REVIEW ARTICLE

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The Potential Adverse Health Effects of Dental Amalgam

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Abstract

There is significant public concern about the potential health effects of exposure to mercury vapour (Hg^0) released from dental amalgam restorations. The purpose of this article is to provide information about the toxicokinetics of Hg^0, evaluate the findings from the recent scientific and medical literature, and identify research gaps that when filled may definitively support or refute the hypothesis that dental amalgam causes adverse health effects.

Dental amalgam is a widely used restorative dental material that was introduced over 150 years ago. Most standard dental amalgam formulations contain approximately 50% elemental mercury. Experimental evidence consistently demonstrates that Hg^0 is released from dental amalgam restorations and is absorbed by the human

body. Numerous studies report positive correlations between the number of dental amalgam restorations or surfaces and urine mercury concentrations in non-occupationally exposed individuals. Although of public concern, it is currently unclear what adverse health effects are caused by the levels of Hg^0 released from this restoration material. Historically, studies of occupationally exposed individuals have provided consistent information about the relationship between exposure to Hg^0 and adverse effects reflecting both nervous system and renal dysfunction. Workers are usually exposed to substantially higher Hg^0 levels than individuals with dental amalgam restorations and are typically exposed 8 hours per day for 20–30 years, whereas persons with dental amalgam restorations are exposed 24 hours per day over some portion of a lifetime. This review has uncovered no convincing evidence pointing to any adverse health effects that are attributable to dental amalgam restorations besides hypersensitivity in some individuals.

1. Overview

Dental amalgam is a widely used restorative dental material that was introduced over 150 years ago. Most standard dental amalgam formulations contain approximately 50% elemental mercury. Mercury vapour (Hg^0) is released from elemental mercury at physiological temperatures and is absorbed by the human body. This fact, along with warnings about the 'dangers' of amalgam restorations in the media and on the Internet, has caused significant public concern about the potential health effects of dental amalgam restorations.

In the last 10 years, the US Public Health Service[1,2] and other agencies, including the European Commission,[3] the health agencies of Canada,[4] Quebec,[5] and Australia,[6] and the World Health Organization (WHO),[7] have reviewed the safety of dental amalgam for human use. These scientific panels concluded that no definitive scientific evidence demonstrated a causal link between dental amalgam and adverse health effects, except in rare instances where individuals experienced localised side effects or hypersensitivity reactions. These reports, however, stressed that further research was required in many critical areas, due to a lack of conclusive scientific studies.

Despite the findings of these panels, the governments of Germany,[8] Austria,[3] and Canada[4] and its province of Quebec[5] recommend that dental amalgam restorations not be placed in certain patient populations that include but are not limited to children, pregnant women, and individuals with renal dysfunction or hypersensitivity to metals. In addition, the governments of Sweden and Denmark have banned and are currently phasing out all mercury-containing materials, including dental amalgam, because of their contribution to environmental contamination. In 2002, a literature review of the health effects of dental amalgam undertaken for the Dental Material Commission of Sweden[9] advocated the timely elimination of dental amalgam from dental practice. It was argued that this step would reduce the occurrence of hypersensitivity reactions and localised side effects observed in some dental patients, remove the occupational exposures to elemental mercury experienced by dental professionals, and prevent further environmental mercury pollution. All of the above-mentioned recommendations and regulatory actions have provoked public debate in the US concerning the safety of dental amalgam.

2. Adverse Health Effects of Elemental Mercury Exposure

Humans experience a spectrum of exposures to Hg^0. Historically, workers employed in the chloralkali, thermometer, and fluorescent lamp industries have received the highest exposures. These exposures, however, have decreased over time due to reductions of the threshold limit value-time weighted average (TLV-TWA) for workers and increased emphasis on industrial hygiene. The current TLV-TWA for elemental mercury exposure is 0.025mg Hg/m^3.[10] This represents the time-weighted average concentration of elemental mercury that most workers can be exposed to 8 hours per day during a 5-day working week without experiencing adverse effects and corresponds to a biological exposure index of 35μg Hg/g creatinine measured in the urine. This level is "intended to minimise the potential for preclinical central nervous system changes and kidney effects, and to provide some assurance that workers will maintain their functional capacity to produce healthy children with normal cognitive and physical functions".[10] As occupational exposures diminish, increased variability in effects reported at low exposure levels may occur.

Tremor, ataxia, slowed nerve conduction velocity, irritability, gingivitis, stomatitis, hearing loss, and emotional instability and irritability may begin to be observed at air concentrations >0.050mg Hg/m^3 (urine mercury ≥60μg Hg/g creatinine).[11] Because the kidneys are the primary site of Hg^{2+} accumulation, chronic exposures to Hg^0 >0.050mg Hg/m^3 can result in adverse effects on renal function.[12] Alterations in cell membrane and mitochondrial morphology and enzymatic activity are early events.[13,14] Such changes are often accompanied by increased urinary excretion of brush border enzymes, such as γ-glutamyltranspeptidase, alkaline phosphatase, and brush border antigens.

With the progression of cellular injury, intracellular enzymes including lactate dehydrogenase, aspartate aminotransferase, and acid phosphatase escape into the bloodstream and urine.[13]

Increased urinary *N*-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme, is an early index of kidney injury. Urinary NAG is sometimes the only renal parameter that is altered in workers exposed to Hg^0.[15-17] As the dose and duration of exposure increases, further tubular injury causes a reduction in the reabsorption of solutes and water and increased urinary excretion of glucose, amino acids, and other proteins. Associated with increasingly severe injury is a decrease and progressive decline in the glomerular filtration rate (GFR). The reduction in GFR results from tubular injury, glomerular injury and/or vasoconstriction.

There is no evidence from epidemiological studies that inhalation of Hg^0 produces cancer in humans or animals.[18] The US Department of Health and Human Services, the International Agency for Research on Cancer, and the US Environmental Protection Agency have not found sufficient evidence to classify elemental mercury as either a carcinogen or noncarcinogen.[18] The American Conference of Governmental Industrial Hygienists has designated elemental mercury "not classifiable as a human carcinogen" based on a lack of evidence for a positive association in rodent carcinogenicity studies and microorganism mutagenicity studies.[11]

Elemental mercury is not included as a chemical of concern in *Reproductive and Developmental Toxicants*, a report published by the US General Accounting Office.[19] It is not recognised as a teratogen, nor is it acknowledged as having reproductive or developmental consequences at low exposure levels.[19]

3. Sources of Mercury Exposure

3.1 Dental Amalgam

Elemental mercury is a dense, metallic, silver-coloured liquid at room temperature. Hg^0 is released at room temperature because of its vapour pressure (0.0013mm at 20ºC). Dental amalgam is an alloy of elemental mercury with other metals, which may include silver, tin, copper and zinc. Today most dental amalgam is sold as an encapsulated preparation. The powdered metals and elemental mercury are divided into separate compartments, and the physical divider is broken just prior to use. The resulting amalgam is mixed on a device referred to as an amalgamator or triturator to achieve a pliable mass that is then placed in the prepared tooth, where it is sculpted and polished to achieve the correct dimensions.[18]

Mercury exposure from dental amalgam is chronic with low levels of Hg^0 released throughout the life of a restoration.[20,21] Most dental amalgam restorations are replaced after 9–20 years of use, but some individuals may have older restorations.[22] Amalgam particles that are created by the process of dental amalgam placement or removal may also be ingested.[20] Occupational exposures to Hg^0 by dentists and dental office personnel have been investigated. Exposure levels have declined over time for these workers because of improved mercury hygiene measures,[23] a decrease in the prevalence of cavities in the general population,[24,25] and wider use of 'white' composite restorative materials that are increasingly preferred by dental patients for cosmetic and perceived 'health' reasons.[26]

3.2 Non-Dental Amalgam Sources

Mercury forms inorganic salts in its Hg^{1+} (mercurous) or Hg^{2+} (mercuric) valence states. Inorganic mercury is methylated in the environment by bacteria that reside in aquatic sediment to produce the organic mercury compound, methylmercury. Human exposures to Hg^0, inorganic mercury (Hg^{2+}) and organic mercury compounds occur by several distinct routes. Anthropogenic Hg^0 emissions are produced by the combustion of fossil fuels (especially coal); the extraction, treatment and recycling of mineral materials; and the incineration of mercury-containing waste.[27] Human exposure to Hg^0 occurring in the ambient environment, however, is considered to be negligible.[27] Elemental mercury has multiple industrial uses, such as in the production of caustic soda and chlorine, and in the manufacture of thermometers, thermostats, fluorescent light bulbs, batteries and manometers. As a result, occupational exposures to Hg^0 have historically provided a considerable amount of information regarding the health effects of chronic human exposure. Residential exposures to Hg^0 may result from accidental elemental mercury spills from broken thermometers, blood pressure gauges or thermostats. Certain ethnic, religious and ritualistic practices also involve the use of elemental mercury.[18] Skin-lightening creams and other cosmetics manufactured outside the US may contain mercury compounds at levels exceeding the 1μg Hg/L limit set by the US FDA.[28] The consumption of fish and other seafood is the primary source of exposure to methylmercury.[29] Although any combination of exposures may contribute to total mercury body burden, the three species of mercury (i.e. elemental, inorganic ion and organic) each have unique absorption, distribution, metabolism and excretion pathways. Knowledge of these pathways is essential when evaluating the relevance of scientific studies.

4. Elemental and Inorganic Mercury

4.1 Toxicokinetics

Approximately 80% of inhaled Hg^0 is absorbed by the lungs, where it diffuses across the alveolar membranes and enters the blood.[30] Approximately 7–14% of the absorbed dose is exhaled in the week following exposure.[31,32] Hg^0 has a half-life of approximately 2 days in the human body.[33] Hg^0 that enters the bloodstream is oxidised to Hg^{2+} by the catalase-hydrogen peroxide pathway in erythrocytes and other tissues including the liver and brain.[33] Several hours after the inhalation of a dose of Hg^0, the catalase oxidation reaction results in a deposition of mercury that is similar to that found after the ingestion of mercuric salts in all organs except the brain (due to the ability of Hg^0, but not Hg^{2+} to cross the blood-brain barrier). This is significant because it is generally recognised that Hg^{2+} is the proximate toxic agent of Hg^0.[18]

The amounts of soluble inorganic mercuric salts and elemental mercury that are absorbed by the gastrointestinal tract differ. Whereas approximately 10–25% of an ingested dose of Hg^{2+} is absorbed by the human gastrointestinal tract,[34] only 0.01% of an ingested dose of elemental mercury is absorbed.[35] Elemental mercury released from dental amalgam is able to dissolve in saliva, but only a small percentage is likely absorbed by the gastrointestinal tract.[36] Aggressive chewing, aged dental amalgam restorations, and dental amalgam removal or placement can also result in the ingestion of amalgam particles. A study of humans fed powdered dental amalgam demonstrated that approximately 0.04% of the administered dose was absorbed.[37] Elemental mercury and inorganic mercury can also be absorbed through the skin.[11,18,38]

Two phases have been observed for the kinetics of Hg^{2+} in plasma. A short half-life of <1 day is followed by a longer half-life of approximately 10 days.[39] Blood levels, therefore, accurately reflect only recent exposure to Hg^0 and inorganic mercuric salts.[40-42] Following absorption, Hg^{2+} is excreted via the urine and faeces with a half-life of about 60 days. This results in an excretion rate of slightly more than 1% of the body burden per day.[31,41] The kidneys are the primary target organ for the accumulation of Hg^{2+}.[13,39,43] As a result, urinary Hg^{2+} is the most commonly measured biomarker for Hg^{2+} and Hg^0 exposures.

One critical difference exists between the distribution of Hg^0 and Hg^{2+} in the human body. Because of its lack of charge, unoxidised Hg^0 is able to cross both the blood-brain and placental barriers.[30] It is estimated that 7% of an absorbed dose is deposited in the brain following direct exposure to Hg^0.[31] No practical means exist, however, to measure Hg^{2+} accumulation in the brain due to Hg^0 exposure while an individual is alive. Hg^0 crosses the placenta.[18] However, following maternal Hg^0 exposure, the concentration of mercury in the fetal circulation and organs is less than maternal levels. The highest concentration of fetal Hg^{2+} is found in the liver, which likely reflects first-pass metabolism of Hg^0 from the umbilical veins to Hg^{2+} by liver catalase.[33] The deposition of Hg^{2+} in the fetal brain is likely limited by the oxidation of Hg^0 in the fetal liver. This is supported by the results of animal *in utero* Hg^0 exposure studies that show less Hg^{2+} accumulation in fetal than maternal brain.[44,45] Although some Hg^{2+} accumulates in the fetal brain, the severe brain damage that is associated with *in utero* exposure to organic mercury species has not been observed.[46,47]

Both inorganic mercury, measured as Hg^{2+}, and methylmercury are present in human milk.[48] The WHO has estimated that the mean total mercury concentration (both Hg^{2+} and methylmercury) in human breast milk is approximately 8μg Hg/L.[49] Although between 10% and 25% of an ingested dose of Hg^{2+} is absorbed by the adult gastrointestinal tract,[34] suckling newborn rats absorb up to 38% of an oral dose of Hg^{2+}.[50] To date, no recommendations have been made regarding mercury in human milk. The beneficial effects associated with breast feeding are currently thought to override any potential effects on development due to low-level contaminants, such as mercury, in human milk.[18]

Hg^{2+} has an extremely high affinity for sulfhydryl groups and is found complexed with sulfhydryl-containing proteins and low molecular weight sulfhydryls, such as cysteine and glutathione.[35] Hg^{2+} that is complexed with glutathione is secreted from liver cells into bile and renal handling of Hg^{2+} likely also involves Hg^{2+}-glutathione complexes.[14] Because numerous sulfhydryl-containing compounds are present in mammalian cells and the reaction with sulfhydryl groups is reversible, pinpointing the specific site of action of Hg^{2+} at the molecular level has been difficult. Nevertheless, it is believed that the formation of the mercury-sulfhydryl bond underlies both the toxicity and mobility of Hg^{2+} in the body. Certain sulfhydryl-containing molecules may play a role in cellular defences. Hg^{2+} can induce cellular expression of metallothionein,[51,52] and intracellular glutathione may also sequester Hg^{2+} and prevent its interaction with sensitive proteins.[14]

4.2 Biomarkers of Exposure

Published estimates of mercury absorption from dental amalgam restorations range from 3 to 17μg Hg/day and are based on total Hg^0 release that is dependent upon the total number and surface area of restorations, chewing and eating habits, and other chemical conditions in the mouth.[18,49] These estimates have been discussed and critiqued at length.[20,21,53,54]

Urinary mercury (HgU) is considered to be the most accurate biomarker for quantifying the systemic dose from chronic Hg^0 exposure. HgU is an index that is proportional to renal Hg^{2+} concentrations and reflects the Hg^{2+} renal burden that results from long-term exposure to either Hg^0 or Hg^{2+}.[18] Because organic mercury represents only a small fraction (<10%) of total HgU, measurements of HgU are less affected by dietary methylmercury exposure than are blood measurements.[18,49] It has been estimated that HgU increases by approximately 1μg Hg/L for every 10 amalgam surfaces.[55]

Besides measuring Hg^0 exposure from dental amalgam, HgU also reflects exposure to inorganic mercury found in skin-lightening creams and Hg^0 from ethnic, religious, or ritualistic uses of elemental mercury.[18] These exposure sources may contribute to HgU and confound exposure measurements for dental amalgam.

Blood mercury may be used as an index of recent Hg^0 exposure, especially in cases of acute accidental or occupational exposures.[42,56] Speciation of the inorganic component of whole blood is required to evaluate low-level Hg^0 exposure because of the significant contribution that dietary methylmercury makes to blood mercury levels. Measurements of Hg^{2+} in cord blood, placenta, and breast milk are used to assess fetal and neonatal exposures that result from maternal elemental mercury exposures.[18]

Hair mercury levels are inappropriate for assessing Hg^0 exposure. Instead, hair mercury reflects exposure to organic mercury species, such as methylmercury. A correlation exists between the amount of fish consumed, the level of methylmercury in fish, and the level of mercury measured in hair.[18]

5. Methylmercury

The consumption of fish and other seafood is the predominant source of human exposure to methylmercury.[29] *In vivo* methylation of inorganic mercury has not been demonstrated in humans,[57] contrary to the findings of some *in vitro* studies.[18]

Methylmercury is slowly metabolised to Hg^{2+} by microflora in the gut at a rate of approximately 1% of the body burden per day.[29] Hg^{2+} is poorly absorbed from the intestines. Therefore, most of an absorbed dose of methylmercury is excreted from the body via the faeces following its conversion to Hg^{2+}. The major target organ for methylmercury is the brain. Methylmercury crosses the blood-brain barrier via active transport as a complex with L-cysteine.[58] Its effects and mechanism of action, however, differ between the adult and fetal brain. In acute adult exposures, a latent period between exposure and the onset of symptoms is observed.[59] Paresthesia is the first symptom to appear, and it may be followed by ataxia, dysarthria, constriction of the visual field, loss of hearing, tremor, and mental deterioration.[60] These signs and symptoms are caused by the loss of neuronal cells in discrete anatomical regions of the brain that include, but are not limited to, the small granule cells of the cerebellum and the neurons of the visual cortex.

Methylmercury crosses the placenta and has neurological effects on the developing foetus.[30] Significantly, maternal exposure to methylmercury causes strikingly different effects than Hg^0 exposure. Following methylmercury exposure, fetal concentrations of mercury are higher than maternal levels, and damage to the fetal brain is more widespread than the focal damage that is observed in the adult brain.[61] High-level *in utero* exposure to methylmercury may result in brain damage, cerebral palsy, blindness, deafness, or severe mental retardation. Paradoxically, women exposed to high levels of methylmercury during pregnancy often lack overt signs of toxicity, but give birth to children with severe brain damage.[62,63] Exposure to low levels of methylmercury *in utero* may produce deficits in vision and hearing, delayed walking and speech development, or other more subtle developmental delays.

6. Co-Exposure to Mercury Vapour and Methylmercury

It is currently unclear whether the neurotoxic effects of methylmercury and Hg^0 are additive. Hg^0 diffuses across the blood/brain barrier and is oxidised to Hg^{2+}, the cytotoxic moiety. In contrast, animal studies suggest that the methylmercury cation, rather than Hg^{2+}, is the toxic moiety of methylmercury in the brain[64-66] where it acts to alter the normal cellular processes of susceptible neuronal populations.[30]

Methylmercury and Hg^0 are not likely to have comparable nephrotoxic potency. Methylmercury exerts only modest renal cytotoxicity and contributes little to systemic Hg^{2+}. In contrast, occupational studies have demonstrated that Hg^0 exposure can exert marked effects on renal function. A large portion of an absorbed dose of Hg^0 is converted to Hg^{2+}, which is eliminated by and represents the principal cytotoxic moiety in the kidneys.

7. Risk Characterisation of Dental Amalgam

7.1 Review Protocol

The literature review of possible adverse effects from dental amalgam was limited to peer-reviewed journal articles published between January 1, 1996, and December 31, 2003. Literature was primarily identified using abstract databases maintained by the National Library of Medicine; from bibliographic reference searching of review articles, books and international scientific

studies; and from literature recommendations submitted by the public in response to the Federal Register Request for Information on Dental Amalgam (docket no. 03N-0169). Review articles published within the timeframe and seminal articles pre-dating this timeframe were used as background material. Guidance documents from various international and federal agencies were also used as sources of information. In total, over 950 papers were considered.

Several decisions were made about how the available literature would be approached. Although other literature reviews of dental amalgam have placed emphasis on animal and *in vitro* studies,[9] human studies of Hg^0 or dental amalgam exposure provided the primary basis of the current review. Numerous *in vitro* cell-based studies were published since the beginning of 1996. It was agreed upon, however, that although *in vitro* studies may aid in understanding mechanism of action, they are unreliable determinants of human health risks. Studies of animal exposures to Hg^0 (including dental amalgam) were evaluated for the toxicokinetic information and threshold values for observed effects that they provided.

HgU was adopted as the most appropriate, widely used biomarker to evaluate human exposure to Hg^0. Generally, studies that evaluated occupational exposures to Hg^0 were better controlled and the exposures were better defined than studies evaluating exposures to dental amalgam (with a few notable exceptions). As a result, the data reported by occupational studies were accorded more weight than the data reported by dental amalgam exposure studies. Criteria commonly used to assess biological plausibility were used to guide discussions of whether the scientific evidence supported a causal relationship between dental amalgam exposure and adverse human health effects.[67]

7.2 Findings

Experimental reports consistently demonstrate that Hg^0 is released from dental amalgam restorations and is absorbed by the human body.[18] Numerous studies report positive correlations between the number of dental amalgam restorations or surfaces and HgU concentrations in non-occupationally exposed individuals.[18] Studies published since 1996 consistently reported mean HgU values of <2μg Hg/L despite the fact that they examined different age groups, sexes and populations (Germany, Italy and the US).[55,68-72] Approximately 95% of the study participants had HgU at or below the WHO estimate of 4–5μg Hg/L for the general population.[49]

The long-term use of nicotine chewing gum (>24 months) combined with intense chewing and >20 dental amalgam surfaces presents the greatest chance that the HgU of non-occupationally exposed individuals may approach levels observed in occupationally exposed workers (24.8μg Hg/L is the highest reported HgU value for a nicotine gum-chewer).[73] Adverse health effects for long-term nicotine gum-chewers due to Hg^0 exposure were not evaluated in the literature. Bruxism (i.e. tooth-grinding)[74] and dental amalgam placement[75] and removal[76-79] appear to have less impact on exposure levels than the use of nicotine chewing gum.

Hg^0-exposed workers, such as chloralkali, natural gas, mercury production, thermometer, and fluorescent lamp factory workers, serve as sentinels, as they are usually exposed to substantially higher Hg^0 levels than persons with dental amalgam restorations. However, it is recognised that occupational exposures are typically 8 hours per day, 5 days per week for 20–30 years, whereas persons with dental amalgam restorations are exposed 24 hours per day over some portion of a lifetime. Only two results were reported by more than one study. Urinary NAG activity, an early and sensitive but nonspecific biomarker of kidney effect, consistently exhibits a modest, reversible increase in workers with HgU ≥25–35μg Hg/L.[15-17] Small transient decreases in circulating tumour necrosis factor-α (TNFα) were also reported in response to occupational exposures to Hg^0.[80,81] Because TNFα is a transient marker of inflammation that is not specific for Hg^0 exposure, the biological significance of the observed reduction in TNFα levels has not been established. Thus, on the basis of such occupational exposure studies, there appears to be a substantial margin of safety between Hg^0 exposure in persons with dental amalgam restorations and occupational Hg^0 exposures that may produce alterations in sensitive biochemical indices.

Case reports and studies of immune function consistently demonstrate that dental amalgam is capable of producing hypersensitivity reactions in some individuals. These reactions usually present with dermatological or oral symptoms.[82,83] For individuals exhibiting positive patch tests to mercury, mercury compounds, or dental metals, the removal of dental amalgam restorations and their replacement with composite materials may promote resolution of the observed symptoms.[84,85] While there is evidence that a small portion of the human population demonstrates this allergic sensitivity, there is insufficient evidence for other types of sensitivity, such as genetic susceptibility. Insufficient evidence was published to support or refute the hypotheses that dental amalgam is an aetiological agent in any autoimmune disease, including multiple sclerosis (MS). MS patients, however, appear to have an increased tendency to develop dental caries when compared with healthy controls.[86,87] The hypothesis that dental amalgam causes antibiotic resistance in human gut or oral flora could not be supported or refuted based on the published data.

Studies investigating the contributions of dental amalgam to altered neuropsychological function were primarily negative or

reported conflicting findings. In some studies, concerns were raised regarding control of relevant confounding variables. The results of three studies investigating the relationship between dental amalgam and neuropsychological function argue against an association between dental amalgam exposure and adverse effects on cognitive function.[88-90] Positive effects on motor coordination, cognition, and emotional functioning that correlated with HgU values were reported in practicing dentists.[91]

In vitro data suggest that Hg^{2+} may affect the cellular function of tubulin and the formation of microtubules at high exposure levels.[92,93] However, human studies failed to demonstrate a correlation between either past occupational exposure to Hg^0 or dental amalgam exposure and the onset of Alzheimer's disease.[94-96] In addition, elevated mercury levels were not reported for any of the 17 brain regions that were analysed in four autopsy studies of patients with Alzheimer's disease.[97-100] Available studies also failed to provide sufficient evidence to support a link between Hg^0 exposure at occupational levels and an increased risk of developing Parkinson's disease.[101-103]

Insufficient evidence was published to support or refute the hypothesis that mercury exposure from dental amalgam restorations contributes to adverse pregnancy outcomes. Studies of human fertility suggest that occupational exposure to Hg^0 has little adverse effect on male fertility,[104] but may increase the prevalence of dysmenorrhoea in females.[105]

The majority of the human reproductive and developmental literature focused on exposure measures. Hg^{2+} in the placenta, maternal blood, and cord blood correlates with maternal dental amalgam load.[106,107] Both methylmercury and Hg^{2+} are found at measurable concentrations in breast milk.[48] The relative proportions of these species depend on the frequency of fish consumption (methylmercury), dental amalgam status (Hg^{2+}) and occupational exposures (Hg^{2+}). Although significant outliers exist, the median total breast milk mercury for all studies published since 1996 is <1.64μg Hg/L, which is substantially below the estimated mean of 8μg Hg/L published by the WHO for human breast milk.[49] High-level exposures of pregnant rats (1.8 mg/m^3 for 1 hour/day on gestational days 14–19)[108] and monkeys (0.5–1.0 mg/m^3 for 4–7 hours/day, 5 days/week between gestational days 3–22, timing and duration varied slightly for each animal)[109] to Hg^0 induce behavioural deficits in the offspring, but no data are available to judge whether low-level exposures such as those expected in foetuses of mothers with dental amalgam restorations also lead to such effects. Co-exposure of rats to high levels of both Hg^0 and methylmercury during gestation caused alterations to both spontaneous and learned behaviours greater than that observed for exposure to the vapour alone.[108]

The current data are insufficient to support an association between mercury release from dental amalgam and the various nonspecific complaints that have been attributed to this restoration material. Common complaints include: fatigue; depression; muscle, joint, or tendon pain; weakness and dizziness; metal taste; headache; anxiety; impaired sensory function; loss of mental concentration and forgetfulness; sleep disorders; decreased sexual function; and gastrointestinal distress.[49] These complaints are nonspecific compared with the well defined set of effects that have been documented for occupational and accidental Hg^0 exposures (i.e. tremor, stomatitis, gingivitis, ataxia, hearing loss, renal impairment, and emotional instability and irritability). Individuals with dental amalgam-attributed complaints had neither elevated HgU[110,111] nor increased prevalence of hypersensitivity to dental amalgam or mercury when compared with controls.[112,113]

Although some individuals undergo chelation therapy to treat neurological, neurobehavioural, or mood complaints attributed to Hg^0 exposure from dental amalgam, animal studies of the toxicokinetics of mercury removal by the chelators, *meso*-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropane-1-sulfonate (DMPS), suggest that these agents mobilise mercury from the kidneys but not the brain.[114] Chelators have not been shown to be efficacious in treating amalgam-related complaints and may cause adverse health effects, such as headache, dizziness, nausea and the loss of essential metals in humans.

8. Research Gaps

In general, the low-level Hg^0 or dental amalgam exposure studies provided insufficient data to link reported health complaints or disease states to amalgam exposure, except hypersensitivity. In many studies, exposures were not well defined, appropriate biomarkers of exposure were not measured, or the duration and cumulative Hg^0 exposures of the study subjects were not provided. Additional deficiencies included studies with too few subjects, studies without appropriate controls, and insufficient consideration of potential confounding factors.

Several important research gaps were identified during the course of the review that when filled may more definitively support or refute the hypothesis that dental amalgam causes adverse health effects. These include:

- Well controlled studies using standardised measures that evaluate whether low-level Hg^0 exposures (air levels <0.025 mg/m^3 or HgU <35 μg/L) produce neurotoxic and/or neuropsychological effects and, if identified, provide dose-response relationships for those effects.
- Studies that determine the effects of co-exposure to Hg^0 and methylmercury. There is currently no pharmacokinetic basis for

assessing whether co-exposure to methylmercury and Hg^0 result in additive nephrotoxicity or neurotoxicity. Blood, brain, kidney and urinary Hg^{2+} time-course data are needed for animals administered a range of doses of methylmercury, Hg^0, and methylmercury plus Hg^0. Target organ Hg^{2+} concentrations should be correlated with adverse renal and neurological effects.

- Animal studies that investigate whether low-level *in utero* exposure to Hg^0 (air levels <0.025 mg/m^3 or HgU <35 μg/L) produces effects on the fetal brain.
- Occupational studies that evaluate reproductive and pregnancy outcomes in large groups of workers with well defined Hg^0 exposures.
- Studies that can be used to determine the amount of Hg^{2+} that is absorbed by the human neonatal gut from breast milk and what, if any, effect this exposure has on the brain development of infants.
- Well controlled studies using standardised measures that investigate whether dental professionals have increased incidences of kidney disease, emotional instability, erethrism, pulmonary dysfunction, or other characteristics of occupational Hg^0 exposure.
- Studies that evaluate whether there is a genetic basis for sensitivity to mercury exposure and whether potential sex differences exist in the pharmacokinetics and toxicity of mercury.

9. Conclusions

Despite public controversy over the use of dental amalgam as a restoration material, this systematic evaluation of current peer-reviewed published studies did not reveal sufficient evidence to support a causal relationship between dental amalgam restorations and human health problems, with the exception of allergic reactions in some individuals. Urine mercury is the most valid measure of Hg^0 exposure due to amalgam restorations. Although the reported urine mercury levels of most populations are low (<2 μg Hg/L), it is expected that levels will be further reduced as dental hygiene continues to improve and patients elect composite materials over dental amalgam for cosmetic and perceived 'health' reasons. As noted in this article, many critical research gaps still exist. Well designed studies that enrol sufficient numbers of subjects and controls, and that address measurement of Hg^0 exposure, while considering confounding factors, should ultimately resolve this dental amalgam controversy.

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