tertiary and quaternary structure. As protein structure is genetically determined, there is ample scope for genetic polymorphism to manifest itself in varying sensitivity and reaction to mercury exposure. It is also likely that mercury exposure from dental amalgam exerts side effects like most potent pharmaceuticals. The clinical support for this assumption is reviewed. An incidence of side effects exceeding 10% is unlikely considering available epidemiological evidence. However, an incidence of 1% or below is highly probable. It is recommended that use of amalgam for dental restorations is abandoned and substituted with available less toxic material and that amalgam restorations in children and women of childbearing age should be avoided due to the potential risk of interference by mercury with brain development.

Key words mercury, amalgam, side effects, risk analysis, foetal brain development

Introduction

From the time amalgam was first introduced for dental fillings, there were concerns raised that mercury toxicity could give rise to unacceptable health risks. With an increased use of amalgam up until the present situation, when the majority of the population in industrialised countries are amalgam bearers, it has clearly emerged that the predominant proportion of amalgam bearers do not display any signs of toxic effects from amalgam. Despite many attempts, it has not been demonstrated in a scientifically indisputable way that amalgam gives rise to any side effects apart from individual cases of local reaction. Despite this, the use of amalgam within the dental service has continued to generate anxiety in the population. Drugs administered to humans may induce side effects in a fraction of the population due to genetic or acquired polymorphism in metabolism and mode of reaction. The incidence of common side effects is typically around 1%. This amounts to 10 000 patients in a population of 1 million amalgam bearers, a sizeable health problem. In WHO's criteria document on inorganic mercury (1), an attempt at a quantitative risk assessment for inorganic mercury is reported. It was established, however, that the scientific knowledge base was not sufficient for a risk assessment for the low exposure levels arising from dental fillings with amalgam. It was also established that the body's uptake of mercury from amalgam constitutes the dominant source for mercury retention which contributes at least as much as all other sources of inorganic mercury intake together.

Owing to political pressure from groups critical of the use of amalgam for dental restoration, in 1997 and 2003 Swedish authorities assigned the author to summarise, assess, and evaluate published research findings on health effects of mercury exposure from dental amalgam. This article summarises the reports (2-3) published from this exercise and recent publications relevant to risk evaluation of mercury exposure from dental amalgam.

Exposure to mercury from amalgam in dental fillings

Mercury from amalgam fillings primarily contributes to the daily absorption of mercury in two ways. Mercury is released in vapour form, inhaled, and up to 80% is reabsorbed in the airways. Abraded amalgam particles are swallowed and to a smaller extent oxidised in the intestinal tract. Less than 10% of such ingested mercury is reabsorbed as Hg^{+2}. Mercury can also be taken up in the nerve ends and transported in a retrograde direction to ganglia and central nerve cells (2). In WHO's criteria document (1), the average daily retention in the population from amalgam is estimated at 3-17µg with the addendum that substantial individual variations exist. The validity for this dose interval has since been confirmed in several studies (4-6). Mercury uptake from amalgam is the dominant source for uptake of inorganic mercury in the

central nervous system and represents the overwhelming share of total mercury uptake in the population. Mercury concentration in plasma and urine in amalgam free subjects amounts to 0.2 µg/l and 2 µg/l respectively (6).

Factors that are of great importance for risk calculation are the size of the variation and the worst probable scenarios for mercury uptake. Bruxism (teeth grinding) and chewing increase the release of mercury from amalgam fillings. Barregård et al (7) described three patients experiencing symptoms of mercury toxicity who all had the common feature that they eliminated large quantities of mercury in their urine (54, 53 and 25 µg/g creatinine[1] respectively) and had no source of exposure other than their amalgam fillings which they worked on with nicotine chewing gum. When the amalgam fillings were removed in the first two cases with the highest elimination, the mercury elimination fell to expected values and the symptoms disappeared. In the third case the patient refused to have the amalgam removed, but the elimination seemed to decrease with reduced chewing gum consumption. A further similar case has been published since then (8). These cases demonstrate a mercury uptake, which amounts to 100 µg/day, which is around 10 times higher than the average uptake from amalgam according to WHO. On the basis of their material, Barregård et al (7) estimated the prevalence of amalgam bearers with an elimination of around 50 µg/g creatinine at one in every 2,000-10,000 amalgam bearers or between 500 and 2,500 persons in Sweden.

Mercury uptake from amalgam increases tissue concentrations in the brain, plasma and kidneys in proportion to the number of amalgam fillings. Mercury content in the brains (occipital cortex) of non-amalgam bearers was found in a study of autopsies to be around 7 ng/g (6.7, range 1.9–22.1). The brains of amalgam bearers contained around 15 ng/g (15.2, range 3.8 – 121.4) (1). In the foetus, an increase also occurs in the brain and kidneys, with an average mercury concentration in those with amalgam bearing mothers around twice that of those with amalgam free mothers (9-10).

Toxic effects of divalent mercury

It has long been known that mercury is cytotoxic. The cytotoxic effect is exercised by Hg^{+2}. Mercury vapour, which is transported by the blood, can diffuse into the cell. Being relatively fat soluble, mercury vapour easily passes through cell membranes. Intracellularly, Hg^0 is oxidised enzymatically to Hg^{2+}. The mercury ion does not pass as easily through cell membranes but is bound in the first instance to the outside of the membrane. In some cases it can then be transported intracellularly actively, via receptors or bound to another transferable molecule. Exposure to mercury vapour and mercury salt is therefore not equivalent from a toxicological viewpoint.

The mercury ion binds to sulphhydryl (SH-) and selenohydryl (SeH-) groups. SH-groups constitute an important component in proteins. Mercury binding to these can entail a change in the proteins' tertiary and quaternary structure and other binding conditions in prosthetic groups in enzymes (11-14) and block or modify receptor binding (15-17) and potassium or calcium ion flows in the cell membrane's pores and ionic channels (18-25). This can affect cell membrane potentials and intra- and inter-cellular signals. The release of transmitter substances in nerve cells is inhibited or accelerated, as is cytokine production in the cells of the

immune system and hormone production in endocrine glands. It has been possible to observe these effects in in vitro experiments with cell cultures of different types of cells, or with the help of intracellular electrodes in single cells, with a 0.1-1 µM mercury concentration in the medium (2).

On the other hand, mercury has occurred in the environment throughout evolution and organisms have acquired the ability to manage limited quantities. Special molecules containing SH-groups or SeH-groups and with an ability to bind strongly to Hg^{+2} have been identified (26). Glutathion and metallothionein are such molecules, which can neutralise the mercury ion and prevent it from disturbing the cell's dynamic biochemical systems. Bound to these molecules, mercury can be transported, stored and eliminated from the body. It has also been shown experimentally that the sensitivity of different cell types to the mercury's cytotoxic effects is related to their ability to synthesise glutathion or metallothionein (27-29). Binding to metallothioneins explains, for example, why such high mercury concentrations can be encountered in the kidneys without disturbances arising.

Clinical, animal experimental, and epidemiological observations have shown that during exposure to mercury vapour, which gives rise to plasma concentrations of mercury of between 0.1 and 1 µmol/l (20 – 200 µg/l) or above, clinical signs of disturbances from several organ systems appear. Symptoms appear early on from the nervous system. These include neurological signs such as tremor, poorer performance in psychomotor tests, reduced colour vision, peripheral nerve conduction velocity, and memory function, altered electrophysiological parameters (evoked response), psychological symptoms such as increased irritability and exhaustion, sleep problems, and an increased tendency to anxiety. In the event of long-term exposure to concentrations of mercury producing symptoms, permanent functional impairment and dementia appear (2).

In the immune system, reduced function of leucocytes and macrophages, and in individual cases autoimmune reactions, have been demonstrated. Sometimes the toxic symptoms first appear with immunological syndromes such as acrodynia (pink disease) or baboon syndrome, a syndrome, which often includes non-specific central nervous system symptoms. In the kidneys, signs of tubular damage appear with leakage of tubular enzymes to the urine (2).

The determination of the risk of effects on health from mercury from amalgam requires that a type of health effect be identified based on scientific information obtained from experimental, clinical or epidemiological observations. A reasonable suspicion of risk can be considered to exist if health effects arise in the dose range closest to the relevant dose or if theoretical preconditions exist in order for the effect to arise. We can thus identify the following health risks:

- Risk of disturbances in central nervous system function
- Risk of disturbances in renal function
- Risk of disturbances in the immune system
- Risk of disturbances in thyroid function
- Risk of disturbances in foetal development, especially the development of the nervous system.

Dose-response relations

The diagram in Figure 1 shows that the range for mercury exposure from amalgam overlaps the dose interval in which subclinical signs from the CNS, kidneys, immune system, and thyroid arise. The first sign from the CNS is a decline in motor performance (30), from the kidney an increase in excretion of NAG (N-acetyl-β-D-glucosaminidase) in urine

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[1] µg/g creatinine is on a group basis approximately the same as µg/l urine

(31), from the immune system an appearance of autoantibodies against myeloperoxidase and proteinase 3 (31), and from the thyroid an increase in rT_3 (reverse triiodothyronine) in plasma (32). The LOAEL (lowest adverse effect exposure level) for all these effects corresponds to a mercury excretion in urine of around 10 μg/l and an incidence around 20%. The median excretion of mercury in amalgam bearers can be estimated to half this value or around 5μg/l.

In order to be able to demonstrate effects of mercury exposure in a population of less than a hundred workers, prevalence around 20% is required. If there is a prevalence of 20% at an exposure that gives a urine elimination of 10 μg mercury per litre of urine, what exposure then gives rise to a prevalence 1%? The only thing that can be said with certainty is that this exposure is lower than the exposure corresponding to 10 μg mercury per litre of urine, and we then find ourselves in the dose interval to which most amalgam bearers are exposed. We can thus state that the dose response curve for the effects of mercury vapour runs within the dose interval that corresponds to exposure from amalgam.

The effects for which the LOAEL has been discussed give rise to sub-clinical signs but have little or no influence on the function or work capacity of the exposed subject. However, as with other potent substances or pharmaceuticals, mercury is likely to induce more serious side effects with illness or in those who are especially susceptible genetically. Several reports in the literature describe patients who, during removal of amalgam restorations and for some days thereafter, experience and exhibit neuropsychological symptoms. These symptoms disappear when the exposure to mercury concomitant to the amalgam removal has ceased and returns at renewed exposure (3). Such mercury sensitive patients have been subjected to blind provocation tests with inhalation of low concentrations of mercury vapour in air (33) or percutanous patch tests with mercury or mercury compounds (34-37). These tests have confirmed the deviant high sensitivity to mercury of these patients.

These mercury sensitive individuals are not common. Several epidemiological studies have been carried out in which the health status among amalgam bearers or dental service personnel with low exposure and non-amalgam bearers and persons with no occupational exposure were compared, including studies on twins discordant with regard to amalgam fillings in the teeth (38-41). In none of these or earlier studies have any health effects which can be related to the mercury exposure been demonstrated. From these studies we can draw the conclusion that the prevalence of health effects from mercury in amalgam probably does not exceed 10%.

Effects on the immune system

In animal experiments, mercury has been shown to modify the functioning of the immune system in various pathological states. Mice treated with injections of subtoxic doses of $HgCl_2$ are, for example, more susceptible to leishmaniasis infestation than untreated animals (42).

Both mercury sensitive and mercury resistant mice show reduced immunity against malaria protozoa after injection of subtoxic doses of $HgCl_2$ (43). In mice with a genetically conditioned tendency to develop the autoimmune syndrome systemic lupus erythematosus (SLE), development of the disease is accelerated if mercury is injected in subtoxic doses (44). In mice with a genetic predisposition for diabetes (non-obese diabetic [NOD] mice), the development of diabetes is inhibited if subtoxic doses of $HgCl_2$ are injected (45).

Mercury vapour exposure as a contributory or causative agent in MS and Alzheimer´s disease has been studied and discussed in the literature. So far there is no conclusive evidence (3). However, where patients are suffering from unclear pathological states and autoimmune diseases, every doctor and dentist should consider whether side effects from mercury released from amalgam may be one contributory cause of the symptoms.
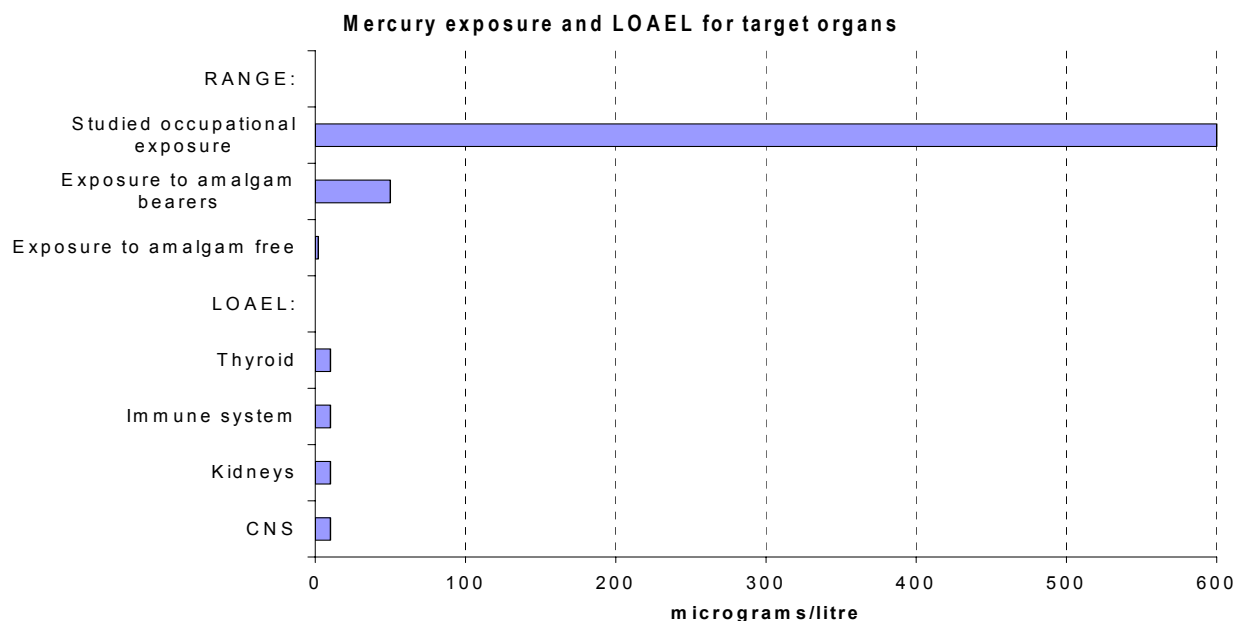
Figure 1 The mercury exposure range, measured as mercury excretion rate in urine, for amalgam bearers, amalgam free subjects, and occupationally exposed workers studied. The LOAEL (lowest adverse effect exposure level) for the central nervous system (CNS), the thyroid, the kidney, and the immune system are also shown

Effect on foetal development

The risk of inhibited brain development in the foetus and child is a special problem. Foetal nerve tissue contains the type of cell which shows most sensitivity to the mercury ion Hg^{2+}. Clear effects arise at the concentration level 5-50 nM or 1-10 ng/g tissue (46-49), which is the concentration level found in neonatal infants of amalgam bearing mothers (9-10). Experimental studies on rats and primates have shown that exposure to mercury vapour gives rise to developmental disorders in the brain resembling those seen after exposure to methylmercury. This means migration disturbances and permanent behavioural changes with reduced abilities / capacity to learn and adapt (50-53). The effects are seen from a mercury concentration in a monkey foetus brain of 10-200 ng/g brain tissue, which is 10 times lower than the concentration required with exposure to methylmercury. In rats, it has been shown that methyl mercury exposure and exposure to mercury vapour has an additive effect on foetal brain development (54). The prevalence of disturbed development in the experiments on monkeys was almost 100% in the studied dose range. There is no reason to assume that the human foetal brain would be less sensitive than other primate brains.

In a Dutch case control study the occupational exposure during the later stages of pregnancy of the mothers of 306 children with mental retardation of unknown origin was compared with the same exposure for mothers of 322 control children, who were mentally retarded for known reasons. A significant odds ratio (OR) of 8.7 for having children with disturbed brain development was found among mothers exposed to mercury as compared to those not exposed (55). A German prospective study of 3946 pregnant women was carried out. The women were interviewed regarding mercury exposure at the workplace. The mothers-to-be exposed to mercury or mercury compounds showed a significantly elevated risk of giving birth to babies who were small for their gestational age (56).

Conclusion

With present knowledge it is impossible to estimate the risk of effects on the foetal brain induced by the mother's exposure to mercury from amalgam. Available facts, however, do not support a dismissal of the risk. Therefore treatment of children and women of childbearing age with amalgam should be avoided. It is also recommended that use of amalgam for dental restorations in the population in general is abandoned and substituted with less toxic material, whenever this is available and affordable.

Competing interests None declared.

References

1. World Health Organisation. *Environmental health criteria 118: inorganic mercury*. Geneva: WHO, 1991.
2. Berlin M. Mercury in dental fillings - an environmental medicine risk assessment. A literature and knowledge summary. In: Novakova V, ed. *Amalgam and health - New perspectives on risks*. Stockholm: The Swedish council for planning and coordination of research, 1999:365-79.
3. Berlin M. Mercury in dental-filling materials - an uppdated risk analysis in environmental medical terms. In: Lidmark A, ed. *Dental materials and health*. Stockholm: SOU (53), 2003:17-57.
4. Halbach S. Estimation of mercury dose by a novel quantitation of elemental and inorganic species released from amalgam. *International Archives of Occupational & Environmental Health* 1995;67:295-300.
5. Weiner JA, Nylander M. An estimation of the uptake of mercury from amalgam fillings based on urinary excretion of mercury in Swedish subjects. *Sci Total Environ* 1995;168:255-65.
6. Sandborgh-Englund G, Elinder CG,Langworth S, Schutz A, Ekstrand J. Mercury in biological fluids after amalgam removal. J. Dent Res 1998; 77: 615-24.
7. Barregard L, Sallsten G, Jarvholm B. People with high mercury uptake from their own dental amalgam fillings. *Occupational & Environmental Medicine* 1995;52:124-8.
8. Langworth S, Stromberg R. A case of high mercury exposure from dental amalgam. *Eur J Oral Sci* 1996;104:320-1.
9. Drasch G, Schupp I, Hofl H, Reinke R, Roider G. Mercury burden of human fetal and infant tissues. *Eur J Pediatr* 1994;153:607-10.
10. Lutz E, Lind B, Herin P, Krakau I, Bui TH, Vahter M. Concentrations of mercury, cadmium and lead in brain and kidney of second trimester fetuses and infants. *J Trace Elem Med Biol* 1996;10:61-7.
11. Palkiewicz P, Zwiers H, Lorscheider FL. ADP-ribosylation of brain neuronal proteins is altered by in vitro and in vivo exposure to inorganic mercury. *J Neurochem* 1994;62:2049-52.
12. Rajanna B, Chetty CS, Rajanna S, Hall E, Fail S, Yallapragada PR. Modulation of protein kinase C by heavy metals. *Toxicol Lett* 1995;81:197-203.
13. Freitas AJ, Rocha JB, Wolosker H, Souza DO. Effects of Hg2+ and CH3Hg+ on Ca2+ fluxes in rat brain microsomes. *Brain Res* 1996;738:257-64.
14. Pendergrass JC, Haley BE. Inhibition of brain tubulin-guanosine 5'-triphosphate interactions by mercury: similarity to observations in Alzheimer's diseased brain. (Review: 35 refs) *Met Ions Biol Syst* 1997;34:461-78.
15. Kim P, Choi BH. Selective inhibition of glutamate uptake by mercury in cultured mouse astrocytes. *Yonsei Med J* 1995;36:299-305.
16. Castoldi AF, Candura SM, Costa P, Manzo L, Costa LG. Interaction of mercury compounds with muscarinic receptor subtypes in the rat brain. *Neurotoxicology* 1996;17:735-41.
17. Albrecht J, Matyja E. Glutamate: a potential mediator of inorganic mercury neurotoxicity. *Metab Brain Dis* 1996;11:175-84.
18. Rossi AD, Larsson O, Manzo L, Orrenius S, Vahter M, Berggren PO, et al. Modifications of Ca2+ signaling by inorganic mercury in PC12 cells. *FASEB J* 1993;7:1507-14.
19. Fejtl M, Gyori J, Carpenter DO. Hg2+ increases the open probability of carbachol-activated Cl-channels in Aplysia neurons. *Neuroreport* 1994;5:2317-20.
20. Busselberg D. Calcium channels as target sites of heavy metals. *Toxicol Lett* 1995;82-83:255-61.
21. Aschner M. Astrocytes as modulators of mercury-induced neurotoxicity. (Review: 59 refs) *Neurotoxicology* 1996;17:663-9.
22. Leonhardt R, Pekel M, Platt B, Haas HL, Busselberg D. Voltage-activated calcium channel currents of rat DRG neurons are reduced by mercuric chloride (HgCl2) and methylmercury (CH3HgCl). *Neurotoxicology* 1996;17:85-92.
23. Dyatlov VA, Platoshin AV, Lawrence DA, Carpenter DO. Mercury (Hg 2+) enhances the depressant effect of

kainate on Ca-inactivated potassium current in telencephalic cells derived from chick embryos. *Toxicology & Applied Pharmacology* 1996;138:285-97.

24. Yallapragada PR, Rajanna S, Fail S, Rajanna B. Inhibition of calcium transport by mercury salts in rat cerebellum and cerebral cortex in vitro. *J Appl Toxicol* 1996;16:325-30.

25. Szucs A, Angiello C, Salanki J, Carpenter DO. Effects of inorganic mercury and methylmercury on the ionic currents of cultured rat hippocampal neurons. *Cellular & Molecular Neurobiology* 1997;17:273-88.

26. Yoneda S, Suzuki KT. Equimolar Hg-Se complex binds to selenoprotein P. *Biochemical & Biophysical Research Communications* 1997;231:7-11.

27. Bohets HH, Van Thielen MN, Van der Biest I, Van Landeghem GF, D'Haese PC, Nouwen EJ, et al. Cytotoxicity of mercury compounds in LLC-PK1, MDCK and human proximal tubular cells. *Kidney Int* 1995;47:395-403.

28. Foulkes EC. Metallothionein and glutathione as determinants of cellular retention and extrusion of cadmium and mercury. *Life Sciences* 1993;52:1617-20.

29. Kim CY, Watanabe C, Kasanuma Y, Satoh H. Inhibition of gamma-glutamyltranspeptidase decreases renal deposition of mercury after mercury vapor exposure. *Arch Toxicol* 1995;69:722-4.

30. Lucchini R, Cortesi I, Facco P, Benedetti L, Camerino D, Carta P, et al. Effetti neurotossici da esposizione a basse dosi di mercurio. *Med Lav* 2002;93(3):202-14.

31. Ellingsen DG, Efskind J, Berg KJ, Gaarder PI, Thomassen Y. Renal and immunologic markers for chloralkali workers with low exposure to mercury vapor. *Scand J Work Environ Health* 2000;26(5):427-35.

32. Ellingsen DG, Efskind J, Haug E, Thomassen Y, Martinsen I, Gaarder PI. Effects of low mercury vapour exposure on the thyroid function in chloralkali workers. *J Appl Toxicol* 2000;20(6):483-9.

33. Stromberg R, Langworth S, Soderman E. Mercury inductions in persons with subjective symptoms alleged to dental amalgam fillings. *Eur J Oral Sci* 1999;107(3):208-14.

34. Marcusson JA. Psychological and somatic subjective symptoms as a result of dermatological patch testing with metallic mercury and phenyl mercuric acetate. *Toxicol Lett* 1996;84:113-22.

35. Marcusson JA, Jarstrand C. Oxidative metabolism of neutrophils in vitro and human mercury intolerance. *Toxicology in Vitro* 1998;12:383-8.

36. Marcusson JA, Carlmark B, Jarstrand C. Mercury intolerance in relation to superoxide dismutase, glutathione peroxidase, catalase, and the nitroblue tetrazolium responses. *Environ Res* 2000;83(2):123-8.

37. Marcusson JA, Cederbrant K, Gunnarsson LG. Serotonin production in lymphocytes and mercury intolerance. *Toxicol In Vitro* 2000;14(2):133-7.

38. Saxe SR, Snowdon DA, Wekstein MW, Henry RG, Grant FT, Donegan SJ, et al. Dental amalgam and cognitive function in older women: findings from the Nun Study. *J Am Dent Assoc* 1995;126:1495-501.

39. Bjorkman L, Pedersen NL, Lichtenstein P. Physical and mental health related to dental amalgam fillings in Swedish twins. *Community Dentistry & Oral Epidemiology* 1996;24:260-7.

40. Langworth S, Sallsten G, Barregard L, Cynkier I, Lind ML, Soderman E. Exposure to mercury vapor and impact on health in the dental profession in Sweden. *J Dent Res* 1997;76:1397-404.

41. Ahlqwist M, Bengtsson C, Lapidus L, Gergdahl IA, Schutz A. Serum mercury concentration in relation to survival, symptoms, and diseases: results from the prospective population study of women in Gothenburg, Sweden. *Acta Odontol Scand* 1999;57(3):168-74.

42. Bagenstose LM, Mentink-Kane MM, Brittingham A, Mosser DM, Monestier M. Mercury enhances susceptibility to murine leishmaniasis. *Parasite Immunol* 2001;23(12):633-40.

43. Silbergeld EK, Sacci Jr JB, Azad AF. Mercury exposure and murine response to plasmodium yoelii infection and immunization. *Immunopharmacol Immunotoxicol* 2000;22(4):685-95.

44. Pollard KM, Pearson DL, Hultman P, Deane TN, Lindh U, Kono DH. Xenobiotic acceleration of idiopathic systemic autoimmunity in lupus-prone bxsb mice. *Environ Health Perspect* 2001;109(1):27-33.

45. Brenden N, Rabbani H, Abedi-Valugerdi M. Analysis of mercury-induced immune activation in nonobese diabetic (NOD) mice. *Clin Exp Immunol* 2001;125(2):202-10.

46. Abdulla EM, Calaminici M, Campbell IC. Comparison of neurite outgrowth with neurofilament protein subunit levels in neuroblastoma cells following mercuric oxide exposure. (Review: 5 refs) *Clinical & Experimental Pharmacology & Physiology* 1995;22:362-3.

47. Soderstrom S, Ebendal T. In vitro toxicity of methyl mercury: effects on nerve growth factor (NGF)-responsive neurons and on NGF synthesis in fibroblasts. *Toxicol Lett* 1995;75:133-44.

48. Monnet-Tschudi F, Zurich MG, Honegger P. Comparison of the developmental effects of two mercury compounds on glial cells and neurons in aggregate cultures of rat telencephalon. *Brain Res* 1996;741:52-9.

49. Monnet-Tschudi F. Induction of apoptosis by mercury compounds depends on maturation and is not associated with microglial activation. *J Neurosci Res* 1998;53(3):361-7.

50. Berlin M, Hua J, Logdberg B, Warfvinge K. Prenatal exposure to mercury vapor: effects on brain development. *Fundam Appl Toxicol* 1992;1:7.

51. Danielsson BR, Fredriksson A, Dahlgren L, Gardlund AT, Olsson L, Dencker L, et al. Behavioural effects of prenatal metallic mercury inhalation exposure in rats. *Neurotoxicol Teratol* 1993;15:391-6.

52. Warfvinge K, Hua J, Logdberg B. Mercury distribution in cortical areas and fiber systems of the neonatal and maternal adult cerebrum after exposure of pregnant squirrel monkeys to mercury vapor. *Environ Res* 1994;67:196-208.

53. Newland MC, Warfvinge K, Berlin M. Behavioral consequences of in utero exposure to mercury vapor: alterations in lever-press durations and learning in squirrel monkeys. *Toxicology & Applied Pharmacology* 1996;139:374-86.

54. Fredriksson A, Dencker L, Archer T, Danielsson BR. Prenatal coexposure to metallic mercury vapour and methylmercury produce interactive behavioural changes in adult rats. *Neurotoxicol Teratol* 1996;18:129-34.

55. Roeleveld N, Zielhuis GA, Gabreels F. Mental retardation and parental occupation: a study on the applicability of job exposure matrices. *Br J Ind Med* 1993;50:945-54.

56. Seidler A, Raum E, Arabin B, Hellenbrand W, Walter U, Schwartz FW. Maternal occupational exposure to chemical substances and the risk of infants small-for-gestational-age. *Am J Ind Med* 1999;36(1):213-22.