

Review

Does Inorganic Mercury Play a Role in Alzheimer's Disease? A Systematic Review and an Integrated Molecular Mechanism

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Abstract. Mercury is one of the most toxic substances known to humans. It has been introduced into the human environment and has also been widely used in medicine. Since circumstantial evidence exists that the pathology of Alzheimer's disease (AD) might be in part caused or exacerbated by inorganic mercury, we conducted a systematic review using a comprehensive search strategy. Studies were screened according to a pre-defined protocol. Two reviewers extracted relevant data independent of each other. One thousand and forty one references were scrutinized, and 106 studies fulfilled the inclusion criteria. Most studies were case control or comparative cohort studies. Thirty-two studies, out of 40 testing memory in individuals exposed to inorganic mercury, found significant memory deficits. Some autopsy studies found increased mercury levels in brain tissues of AD patients. Measurements of mercury levels in blood, urine, hair, nails, and cerebrospinal fluid were inconsistent. *In vitro* models showed that inorganic mercury reproduces all pathological changes seen in AD, and in animal models inorganic mercury produced changes that are similar to those seen in AD. Its high affinity for selenium and selenoproteins suggests that inorganic mercury may promote neurodegenerative disorders via disruption of redox regulation. Inorganic mercury may play a role as a co-factor in the development of AD. It may also increase the pathological influence of other metals. Our mechanistic model describes potential causal pathways. As the single most effective public health primary preventive measure, industrial, and medical usage of mercury should be eliminated as soon as possible.

Keywords: Alzheimer's disease, inorganic mercury, neurotoxicity, selenium, systematic review

INTRODUCTION

Mercury (hydrargyrium = Hg) is well known as the most toxic, non-radioactive element, with a well-

described neurotoxicology [1–4]. There are various forms of mercury: Organic mercury and inorganic mercury (IM), which includes elemental mercury (Hg⁰) and mercury ions (Hg⁺ and Hg⁺⁺). Mercury has been used by humans since ancient times, when the Chinese and Romans used mercury sulfide (cinnabar) for red dye and ink. Widespread use of inorganic mercury started around 1830, when dental amalgams became popular, and calomel (mercury chloride) was used as teething powder in infants [5]. In the early 1900s, the organ-

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ic mercurial ethyl-mercury was synthesized, and has been used until today as a fungicidal and antimicrobial agent.

Mercury toxicity arises from several strands: Elemental or metallic mercury (Hg^0) is the only metal that is liquid at room temperature and can evaporate quickly. As mercury vapor, it is taken up via the lungs, and 80% of it is absorbed. Due to its uncharged monoatomic form, it is highly diffusible and lipid soluble. It crosses the blood-brain barrier easily, as well as the lipid bilayers of cells and cell organelles, such as mitochondria. Mercury vapor also penetrates the mucosa and connective tissue of the oral or nasal cavities and may be transported into nerve cells [6–8]. Intracellularly, it is oxidized from its comparatively inactive Hg^0 state to its ionic form, Hg^{++} . This mercuric ion reacts immediately with intracellular molecules or structures (e.g., enzymes, glutathione, tubulin, ion channels, or transporters), inhibiting their activities and interfering with normal cellular function.

Very low levels (180 nM) of Hg^{++} decrease glutathione levels (GSH) and increase oxidative and nitrosative stress, which may lead to cytotoxicity [9]. The extraordinarily high affinity of Hg^{++} for selenium, and selenoproteins (dissociation constant = 10^{-45}) [10] can disrupt cellular redox balance [11,12], especially in the brain, which uniquely depends upon selenoenzymes for antioxidant protection and hence selenium [13,14]. The role of extracellular thiol groups for the transport and absorption of organic mercurials is well described for methylmercury [15], but for IM, their role as a vector is still under discussion. When bound to a thiol group (e.g., cysteine) methylmercury can cross the blood brain barrier easily and is transported into glial cells and neurons using molecular mimicry [16], where it is converted to IM. Due to its charge it is less able to cross cell membranes and can be trapped in cells and held within the brain. Further, IM has a very high affinity for thiol groups and forms strong bonds with them, giving rise to the term “mercaptans” [15,17,18].

The brain is the major target organ for elemental, gaseous Hg^0 . The half-life of mercury in the brain is unclear. Modeling mercury deposition in the brain using autopsy data of traffic victims and intake streams through food yielded a half-life estimate of 22 years [19], and autopsies of proven clinical cases of Hg^0 poisoning have found high mercury levels in the brain as long as 17 years after the event [20,21].

In contrast, the half-life of mercury in the body is around 30 to 60 days [22]. IM binding to selenium is almost irreversible and contributes to its long-

term brain retention [23,24]. Mercury from gaseous sources, such as coal burning, and from human activities through waste water, is accumulated in the food chain, and comes back to humans mainly via fish as methyl-mercury. Methyl-mercury is also transported via the bloodstream to the brain, where it is again converted to IM. Administration of oral methyl-mercury to non-human primates yielded a plasma clearance half-life of 21 days, while the half-life for clearance of IM from the brain was too slow to be estimated (> 120 days) during a 28 day washout period [25]. IM outside of the brain is accumulated in the kidneys, and is slowly excreted.

The potential role for mercury toxicity in Alzheimer's disease (AD) stems from (i) the relevance of the gaseous phase of elemental mercury for the brain with (ii) subsequent transformation to ionic mercury, and (iii) the conversion of methyl-mercury to inorganic mercury (Hg^{++}) in the brain. Humans take in about 2.4 μg of organic mercury per week, if consuming one fish meal per week, 2.3 μg of which is retained [22]. The main source for the intake of Hg^0 are dental amalgam fillings [22]. Such fillings consist of 50% of mercury, which evaporates at a slow rate, but is released at a higher rate, when the fillings are put in place or removed. From this source, and other, less common ones, 1.2 to 27.0 μg of Hg^0 are taken up per day, and 1.0 to 22.0 μg of Hg^0 are retained. Other variable factors of mercury release include the number, age, and size of the fillings, the presence of dental alloys, individual chewing habits and drinking hot liquids, as well as bruxism.

AD, first described in 1907, is one of the major forms of dementia, with about 15–50% of over 80 year old elderly being affected [26–34]. Currently about 24 million people worldwide suffer from dementia, with the numbers projected to double every 20 years [29], and by 2050 nearly 1 in 45 Americans are predicted to suffer from AD [35]. Since the population of most countries is aging, the problem will continue to increase. As of 1998, the lifetime risk of a 55 year old healthy woman developing dementia was 33% compared to 16% for men [27].

Clinically, AD reveals itself through increasing cognitive decline, impaired attention and short-term memory, and, at later stages, other forms of cognitive incompetence, such as impaired language, face recognition, spatial orientation, and hearing. Pathologically, this is thought to result from a gradual build up of amyloid plaques that form as a consequence of amyloid- β ($\text{A}\beta$) being produced at a higher rate than can be removed [36]. Amyloid plaques induce inflammation and

free oxygen radical production, which eventually yields a self-reinforcing cycle of neuroinflammation, neurodegeneration, and further inflammation. A second, apparently independent process, involves hyperphosphorylation of the tau-protein, which leads to a breakdown of microtubules and the neuronal cytoskeleton. Accumulating neurofibrillary tangles (NFT) promote neuroinflammation and reinforce the cycle [37]. Both these processes play a pathological role in the causation of AD [38], potentially exacerbated by deficient micro-vascularization in the brain [31,39].

The degeneration process starts in the entorhinal cortex and the basal ganglia, especially in the nucleus basalis Meynert, spreads to the hippocampus, and eventually affects other parts of the cortex as well. Due to the loss of neurons of the projective cholinergic system, brain cognitive functions such as short term memory are the first to be noticeably affected.

At present, we do not know what causes AD. Several genetic factors contributing to AD have been revealed [36,40], however, no clear-cut genetic cause has been isolated. Apolipoprotein E (ApoE) genotype is a consistent risk factor [41–46], and the $\epsilon 4$ genotype confers up to a 15-fold risk relative to the $\epsilon 3$ genotype [47, 48], which is the most widely distributed, whereas the $\epsilon 2$ genotype is protective. However, it is not entirely clear, how this risk can be fitted within a mechanistic model. ApoE is a transporter protein that may also operate as a free-radical scavenger. It is important to notice here that all three ApoE forms consist of 299 amino-acids, and the only differences are that ApoE $\epsilon 4$ has an arginine in position 112 and 158, where ApoE $\epsilon 2$ has two cysteines, and ApoE $\epsilon 3$ one arginine and one cysteine [49]. Interestingly, cysteine contains a sulfhydryl, which is capable of binding metals, especially bivalent metals such as lead, copper, zinc, and mercury. This has led to the hypothesis that the well-known differential genetic epidemiology of ApoE might have to do in part with the differential detoxification capacity regarding mercury [50], and potentially other metals as well. The ApoE lipoprotein complex is taken up into neurons via the ApoER2 receptor. Selenoprotein P (SeP), which provides selenium for selenoprotein synthesis, is also taken up by ApoER2 [51]. Differential competition for uptake between ApoE isoforms and SeP might therefore affect selenoprotein status and vulnerability to oxidative stress. Notably, SeP is physically associated with both A β plaques and NFTs in the AD brain [52], further suggesting a role for impaired selenoprotein function in AD pathology.

Because of the potential relevance of mercury as a causal factor for initiating AD, we set out to system-

atically review the literature. Because of the apparent special relevance of IM, we restricted our review to this form of mercury. Other forms of mercury toxicity, such as ethylmercury added as a preservative to vaccines, or methylmercury from fish, or the presence of other metals, like aluminum or lead, may synergistically enhance IM toxicity. This will be reviewed separately.

METHODS

We aimed at capturing all relevant papers that contained the semantic fields of “Alzheimer”, “mercury” and “neurotoxic”, limiting them to IM, using the strategy most appropriate for each database. We searched the following databases: EMBASE (Excerpta Medica); HSDB (Hazardous Substances Data Base); XTOXLINE; MEDLINE; Biosis; Science Citation Index; Publisher databases of Kluwer, Springer, Thieme from their start date to 2006.

Since each database has a different structure and the thesaurus available differs among them, we devised a new search strategy for each one. A full report, containing each strategy in detail, can be obtained from the authors [53]. An example of the Medline search strategy is reproduced in Table 1.

We included studies using any type of research design and any type of work relevant to the topic of this review. We excluded studies that were published in a language other than German or English and that were irrelevant for this topic. All titles and abstracts of the references that were retrieved were scrutinized by two independent reviewers, and original papers retrieved. For each paper whose inclusion was not immediately clear, two reviewers discussed the inclusion and reached consensus in all cases. Reference lists of all included papers were hand searched for more relevant articles, again by two independent reviewers.

Duplicates were eliminated. References fulfilling inclusion criteria were checked as full papers, for inclusion by two independent reviewers. All articles were coded for their potential internal validity following the procedures adopted by Dettenkofer and colleagues [54]. Other types of publications were coded as animal experiments or *in vitro* experiments. Coding was done by two independent reviewers, and in case of differing opinion a third reviewer's opinion was heard. Controlled studies used, as a rule, unaffected controls that were normally matched for age and gender, unless specified otherwise. Trace metal detection followed the state of the art of the time and used mostly

Table 1
Example search profile: Medline

#	Search history	Results
1	exp Mercury Poisoning/	3067
2	exp Mercury Compounds/	1883
3	Mercury/	11760
4	Dental Amalgam/	6745
5	amalgam\$.ti.	4408
6	mercur\$.ti.	9274
7	(mercury or mercury).rw.	12909
8	or/1-7 mercury, amalgam	22355
9	exp Organomercury Compounds/	8757
10	dementia/ or alzheimer disease/ or tauopathies/	45869
11	tau Proteins/	2905
12	exp Neurofibrils/	3680
13	exp Axons/	38597
14	exp Cytoplasmic Streaming/	6597
15	exp Nerve Degeneration/	14016
16	neurotoxicity syndromes/ or exp mercury poisoning, nervous system/	612
17	(neurotoxic\$ or neuro toxic\$ or neurodegenerati\$ or neuro degenerati\$ or neuropatholog\$ or neuro patholog\$ or neurophysiolog\$ or neuro physiolog\$).ti.	14556
18	or/10-17 Alzheimer, neurotoxicity	113817
19	(organic adj2 mercur\$).tw.	644
20	(organomercur\$ or organo mercur\$).tw.	490
21	(methylmercur\$ or methyl mercur\$ or phenylmercur\$ or phenyl mercur\$ or ethylmercur\$ or ethyl mercur\$ or aethylmercur\$ or aethyl mercur\$).tw.	3173
22	Mehg.tw.	507
23	or/19-22	4042
24	9 or 23 organic merury	10063
25	8 not 24 Exclude organic mercury	18828
26	18 and 25	272
27	(dement\$ or alzheimer\$).ti. important notions in title	32100
28	(17 or 27) and (5 or 6) important notions in title	73
29	28 not 24 exclude organic mercury	42
30	26 or 29 (combine notions in title and MeSH, specific search)	272
31	exp Nervous System Diseases/ci, pa, pp, et [Chemically Induced, Pathology, Physiopathology, Etiology]	537567
32	exp Nervous System/pa, ch, pp, de [Pathology, Chemistry, Physiopathology, Drug Effects]	380626
33	31 or 32 broader search with MeSH tree nervous system and nervous system diseases	793625
34	33 and 25 combine broader MeSH-trees withmercury	765
35	exp *Nervous System Diseases/ci, pa, pp, et specific: focussing on broader MeSH-Tree	277713
36	exp *Nervous System/pa, ch, pp, de more specific: focussing on broader MeSH-Tree	169402
37	35 or 36	405919
38	37 and 25 combine broad MeSH-Trees (focus) with mercury	438
39	exp case-control studies/ Nr. 39-66: search study designs	234292
40	exp Cohort studies/	466831
41	Cross-sectional studies/	47823
42	exp risk/	333093
43	Odds ratio/	18629
44	exp epidemiologic factors/	570299
45	or/39-44	1220586
46	et.fs.	1286714
47	ep.fs.	538694
48	ge.fs.	1159441
49	pc.fs.	518779
50	ae.fs.	782299
51	po.fs.	43531

Table 1, continued

#	Search history	Results
52	to.fs.	174881
53	ci.fs.	323514
54	or/46-53	3806275
55	et.xs.	4024450
56	54 or 55	4947481
57	cohort\$.tw.	60478
58	case control\$.tw.	25716
59	case comparison.tw.	255
60	case referent.tw.	458
61	risk\$.tw.	449172
62	(causation\$ or causal\$.tw.	28325
63	Odds ratio\$.tw.	32567
64	(etiolo\$ or aetiolo\$.tw.	117475
65	or/57-64	627662
66	45 or 56 or 65	5574948
67	30 and 66 (specific MeSHs and study designs)	223
68	38 and 66 (Focus MeSH-Tree and study design, more specific search)	361
69	34 and 66 (MeSH-Tree and study design, sensitive search)	608
70	(letter or editorial or comment).pt.	690654
71	Case Report/	1096485
72	70 or 71 publication types from 70 und 71	1688674
73	67 not 72 exclude these publication types from 70 and 71 (specific MeSHs) (163) (1 twice → 162)	
74	68 not 72 exclude publication types from 70 and 71 (MeSH Focus)	282
75	69 not 72 exclude publication types from 70 and 71 (broad MeSH)	478
76	74 not 73 (Focus MeSH without specific MeSHs)	206
77	76 or 73	369
78	75 not 77 (final MeSHs without specific and focus)	150
79	73 or 76 or 78	518
	Same strategy – locating reviews	
80	Review.pt.	961226
81	79 and 80 Reviews (all languages, all articles)	72
82	79 not 81 all articles, without reviews (all languages)	448
83	limit 82 to (german or english) limit articles to German and English	342 (1 in duplicate)

cold vapor fluorescence spectroscopy and instrumental neutron activation analysis.

Because of the extremely heterogeneous nature of the material, we present it in a condensed form and conduct a simple vote count, following the conclusions of the authors.

RESULTS

Out of the 158 studies deemed potentially relevant, 86 were included after in-depth scrutiny (precision = $86/1041 = 0.082$). Further checks of reference lists uncovered another 22 relevant studies. An updated search after one year produced another study. Out of these, 15 were only available as abstracts. One study was published twice. Further, 18 of these studies were reviews and were excluded, making the full sample 88 studies (see Fig. 1). A summary of findings is presented in Table 2.

One of the studies was a meta-analysis [55]. Out of 44 studies on documented mercury exposure in workers

the analysis synthesized 12 formally and quantitatively. Typical controls consisted in age and gender matched healthy individuals. The effect-sizes for attention measures and memory measures were significant and in the medium range (effect size g [according to Hedges and Olkin [56], a more conservative estimate of a standardized mean difference than the more widely used Cohen's d] = -0.46 for attention and $g = -0.40$ for memory) when exposed and non-exposed groups were compared. Exposed individuals excreted between 18 to 34 $\mu\text{g Hg/g}$ creatinine on average in urine. There was a dose-response relationship between mercury exposure and decrease in performance measures. All of the studies included in the meta-analysis are also primary studies in the present review.

Mercury exposure in workers

Studies on current exposure of workers to mercury [57–69] were mostly conducted on workers in industry (chlorine-alkaline factories, thermometer factories, mercury extraction plants), and in one case on gold

Table 2
Summary of findings

Category of study	Number of studies	Negative effects of mercury on memory and/or brain/brain function		Study design	Comments	
		yes	no			
<i>Studies in Humans Exposed to Mercury</i>						
<i>High Dose Exposures</i>						
Past and current exposure of workers [55]	1	1	1	Meta-analysis	Summary of studies; significant correlation between measures of cognitive functioning and Hg excretion in urine for a mean excretion of 34 µg; significant effect sizes for difference in cognitive performance measures between exposed and non-exposed for attention and memory; dose-response relationship	
Current exposure of workers [57-69]	13	10	3	Cross-sectional studies with controls, 1 longitudinal controlled cohort study	Current exposure documented; Hg excretion in urine correlated with measures of cognitive functioning; not always difference against controls in all measures	
Past exposure of workers [70-74,188-191]	9	8	1	5 retrospective cohort studies, 4 case histories	Past exposure to mercury documented; exposure dating back 5 to 30 years; two of the case histories likely covering the same two cases; the study with a 30 year retrospective focus found little evidence, but some neurological signs of mercurialism were still present	
<i>Low Dose Exposures</i>						
Dentists and dental personnel [75-86];	12	11	1	Comparative/cross-sectional	Relationship between strength of exposure (dentists vs. personnel), markers of exposure and test results	
General older population [87]	1	1	1	Cross-sectional	General population; blood Hg level and MMSE results	
Amalgam bearers [88-94]	7	1	5	1 cohort study	Studies on older individuals often do not take previous status into account; the only study with true amalgam free individuals shows effects	
<i>Studies in Alzheimer Patients</i>						
Living Patients [95-101]	7	3	1	3	Comparative cross-sectional	Most studies very small, no large, longitudinal studies; hardly any convincing evidence
Autopsy studies [102-110]	9	4	4	1	Case control studies	Studies assessed different areas of the brain, some in larger anatomical portions, some in more specific ones; time between autopsy and mercury analysis often very large with danger of evaporation
<i>Animal Studies</i> [111-119]						
In vitro Studies [9,112,119,122-135]	16	9	16	Experimental studies	Some studies only available as abstracts	
				Experimental studies	All studies confirm toxic effects of mercury on neurons or neuronal tissue, reproducing pathological signs of Alzheimer's disease	

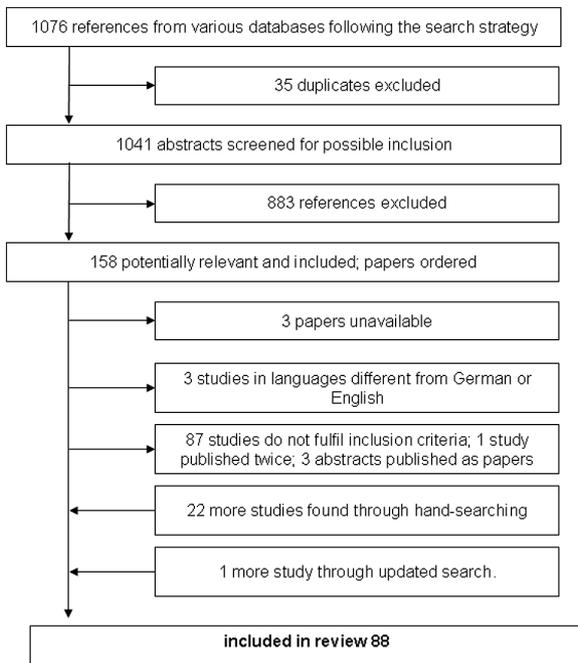


Fig. 1. Flow diagram of study inclusion.

miners in the Philippines who use large amounts of mercury without any protection [59]. Correlations between the amount of Hg excreted in urine and measures of cognitive abilities (memory tests, attention span) were always significant and negative, i.e., the more mercury excreted the worse the test results. Although all studies except one had control groups, the differences between exposed and control groups were not always significant and clear-cut. The Mt. Diwata Study [59] might give a hint as to why: although there was a significant correlation between mercury excretion and clinical symptoms, as well as test results, and although the workers were clearly exposed to large amounts of mercury, the correlations were moderate and showed great variation across individuals. Some individuals showed severe clinical signs of mercurialism, but excreted hardly any mercury, whereas others excreted much more, but had fewer clinical problems. Also, the control group living downstream by the sea showed little difference in excretion rates compared to the mercury exposed group. It is very likely, the authors concluded, that depending on individual factors mercury might be excreted at different rates and captured in body compartments for a long time, making urinary excretion of mercury a very unreliable marker both of mercury load and of clinical significance.

Studies on past exposures to high doses of mercury spanned times between five and 30 years after the ex-

posure. Five of these studies were on groups of workers after their exposure, four were case histories. Four studies [70–73] show evidence that workers exposed to mercury 5 to 18 years previously still had significantly worse results in neurological tests and clinical symptoms than those without significant exposure, even though one study had excluded all neurologically and psychiatrically ill persons. The study that found no significant differences [74] investigated workers 30 years after exposure. Although differences from controls were not significant, clinical signs such as tremor and lack of coordination were documented in exposed workers only.

Dentists and their staff are professionally exposed to low doses of mercury long term. All studies found significant correlations between level of mercury in blood, urine, nails, hairs, or air, and results for the tests used in the respective studies (neurological, psychological, or both) [75–83]. One study found more physical and psychological symptoms in dentists and their personnel than in controls [84], and one single-group cross-sectional study found moderate to severe deviations from norm results of a standardized neuropsychological test-battery (memory, attention, language tasks, visuo-spatial capacity) in 17% of the tested persons and one standard-deviation from population norms for the group as a whole [85]. One study that used sodium-2,3-dimercapto-propane-1-sulfonate (DMPS) found better correlations of symptoms and test results with mercury burden after the application of this chelating agent, which points to the fact that mercury can be trapped in body compartments [86]. Blood mercury levels and mini-mental state examinations (a standard examination to quickly assess cognitive functioning) do not always correlate, as can be seen in one general population study on low level exposure [87].

Health effects of dental amalgams

Studies on health effects in persons with amalgams have been largely negative [88–93]. The only study showing effects involved a young sample (mean age 22.4 and 23.3 years respectively), where the control group had never had any exposure to amalgam [94]. There was a positive correlation between number of fillings and mercury excretion in urine and hair, as well as with forgetfulness and symptoms. All other studies in this section investigated older people. Patients with no teeth left, usually the older ones, often did worse than those with teeth and amalgams. Clearly, without detailed knowledge of the previous history of dental treatment regarding actual mercury exposure it is difficult to draw any conclusions from such studies.

Mercury exposure, accumulation, and excretion in AD patients

AD patients are an obvious choice for studies of potential long term effects of mercury exposures. In a prospective cohort study there was a negative correlation between mercury content in nails and age or progression of dementia, respectively [95]. Since mercury content in nails reflects the mercury load over the past few weeks and its excretion, this finding means that more severely demented people do not excrete as much mercury as less severely ill patients. This might be due to the fact that their body is less able to excrete mercury, or mercury has been excreted earlier on, or perhaps a reduction in the proportion of mercury distributed to the periphery versus the brain with AD progression. Alternatively, this finding could indeed suggest that higher levels of mercury protect against severe AD, although this possibility is counter-intuitive.

A cross-sectional controlled study found differences: significantly more Hg in plasma and non-significantly more in cerebrospinal fluid of AD patients [96]. In a series of small studies there was more Hg excretion in urine of AD patients than in age-matched controls, and less Hg in blood of AD patients. These findings were, however, not significant due to the small sample size of nine patients only [97]. A retrospective cohort study found a probable exposure to mercury in 4.1% of 170 patients with AD and 2.4% likely exposure in controls, but the results relied upon retrospective recall by relatives [98]. One study found a non-significantly different higher amount of Hg in hair of ill patients compared with controls [99], while another found that the number of amalgam fillings was not different in 66 AD patients compared to controls [100]. AD patients had higher blood mercury levels in one study, which was correlated with higher A β levels in cerebrospinal fluid [101]. Four of nine autopsy studies document various changes in AD brains that are suggestive of mercury effects: One study treated brains of control persons with an EDTA-mercury complex and found that the interaction of GTP with β -tubulin was compromised similar to what they saw in AD brains [102].

Another study found significantly more mercury in 81 brain samples of 14 AD patients compared with age-matched controls, and more mercury in grey matter of AD brains compared with white matter. Mercury accumulated in the cerebellum, thalamus, putamen, and in the upper parietal and occipital lobes of AD patients' brains [103]. Thompson and colleagues found significantly higher mercury levels in the amyg-

dala, the nucleus basalis Meynert and non-significantly higher levels in the hippocampus of 14 AD patients compared with age-matched controls [104], while another study found significantly higher mercury levels in microsomes from AD brains [105]. One study reported higher mercury levels in brains and lower mercury levels in nails of 3 AD patients compared to 10 controls but due to the small patient number cannot be considered conclusive [106]. Four studies found either no significant differences or slightly and non-significantly lower levels in AD brains compared with controls [107–110].

Experimental animal and in vitro studies

Eight animal studies were included. Five of them showed that in rats which had been exposed to mercury vapors, mercury content of brain tissue was higher than in controls [111–115]. In one study where rats took up Hg⁺⁺ with food, GTP-tubulin interactions were observed that were similar to those known from AD brains [116]. Two studies found that Purkinje cells of the cerebellum were specifically prone to accumulate mercury after exposure of the animals [117, 118], while another one documented the inhibition of ADP-ribosylation *in vitro* and *in vivo* [119]. ADP-ribosylation inhibits tubulin polymerization and leads to depolymerization of microfilaments [120]. The latter finding is interesting in so far as ADP-ribosylation is an important DNA repair mechanism that is activated under conditions of oxidative stress which is normally found to be enhanced in AD patients [121].

In vitro studies produced the following results: Mercury interferes with polymerization of microtubules [122,123], increases secretion of both 1–40 and 1–42 forms of A β and promotes hyperphosphorylation of tau protein [9,124–127], changes mitochondrial structure inducing a stress-response in astrocytes [128], and interferes with cell-maturation [129] or other aspects of cell functioning, such as DNA repair, glutathione level, or linkage and structure of microtubules [119,130,131]. Mercury disturbs the interaction between tubulin and GTP [132], and the chelator DMSA can reverse this process [133], while amalgam exposure is toxic for nerve cells *in vitro* [134]. Mercury interferes with membrane structures, leading to axonal degeneration and neurofibrillary aggregates [135].

DISCUSSION

This systematic review produced a mixed and paradoxical picture: Experimental studies in animals and *in*

in vitro systems not only confirmed the well-known toxicology of mercury, but also reproduced the pathological signs of AD quite accurately and without any negative results: hyperphosphorylation of tau protein, the degeneration of microtubules, and the increased formation of A β protein. Animal studies also confirmed that mercury vapor, inhaled in low doses, accumulates in the brain.

Human studies, however, do not parallel this clear picture. Studies of exposed workers demonstrate quite clearly that continuous contact with mercury as an occupational hazard leads to effects on memory, attention and produces a variety of symptoms. Some of them, such as memory and attention deficits are relevant to AD, others, like sleep disturbance, mood swings or pain are rather non-specific. A meta-analysis confirms significant effect sizes, but they are only medium sized. Autopsy studies speak a mixed language: while some find more mercury content in brain tissues of AD patients, some do not. Some of the autopsy studies are fraught with potential problems: gross averaging of mercury content across large brain areas, long lags between autopsy and measurement, not taking into account the volatile nature of Hg. This may decrease Hg values in specimens through deposition of Hg in plastic test tubes over several months as described by Hock and colleagues [101]. In addition, the lack of staging of AD brains makes it impossible to draw firm conclusions especially from the studies reporting no effects.

Quite naturally, there is a lack of good evidence for our study question in human studies. Experimentation is prohibited for obvious ethical reasons, and evidence has to come from indirect sources. Exposure to high and low doses of mercury through the workplace has unequivocally led to neuropsychological deficits, both in workers (high doses) and in dental personnel (low dose exposure). The question not answered by our data is whether such mild cognitive deficits in attention and memory will transition into dementias. This question could only be answered by large longitudinal studies which do not exist. However, we do know from autopsy studies that brains of deceased persons without any clinical signs of dementia show pathological symptoms of degeneration pathognomic for AD at later stages [136], making it quite plausible that a pathological process might start many years before it manifests clinically as AD. Hence, it would be crucial to study larger cohorts of exposed persons longitudinally.

Epidemiological studies that have correlated the incidence of dementia with dental status have in general been unable to find any evidence for such a cor-

relation, and these negative findings are normally cited in support of the lack of harmful effects of amalgams. Most of these studies have investigated cohorts that were comparatively old and have used the present count of amalgam fillings to estimate the mercury load across a lifespan. None of these studies has taken into account the fact that most people who do not have teeth any longer at old age or who have dental repairs other than amalgam will have had amalgams in their teeth at previous times. This might explain the counterintuitive findings of some studies that many amalgam fillings correlate with better cognitive status: those with less fillings at present were likely to have had more earlier and thus have a higher likelihood of mercury accumulation in their lifetime and hence have a worse cognitive status at the time of measurements, when no fillings were present any longer, giving persons with "more amalgam fillings" a spurious benefit over those with "no or less amalgam fillings" [137,138]. Strictly speaking, such studies should not even be considered to bring clarity to the debate, since they are of doubtful methodological quality. However, since they are among the most cited ones we thought it is important to include these studies in the current review and qualify their validity. Indeed, the only study in our sample that had a completely amalgam free control showed effects: there was more excretion of mercury in urine and hair directly related to the number of fillings and more symptoms, including forgetfulness, in those exposed to amalgam compared to amalgam free controls. However, since the individuals in that study were rather young and no longitudinal data exist, this can only be taken as a hint. Longitudinal studies of cohorts completely free of amalgams compared with cases with amalgams would be a way of answering the question conclusively. These studies do not exist.

The findings of this review, thus, are paradoxical and pose a challenge: experimental data from animal research and *in vitro* studies strongly suggest an influence of inorganic mercury on the nervous system, but epidemiological and other studies suggest a much weaker relationship. It is likely that two processes play a modifying role here: Humans may be differentially susceptible to mercury toxicity, as compared to other species, and some individuals might be better able to chelate and detoxify mercury than others, reducing the strength of correlations between mercury exposure and AD.

A mechanistic model of mercury toxicity

Genetic risk factors for AD can provide the basis for differential susceptibility to the neurotoxic effects of

mercury, particularly since genetic variation is robust among humans, as compared to inbred laboratory animals. Thus the influence of any single factor in a multifactorial disorder such as AD is dependent upon the presence of other factors. For an environmental factor such as mercury, the extent of genetic loading, as well as the presence of other environmental factors, will determine the magnitude of its contribution. Indeed, in the absence of genetic risk factors, exposure to an environmental factor may not cause disease. In other words, an environmental stressor can reveal genetic limitations which otherwise might not be associated with pathological consequences. In the case of AD, age-related metabolic changes undoubtedly enhance risk, and mercury's high affinity for selenoproteins and thiols makes redox and methylation metabolism especially prominent targets for its toxicity [10–12,24,139].

The ability to maintain a homeostatic balance between reduction and oxidation (i.e., redox equilibrium) is essential for all cells, and the ability of selenium and sulphur to reversibly transfer electrons makes them ideal for redox buffering. This role is particularly important in the brain, since CSF levels of cysteine, the limiting material for glutathione synthesis, are more than 100-fold lower than in plasma [140], while oxygen consumption is disproportionately higher. To meet this higher demand for antioxidant, selenoproteins, such as thioredoxin reductases and glutathione peroxidases and SelP, play a more prominent role in the brain [13,14], and mechanisms have evolved to assure an adequate selenium supply to the brain, even when other tissues are depleted [14,141]. Selenoprotein mRNAs contain one or more UGA codons, which normally terminate translation but in the presence of a selenocysteine insertion sequence (SECIS) they effect direct incorporation of a selenocysteine into the nascent peptide chain. Selenocysteine tRNA is initially loaded with serine which is subsequently converted to a selenocysteine in a reaction with activated selenide (SeP) [142]. Mercury's extremely high affinity for selenium can potentially cause a functional selenium deficiency in the brain, interfering with its critical role in maintaining redox equilibrium.

SelP contains ten selenocysteine residues and is considered to be the primary source of selenium for cellular synthesis of other selenoproteins, which typically contain only a single selenocysteine in their active site [143]. SelP forms higher order multimeric complexes with inorganic mercury and free selenium, and, although it has 10 selenocysteines, and 17 cysteine residues, it has been estimated that a single SelP

molecule can bind more than 100 molecules of mercury [144]. Thus SelP not only serves as a selenium reservoir to support selenoprotein synthesis, but may also function as a high-affinity binding site for mercury, protecting other selenoproteins from its toxic effect.

In the brain, a remarkably high level of SelP is found in ependymal cells [145], whose asymmetric division gives rise to neural stem cells in the subventricular zone and subgranular layer [146,147]. Accordingly, ependymal cells have the highest level of glutathione, more than 10-fold higher than neurons, and 3-fold higher than astrocytes [148]. Mercury potently interferes with neural stem cell development [149,150], which could contribute to reduced cortical and hippocampal neuronal density in AD. SelP gene expression in human brain increases with age [151], and its expression level is higher in AD patients [152]. Moreover, SelP is preferentially associated with amyloid plaques and NFTs [52], which may limit its utilization for synthesis of other selenoproteins.

Neurons take up SelP via the lipoprotein receptor ApoER2 [51], suggesting that the adequacy of selenium supply to the cell might be related to the differential competition between variant forms of ApoE and SelP. Indeed, in a Chinese cohort, carriers of the ApoE4 allele had significantly lower selenium levels, as measured in nail samples [153]. ApoER2 also mediates signalling by reelin, which guides neural migration into layers of the cortex and promotes synaptic memory [154]. Increased levels of A β or low levels of SelP impair synaptic memory, which can be offset by increased reelin [155]. Thus ApoER2 is a critical nexus, at which the roles of SelP, ApoE, and A β are integrated, linking ApoE4 to selenium status.

Elevated plasma levels of homocysteine (HCY) in AD have been reported in numerous studies, as confirmed by a systematic review [156], and the rate of cognitive decline is related to the extent of HCY elevation [157]. Formed during methylation reactions, HCY is converted to methionine by the vitamin B12 and methyl-folate-dependent enzyme methionine synthase, which is highly sensitive to cellular redox status and is potently inhibited by mercury in cultured human neuronal cells [158] at levels found in post-mortem brain [159]. Plasma levels of B12 and folate are lower in AD patients [160–162], and a genetic polymorphism in methionine synthase (MTR 2756 C > G) has been associated with AD in several [163–165] but not all [166,167] studies. Similarly, genetic variants of methylenetetrahydrofolate reductase (MTHFR), which provides methylfolate for methionine synthase,

have been linked to AD in some studies [168–172], including a meta-analysis [173]. Lower methionine synthase activity increases levels of both HCY and S-adenosylhomocysteine (SAH), a general inhibitor of methylation, while lowering the level of the methyl donor S-adenosylmethionine (SAM). Lower SAM levels in CSF and brain of AD subjects have been reported by most [174–176], but not all [177] studies. The combined influence of lower SAM and higher SAH dramatically inhibits methylation reactions and the value of SAM/SAH is correlated with CSF levels of phosphorylated tau [178].

We recently found a progressive decrease in methionine synthase mRNA levels in human cortex across the lifespan, amounting to more than several hundred-fold Muratore et al., unpublished observation. Since lower methionine synthase activity increases diversion of HCY toward glutathione synthesis [179], this remarkable decrease appears to be an adaptive response to increased antioxidant demand with age, and implies that methylation capacity gradually decreases with age. Taken together, the above findings suggest that genetic variations affecting methylation metabolism may contribute to differential mercury susceptibility, and that impaired methylation may account for some of mercury's neurotoxic actions, particularly in aged individuals.

The mechanism linking impaired methionine synthase activity to the primary pathological features of AD has been greatly illuminated by recent studies detailing the regulation of protein phosphatase 2A (PP2A) by methylation [180–183]. PP2A is responsible for de-phosphorylation of tau and a decrease in its activity leads to tau hyperphosphorylation and formation of NFTs. Methylation of the catalytic subunit of PP2A, increases its activity and decreases tau phosphorylation, while folate-deficiency, which lowers methionine synthase activity, has the opposite effect [184]. Reduced PP2A activity also increases A β production, so impaired methylation can contribute to both NFTs and amyloid plaque formation [182].

An integration of the foregoing metabolic relationships is provided in Fig. 2. In summary, mercury's high affinity for selenium, and for SelP in particular, disrupts redox regulation, which inactivates methionine synthase, increasing HCY and SAH while lowering SAM levels. The resultant decrease in methylation of PP2A can promote tau hyperphosphorylation and A β secretion. Accumulation of A β can interfere with ApoER2-mediated SelP uptake, further limiting selenium availability and creating a self-reinforcing patho-

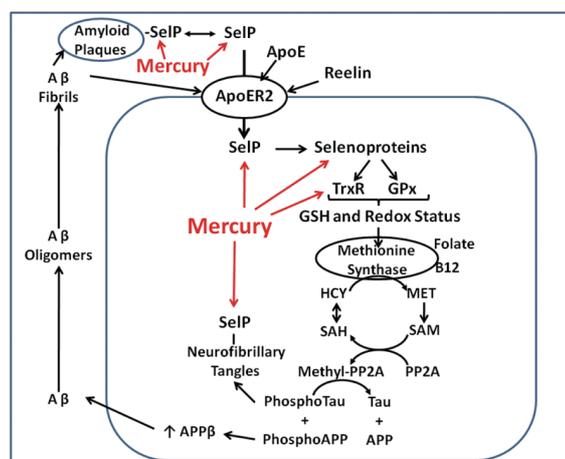


Fig. 2. Mechanistic summary of mercury actions in relation to the primary pathological features of AD. Formation of both A β -containing amyloid plaques and tau-containing neurofibrillary tangles is promoted by phosphorylation, which can be decreased by the protein phosphatase 2A (PP2A). PP2A activity is enhanced by its methylation, which is in turn dependent upon the ratio of SAM to SAH and the activity of methionine synthase, which is highly redox sensitive. During oxidative stress, methylation of PP2A is decreased favoring accumulation of hyperphosphorylated tau and phosphorylated amyloid precursor protein- β (APP β). Selenoproteins, including selenoprotein P (SelP), thioredoxin reductases (TrxR) and glutathione peroxidases (GPx), are critical for maintaining normal redox status in the brain, including adequate levels of reduced glutathione (GSH). SelP, the major source of intracellular selenium for synthesis of selenoproteins, is taken up via the apolipoprotein E receptor-2 (ApoER2), which also traffics ApoE and Reelin. Binding of SelP to amyloid plaques and neurofibrillary tangles may restrict selenium availability for selenoprotein synthesis, thereby promoting oxidative stress. The exceptionally high affinity of mercury for selenocysteine causes an essentially irreversible inhibition of selenoproteins, increasing oxidative stress and inhibiting the activity of methionine synthase, resulting in lower PP2A activity. By virtue of its high capacity for binding mercury, SelP, including SelP bound to amyloid plaques and neurofibrillary tangles, may partially protect other selenoproteins. Accumulation of mercury in the brain, in excess of the ability of SelP to fully buffer its toxicity, can therefore contribute to oxidative stress and apoptosis in AD.

logical cycle. The normal age-related decrease in methionine synthase causes this cycle to emerge in later life, particularly in the presence of genetic risk factors affecting redox buffering or methylation status. Moreover, we propose that the contributory role of accumulated mercury to AD disease depends upon these same genetic risk factors.

Our review of the literature has identified serious knowledge gaps: No solid longitudinal evidence exists, linking mercury toxicity with AD. At the moment, the evidence consists of pieces of the puzzle that are coherent and suggestive, but not absolutely compelling. Long-term studies are needed that could predict a tran-

sition from early stages of cognitive impairment to full-blown dementia as a function of mercury load through amalgams and other sources. However, individual differences in detoxification capacity and genetic vulnerability make this a daunting task. We hope that the mechanistic relationships outlined above provide a molecular framework which can help to clarify the relationship between mercury and AD.

The situation, it seems to us, is comparable to the status of knowledge in the 1970s regarding the relationship between smoking and cancer. There was some experimental evidence. There was a little epidemiological data. However, based on methodological dogma, a lot of the epidemiological evidence was dismissed. It was an uphill battle, mainly against strong economic interests, to make the public aware of the dangers and it took more than 20 years to transform knowledge into legislation and behavior. We have a very similar situation nowadays regarding the relationship between mercury and AD (and potentially other neurological diseases) [185–189]. The evidence is highly suggestive, but some links are missing. Inertia and economic interests due to the potential cost of litigation are drivers for maintaining the status quo, whereas the danger of inactivity and the huge costs of dementia care for public health urge us to become active. The data we have reviewed present a case for caution against complacency. There is a chance of false positives here and we might be overestimating the role of mercury on dementia, but the danger of doing so is comparatively small in the face of the danger of overlooking such a relationship or coming to a wrong negative conclusion. While there are clearly knowledge gaps to be filled, we feel that the available data are strongly suggestive of a potential causal link between mercury and AD. We therefore suggest the removal of mercury from public and ecologic circuits and replacing it wherever possible by less toxic alternatives. This would be a sensible public health measure that is supported by current data.

ABBREVIATIONS

SelP	–	Selenoproteine P
TrxR	–	thioredoxin reductase
GPx	–	glutathion reductase
GSH	–	glutathione
HCY	–	homocysteine
SAH	–	S-adenosylhomocysteine
SAM	–	S-adenosylmethionine
MET	–	methionin

PP2A	–	phosphatase 2 A
Phospho	–	phosphorylation
APP	–	amyloid precursor protein
Abeta	–	amyloid beta
ApoE	–	apolipoprotein e
ApoER2	–	apolipoprotein e receptor

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