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Lead and cognitive function in adults: A questions and answers approach to a review of the evidence for cause, treatment, and prevention

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Abstract
Lead has been extensively used worldwide in gasoline, consumer products, commercial applications, and industrial settings. Its use in gasoline and paint has been particularly hazardous to public health leading to widespread population exposure and substantial lifetime cumulative doses in most Americans over age 40 years. Cumulative lead dose can be estimated by measuring the current concentration of lead in tibia bone by X-ray fluorescence. A growing literature has documented that tibia lead levels are associated with decrements in cognitive function and declines in cognitive function over time. Furthermore, there are several interesting lines of biochemical and epidemiological investigation that have demonstrated potential links of lead to neurodegenerative diseases. These studies support the inference that a proportion of what has been termed 'normal' age-related cognitive decline may, in fact, be due to exposure to neurotoxicants such as lead. Well-designed studies of cumulative lead dose and Alzheimer's disease risk should be conducted to follow-up on these leads. The strong and compelling body of literature on lead and cognitive dysfunction and decline also supports a need for intervention studies to prevent lead-related cognitive decline.

Introduction and overview

'The United States is lead poisoned.' So writes Christian Warren in his comprehensive book on the subject entitled *Brush with death*: *A social history of lead poisoning* (Warren, 2000). The effects of this national poisoning were first investigated in children, with a strong focus on cognitive, emotional, behavioural, and other brain-related outcomes (Baghurst et al., 1995; Baghurst et al., 1992; Bellinger, Hu, Titlebaum, & Needleman, 1994a; Bellinger, Leviton, Allred, & Rabinowitz, 1994b; Bellinger, Leviton, Needleman, Waternaux, Rabinowitz, 1986; Lanphear et al., 2005; McMichael et al., 1994; McMichael et al., 1988; Needleman, 1973, 1979, 1992; Needleman, McFarland, Ness, Fienberg, & Tobin, 2002). In the clear light of historical investigation, it is now well documented that Robert Kehoe at the Kettering Laboratory at the University of Cincinnati, and other prominent researchers with heavy research funding from the lead industry, gained the power for decades to define what it meant to be lead poisoned (Flegal, 1998; Needleman, 1998; Warren, 2000), with a profoundly adverse impact on public health.

For decades, blood lead levels as high as 80 μg/dL of whole blood were considered normal, with claims that lead was naturally ubiquitous, a notion later disproved by Clair Patterson, a geochemist working with lead isotopes in geological samples to date the age of the Earth (Casanova, 1998). Lead appears to have first emerged in the general environment with the Romans, approximately 2000 years ago (Warren, 2000), supporting the conclusion that only very low levels of lead in blood could be considered normal before widespread human use began.

In this paper we discuss the occupational and environmental legacies of lead use with a specific focus on adult exposure and cognitive function and whether and how the long-term consequences of lead on the brain can be mitigated.

Methods

We relied on five previous reviews of the cognitive effects of lead in adults (Balbus-Kornfeld, Stewart,

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Bolla, & Schwartz, 1995; Ehle and McKee, 1990; Goodman et al., 2002; Meyer-Baron and Seeber, 2000; Shih, Hu, Weisskopf, & Schwartz, 2007) supplemented by PUBMED searches and cross-checking of references to ascertain whether any relevant papers had been missed. We cite all English language publications on adult lead exposure and cognitive function, but limit our more detailed review to recent studies that measured lead dose by both blood lead and bone lead, for reasons that will be discussed in detail below. To facilitate the presentation of results, we have organized the results of the review as a series of key questions and their answers.

Results in question and answer format

Why review lead and cognitive function in adults?

For decades, concerns about the brain effects of lead have been dominated by a focus on perinatal and childhood exposure, with unquestionable evidence of adverse short- and long-term cognitive and behavioral consequences. In contrast, adults were thought to be resistant to long-term cognitive consequences of lead exposure. Until recently, the numerous studies of adult lead exposure were too limited to offer convincing evidence for or against associations between cumulative lead dose and cognitive dysfunction (Balbus-Kornfeld et al., 1995). Most studies have been under-powered, focused on acute effects in current workers, and did not utilize a measure of cumulative exposure or dose. More recent evidence (Table I) (Shih et al., 2007) from larger comprehensive studies is compelling, motivating both a specific interest in the persistent neurotoxic effect of lead and a general interest in approaches to measuring the effects of neurotoxicants on the brain. In addition to this growing body of evidence, it is increasingly recognized that the brain continues to change throughout life (e.g., myelinating into the fourth and fifth decade of life) with possible age-specific periods of susceptibility to neurotoxicants. In this context, we consider whether lead mediates risk of common neurodegenerative conditions like Alzheimer's disease (AD). Finally, lead exposure in the 20th century represents the most significant human-induced environmental disaster in history with known profound effects on brains of children. It is thus logical to investigate whether there is also an effect in adults.

There are interesting linkages between the aging brain and neurotoxicant exposure. Neurodegenerative conditions may be the latent outcome of impairment throughout life, an overt endpoint that emerges when the structural integrity of the brain deteriorates (Calne, Eisen, McGeer, & Spencer, 1986). Sub-clinical premature neuronal loss (Gowers, 1902) caused by neurotoxicants, combined with neuronal loss associated with aging, is hypothesized as a causal process by which neurotoxicants exert a neurodegenerative effect, a model that may broadly apply. If normal age-related cell loss is hastened by neurotoxicants, minor shifts in individual trajectories can substantially influence variation in functioning in later life.

Why is there a concern about adult lead exposure? Didn't we eliminate it from most uses in the 1980s?

Once introduced into the environment, lead persists for decades and humans continue to be exposed. Lead in gasoline and paint have been dominant sources of environmental contamination. Other more selective exposures have occurred or continue in commercial products including solder (and thus drinking water pipes and tin cans), cosmetics, batteries (especially for automobiles), drugs, plastics, pesticides, lead crystal, and homemade alcohol (moonshine) from pipes and solder. Occupational exposure occurs at higher levels and is found in primary (from lead ore) or secondary (especially in recycling old car batteries) smelters and among potters, plumbers, pipe fitters, welders, sheet metal workers, painters (mainly in old paint removal by chipping, sanding, grinding, or burning), some cable workers (lead-shielded cables), and automobile mechanics (especially those involved with radiator repair). This pervasive use of lead accounts for its ubiquitous presence in soils and dust of cities, roadways, and indoor environments.

White lead (lead carbonate) was first added to paint in the late 19th and early 20th centuries, peaking in the early 1920s with over 150 tons of lead added to paint annually. Organic lead compounds were first added to gasoline in the 1920s with use peaking in 1969 with an annual production of more than 250 tons. Combustion of leaded gasoline causes inorganic lead to be distributed out the tailpipe and into the environment. An annual contamination of 250 tons of lead per year translates into almost 1 000 000 μg lead for every man, woman, and child in the USA (assuming a 1970 USA population of 200 million), an enormous quantity of distributed lead (Warren, 2000). Today, over 90% of lead in products is used in automotive batteries.

The average blood lead level in Americans was over 20 μg/dL in 1965 (Patterson, 1965). NHANES II measured blood lead levels from 1976 to 1980 (Pirkle et al., 1994), during a time of rapid decline in the use of lead in gasoline. Even during this period, the average levels were 12 to 15 μg/dL in all age groups, but steadily declined thereafter

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Table I. Selected key features of studies included in five reviews of lead and cognitive function in adults, 1990–2007.

Study	Included in reviews? Ehle, 1990	Balbus, 1995	Meyer-Baron, 2000	Goodman, 2002	Shih, 2007	Sample Size	Blood lead, μg/dL**	Tibia lead, μg/g	Summary of key findings for selected studies (with our comments)
Morgan, 1974†				Y		Oc = 195 C = NP	NP	NM	(Could not obtain reference) (Note that Morgan, 1974, Repko, 1975, Repko, 1977, and Repko, 1978 were performed by common investigators and may have had overlapping subjects)
Repko, 1975†				Y		Oc = 316 C = 112	Mean = 63	NM	(Could not obtain reference)
Milburn, 1976 (Milburn et al., 1976)		Y		Y		Oc = 16 C = 15	Mean = 61	NM	(Probably insufficiently powered)
Repko, 1977 (Repko, Jones, Garcia, & Corum, 1977)		Y				Oc = 85 C = 55	Mean = 46	NM	Exposed subjects were paid volunteers (concern about selection bias); no association of lead dose measures with cognitive function (cumulative dose not assessed)
Grandjean, 1978 (Grandjean, Arnvig, & Beckmann, 1978)	Y	Y	O			Oc = 42 C = 22	Median = 46	NM	(Considered of low usefulness by Balbus)
Haenninen, 1978 (Haenninen, Hernberg, Mantere, Vesanto, & Jalkanen, 1978)	Y	Y	Y	Y		Oc = 49 C = 24	Mean = 32	NM	(Considered of low usefulness by Balbus)
Repko, 1978†	Y		Y	Y		Oc = 85 C = 85	Mean = 46	NM	(Could not obtain reference)
Valciukas, 1978 (Valciukas et al., 1978)	Y	Y	Y	Y		Oc = 90 C = 25	NP	NM	Higher zinc protoporphyrin levels associated with worse performance in several cognitive domains (no assessment of cumulative dose)
Spivey, 1979 (Spivey et al., 1979)			O			Oc = 70 C = 35	Mean = 61	NM	(This paper focused on symptoms only)
Arnvig, 1980 (Arnvig, Grandjean, & Beckmann, 1980)	Y	Y	O			Oc = 9 C = 0	Mean = 69	NM	(Probably insufficiently powered)
Johnson, 1980†	Y	Y		Y		Oc = 403 C = 305	Mean = 56	NM	(Could not obtain reference)
Valciukas, 1980 (Valciukas et al., 1980)	Y	Y	O			Oc = 141 C = 265	Range = 30 – 80	NM	(Considered of low usefulness by Balbus)
Bleecker, 1982†	Y					Oc = 13 C = 20	Median = 72	NM	(Could not obtain reference)

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Table I. Continued.

Study	Included in reviews? Ehle, 1990	Balbus, 1995	Meyer-Baron, 2000	Goodman, 2002	Shih, 2007	Sample Size	Blood lead, μg/dL**	Tibia lead, μg/g	Summary of key findings for selected studies (with our comments)
Hogstedt, 1983 (Hogstedt, Hane, Agrell, & Bodin, 1983)	Y	Y	O	Y		Oc = 49 C = 27	TWA Mean = 48	NM	(Considered of low usefulness by Balbus)
Baker, 1984 (Baker et al., 1984)	Y	Y	Y	Y		Oc = 99 C = 61	Mean = 33	NM	(Considered of low usefulness by Balbus)
Campara, 1984 (Campara, D'Andrea, Micciolo, Savonitto, Tansella, & Zimmermann-Tansella, 1984)	Y	Y	Y	Y		Oc = 40 C = 20	Range = 45 – 50	NM	(Considered of low usefulness by Balbus)
Mantere, 1984 (Mantere, Hanninen, Hernberg, & Luukkonen, 1984)	Y	Y	Y			Oc = 24 C = 33	Mean = 29	NM	(Considered of low usefulness by Balbus)
Baker, 1985 (Baker et al., 1985)		Y				Oc = 36 C = 14	NP	NM	(Considered of low usefulness by Balbus)
Araki, 1986 (Araki, Yokoyama, Aono, & Murata, 1986)				Y		Oc = 19 C = 12	Mean = 42	NM	(Probably insufficiently powered)
Jeyaratnam, 1986 (Jeyaratnam, Boey, Ong, Chia, & Phoon, 1986)		Y	Y	Y		Oc = 49 C = 36	Mean = 49	NM	(Considered of low usefulness by Balbus)
Parkinson, 1986 (Parkinson, Ryan, Bromet, & Connell, 1986)	Y		Y	Y		Oc = 288 C = 181	Mean = 40	NM	Authors reported 'Dose-response analyses indicated that among lead-exposed workers, cumulative and current exposure were unrelated to neuropsychologic performance' (null association with cumulative exposure based on dichotomous comparison of 54 lead workers with > 13 years exposure duration with 81 controls)
Williamson, 1986 (Williamson and Teo, 1986)	Y	Y	Y	Y		Oc = 59 C = 59	Mean = 50	NM	(Focused on exposed versus non-exposed comparisons but blood lead not measured in 'controls')
Ahmed, 1987 (Ahmed et al., 1987)		Y				Oc = 45 C = 0	Mean = 68	NM	(A generally poorly conducted and controlled study)

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Ryan, 1987 (Ryan, Morrow, Parkinson, & Bromet, 1987)	Y		Y	Oc = 288 C = 181	Mean = 40	NM	Authors reported 'There is little support for the view that older adults with current blood lead levels in the low to moderate range are at risk for developing CNS dysfunction'
Yokoyama, 1988 (Yokoyama, Araki, & Aono, 1988)	Y	O		Oc = 17 C = 11	Mean = 40	NM	(Probably insufficiently powered)
Pasternak, 1989 (Pasternak et al., 1989)	Y	O	Y	Oc = 24 C = 29	Mean = 47	NM	(Probably insufficiently powered)
Stollery, 1989 (Stollery, Banks, Broadbent, & Lee, 1989)	Y			Oc = 91 C = 0	Mean = 50	NM	Authors reported '... workers with high blood lead concentrations showed clear impairment of sensory motor functions in the absence of correspondingly strong evidence for impaired processing and memory functions'
Dotzauer, 1990†		O		NA	NA	NM	(Could not obtain reference)
Espinosa, 1990 (Espinosa et al., 1990)			Y	Oc = 31 C = 31	Mean = 41	NM	Group differences only, no associations with blood lead levels (published in text book, not clear how peer-reviewed, small study, concerns about selection bias)
Braun, 1991†			Y	Oc = 41 C = 37	Mean = 53	NM	(Could not obtain reference; published in German)
Stollery, 1991 (Stollery, Broadbent, Banks, & Lee, 1991)	Y	O		Oc = 70 C = 0	Mean = 52	NM	(Focused on associations of recent exposure and dose measures; exposure duration not associated with cognitive function)
Maizlish, 1995 (Maizlish et al., 1995)		Y	Y	Oc = 43 C = 47	Mean = 42	NM	Group differences but no association of blood lead with cognitive function ('non-exposed' group had mean blood lead level of 15 μg/dL)
Bolla, 1995 (Bolla et al., 1995)			Y	Oc = 190 C = 52	Mean = 24	NM	(The main goal of this study was to compare lead- and solvent-exposed workers; lead associations were reported in greater detail in (Schwartz et al., 1993), a study that reported adverse associations of cumulative exposure measures with cognitive function)

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Table I. Continued.

Study	Included in reviews? Ehle, 1990	Balbus, 1995	Meyer-Baron, 2000	Goodman, 2002	Shih, 2007	Sample Size	Blood lead, μg/dL**	Tibia lead, μg/g	Summary of key findings for selected studies (with our comments)
Lindgren, 1996 (Lindgren, Masten, Ford, & Bleecker, 1996)			Y		Y	Oc = 467 C = 0	Mean = 36	NM	Higher integrated blood lead index, but not current blood lead, associated with worse performance in several cognitive domains
Bleecker, 1997 (Bleecker, Lindgren, & Ford, 1997)					Y	Oc = 80 C = 0	Mean = 26	Mean = 41	Higher blood lead associated with worse verbal memory, higher integrated blood lead index associated with worse visuo-motor performance
Chia, 1997 (Chia, Chia, Ong, & Jeyaratnam, 1997)			Y	Y	Y	Oc = 50 C = 97	Mean = 37	NM	Higher cumulative blood lead index associated with worse performance in two cognitive domains
Österberg, 1997 (Osterberg, Borjesson, Gerhardsson, Schutz, & Skerfving, 1997)			O		Y	Oc = 38 C = 19	Median = 38	NM	Null findings for blood lead and finger bone lead (probably insufficiently powered)
Haenninen, 1998 (Hanninen et al., 1998)					Y	Oc = 54 C = 0	NP	Mean = 35	Null findings with tibia lead (probably insufficiently powered)
Payton, 1998 (Payton, Riggs, Spiro, Weiss, & Hu, 1998)					Y	E = 141	Mean = 6	Mean = 23	Higher blood lead and tibia lead each associated with worse performance in several cognitive domains
Stokes, 1998 (Stokes et al., 1998)					Y	E = 533	Mean = 2	Mean = 5	Tibia lead not associated with cognitive function (very low tibia lead levels)
Pfister, 1999 (Pfister, Bockelmann, Darius & Wurthmann, 1999)				Y		Oc = 26 C = 48	Mean = 38	NM	(Published in German – not evaluated by us)
Stewart, 1999 (Stewart et al., 1999)					Y	Oc = 543 C = 0	Mean = 5	Mean = 14	Higher tibia lead associated with worse performance in four cognitive domains
Lucchini, 2000 (Lucchini et al., 2000)					Y	Oc = 66 C = 83	Mean = 28	NM	Dichotomous comparisons by integrated blood lead index; high group had worse performance than low group

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Schwartz, 2000 (Schwartz et al., 2000)	Y	Oc = 535 C = 118	Mean = 5	Mean = 14	Higher tibia lead associated with declines in cognitive function over time in several domains
Schwartz, 2001 (Schwartz et al., 2001)	Y	Oc = 803 C = 135	Mean = 32	Mean = 37	Higher blood lead associated with worse performance in several domains (in currently-exposed workers with high blood lead levels, acute effects of recent dose predominate)
Barth, 2002 (Barth et al., 2002)	Y	Oc = 47 C = 53	Mean = 31	NM	Higher blood lead, but not cumulative blood lead index, associated with worse performance in two domains (in currently-exposed workers with high blood lead levels, acute effects of recent dose predominate)
Wright, 2003 (Wright et al., 2003)	Y	E = 1031	Mean = 5	Mean = 22	Higher blood lead and tibia lead each associated with lower scores on MMSE
Weisskopf, 2004 (Weisskopf et al., 2004)	Y	E = 466	Median = 5	Median = 20	Higher patella lead (and less so, tibia lead) associated with declines in MMSE scores over time
Bleecker, 2005 (Bleecker et al., 2005)	Y	Oc = 254 C = 0	Mean = 28	NM	Higher integrated blood lead index associated with worse performance on verbal memory and learning
Schwartz, 2005 (Schwartz et al., 2005)	Y	Oc = 576 C = 0	Mean = 31	Mean = 38	Higher blood lead at baseline, changes in blood lead over time, and tibia lead at beginning of each follow-up interval each associated with worse performance in several cognitive domains
Winker, 2005 (Winker et al., 2005)	Y	Oc = 48 C = 48	Mean = 5	NM	Higher blood lead associated with worse performance in several domains; integrated blood lead index with fewer associations
Dorsey, 2006 (Dorsey et al., 2006)	Y	Oc = 652 C = 0	Mean = 31	Mean = 34	Higher blood lead associated with worse performance in several domains; associations with tibia lead and patella lead somewhat weaker

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Table I. Continued.

Study	Included in reviews? Ehle, 1990	Balbus, 1995	Meyer-Baron, 2000	Goodman, 2002	Shih, 2007	Sample Size	Blood lead, μg/dL**	Tibia lead, μg/g	Summary of key findings for selected studies (with our comments)
Shih, 2006 (Shih et al., 2006)					Y	E = 994	Mean = 4	Mean = 19	Higher tibia lead was associated with worse performance in all seven cognitive domains assessed; blood lead was not so associated
Winker, 2006 (Winker, Ponocny-Seliger, Rudiger, & Barth, 2006)					Y	Oc = 47 C = 48	Mean = 31	NM	Generally focused on group comparisons only
Weisskopf, 2007 (Weisskopf et al., 2007)					Y	E = 1089	Median = 5	Median = 20	Higher tibia or patella lead associated with declines over time in two cognitive domains
Total	14	21	22	22	20				

Abbreviations: C, controls; E, environmentally-exposed subjects; MMSE, Mini-Mental State Examination; NA, not applicable; NM, not measured; NP, not provided; O, considered but did not meet authors' inclusion criteria; Oc, occupationally-exposed subjects; TWA, time-weighted average blood lead levels; Y, yes.
*In occupationally-exposed only if controls were included or in all subjects in general population studies.
†Reference could not be obtained; most of these were chapters from textbooks, government reports, or published in languages other than English.

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(Pirkle et al., 1994), with a mean blood lead of less than 2 μg/dL in 1999-2001 (Muntner, Menke, DeSalvo, Rabito, & Batuman, 2005).

While ongoing sources of exposure have been substantially reduced, lead has accumulated in cortical and trabecular bones. Lead in cortical bone has a clearance half-time of two to three decades. The amount of lead that accumulates in the body is denoted the body burden of lead. Before the human uses of lead, the average body burden in a 70 kg adult was estimated at 2 mg; today, the average body burden is estimated to be between 90 and 400 mg, or 45 to 200 times the 'natural' levels (Patterson, 1965). Individuals who are currently 50 to 80 years of age have thus accumulated substantial body burdens of lead. As bone demineralizes with age, especially in women, lead can be released back into the bloodstream and gain access to critical target organs, including the brain.

How is lead dose measured and what does it mean?

Lead can enter the body and be excreted through several different routes. Measuring the amount that stays in the body is conceptually complex and involves the use of sophisticated technology. We first consider the toxicokinetic model for lead, the model that defines absorption, distribution, metabolism, and excretion of xenobiotics. In this framework, we will see that blood lead is a measure of recent dose, and tibia bone lead is a measure of cumulative dose. The term 'exposure' refers to lead external to the body and 'dose' to lead inside the body. For a review of lead and cognitive function, the most relevant dose is brain dose; since this is not available, we must consider the degree to which the available dose metrics are reasonable surrogates for cumulative brain dose.

Lead can be internalized through various routes (e.g., absorbed by inhalation, ingestion, and dermal for organic forms) and gains access to the bloodstream. Absorption depends on the route (Hursh and Suomela, 1968), levels of exposure, lead form, particle size, ventilatory rate, and other factors. After gaining access to the bloodstream, lead binds to several erythrocyte proteins (Bergdahl et al., 1997; Castellino, Castellino, & Sannolo, 1995; Ong and Lee, 1980; Raghavan and Gonick, 1977). The binding of lead by erythrocytes is important in determining its clearance half-time from blood. On average, erythrocytes have a 120-day lifespan and this explains in large part why lead has approximately a 30 to 35 day clearance half-time from blood (Rabinowitz, Wetherill, & Kopple, 1976). Lead leaves the blood either through excretion (i.e., primarily via urine) or by deposition in most organs, importantly including both brain and bone.

Lead crosses the blood-brain barrier in adults, apparently quite rapidly (Bradbury and Deane, 1993). Lead levels in plasma and cerebrospinal fluid are correlated, suggesting that lead leaves its binding sites on erythrocytes, enters the plasma, then gains access to the brain (Cavalleri, Minoia, Ceroni, & Poloni, 1984). Lead, through direct toxicity, is thought to alter blood-brain barrier function (Zheng, 2001). In the brain, lead is apparently widely deposited, but evidence is mixed as to whether deposition and clearance of lead varies by brain region (Widzowski and Cory-Slechta, 1994), as there may be preferential concentration of lead in such areas as the hippocampus and hypothalamus (Cholewa, Hanson, Jones, McNally, & Fand, 1986; Lever and Scheffel, 1998).

Lead is also deposited in the hydroxyapatite crystal of bone, apparently mimicking calcium in its uptake and deposition there (Rabinowitz, 1991) and is of interest because it can be measured and used as a 'dosimeter'. Bone lead stores far exceed those in other storage pools. Lead in cortical bone has a residence time of 25 to 30 years (Todd and Chettle, 1994; Todd and Landrigan, 1993). Cortical bone, also known as dense lamellar bone (e.g., tibia), has lead deposited decades ago that may be less bioavailable over time. Trabecular bone, also known as spongy bone (e.g., patella, calcaneus, rib, vertebral body), has more complex kinetics, with various models identifying three or more phases of elimination with clearance half-times of weeks, months, and years, respectively, but an overall clearance half-time of probably three to five years (Leggett, 1993; Tsaih et al., 2001).

Lead in bone can be measured by ^{109}Cd-induced K-shell X-ray fluorescence (XRF) (Chettle, Scott, & Somervaille, 1991; Todd and Landrigan, 1993; Todd, McNeill, & Fowler, 1992), as concentration in micrograms of lead per gram bone mineral. This is a low radiation dose technique that requires approximately 30 minutes to complete. Although the hardware to perform the measurement is relatively inexpensive, the systems are nonetheless not widely available, with only about six or seven groups using systems in research settings in North America. The measurement has been validated in a variety of ways (Todd, Moshier, Carroll, & Casteel, 2001) and is also highly reliable (Todd, Ehrlich, Selby, & Jordaan, 2000). Although lead is deposited in both brain and bone, and it can be measured in the latter site long after deposition occurred, we do not know the degree to which cumulative deposition in the two sites is correlated. Lead that is measured in cortical bone offers an estimate of lifetime retained cumulative dose. Lead in trabecular bone, most often measured in calcaneus or patella, is an estimate of bioavailable bone lead stores available for redistribution to blood.

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It should be noted that if historical blood lead levels are available, the area-under-the-curve of blood lead levels versus time, termed the cumulative blood lead index (CBLI) or time-integrated blood lead (IBL), is highly correlated with tibia lead levels and is also treated as a surrogate for cumulative lead dose (Roels et al., 1995). Thus, because lead can accumulate in the body, the resulting 'body burden' is approximately 90–95% contained in bone, 3–5% in soft tissues, and 2–5% in blood.

In summary, blood lead is mainly an estimate of recent dose (from both internal and external sources) and tibia lead of lifetime cumulative dose. By measuring both in epidemiologic studies, researchers can separate the acute effects of lead on the brain that are explained by recent exposure (i.e., blood lead), which are more likely to be reversible, and the chronic effects of cumulative dose (i.e., tibia lead), which are more likely to be irreversible.

What is the evidence that adult lead exposure affects cognitive function?

Epidemiologic investigations of adult lead exposure and cognitive function have included subjects with current occupational exposure, past occupational exposure, and non-occupational, environmental exposure to lead, and the methods used to measure exposure or dose have differed across studies. Occupational exposures are generally higher than environmental exposure to lead. Studies of currently exposed workers pose challenges in separating the acute effects of recent dose from the chronic effects of cumulative dose. Study of workers with past exposure, especially using a longitudinal design, allows better separation of reversible, persistent, and progressive effects. Finally, studies of those with environmental exposure can include all adults, with a range of sociodemographic features, and usually better evaluation of the low to moderate end of the dose-effect range.

There have been five reviews of lead and cognitive function in adults from 1990 to 2006 (Table I). In the following sections, we will briefly summarize each of these reviews, but then focus on the recent review by Shih et al. because it only included studies that measured both blood lead and bone lead (Shih et al., 2007).

Inclusion criteria. The five studies had different inclusion criteria for the studies that were considered as part of the review. Altogether, 55 separate papers were considered for inclusion by the five reviews. Ehle and McKee (1990) was a review of occupational studies with blood lead levels up to 60 μg/dL (as the 'upper limit of low-level industrial exposure') and did not utilize a measure of cumulative dose (Ehle and McKee, 1990). Balbus-Kornfeld et al. (1995) evaluated evidence for the association between cumulative exposure to lead and decrements in cognitive function (Balbus-Kornfeld et al., 1995). The Meyer-Baron and Goodman et al. papers (Goodman et al., 2002; Meyer-Baron and Seeber, 2000) were each apparently motivated by considerations in Germany regarding lowering the biological tolerance value for occupational exposure from 70 μg/dL, a level that was the regulatory limit since 1980 and thus only included occupational studies. Neither study considered cumulative lead exposure or dose. Shih et al. selected only occupational or environmental studies which compared blood lead to cumulative dose measures (e.g., tibia lead, CBLI, IBL) in their relations with cognitive function (Shih et al., 2007).

Key features of the studies in each review. Ehle and McKee included 14 studies with a median sample size of 49 lead workers and 33 subjects in the comparison group (Ehle and McKee, 1990). A total of 1391 lead workers were reported on. Most of the studies consisted of workers with moderate to high levels of exposure. No studies tried to estimate cumulative lead dose. Balbus-Kornfeld et al. included 21 unique studies from 29 published manuscripts, with a median sample size of 49 lead workers and 24 comparison subjects (Balbus-Kornfeld et al., 1995). A total of 1753 lead workers were reported on. No studies used an estimate of cumulative lead dose. The twelve papers that met the criteria for inclusion in the Meyer-Baron and Seeber review had a median number of exposed and control subjects of 55 and 53, respectively (Meyer-Baron and Seeber, 2000). A total of 1016 lead workers were reported on. The median blood lead level across studies was 45 μg/dL. Analysis was confined to associations of blood lead levels with cognitive test scores. The 22 papers included in the Goodman et al. review had a median number of exposed and control subjects of 50 and 37, respectively, and a total of 2460 lead workers were reported on (Goodman et al., 2002). Associations were evaluated with blood lead levels only.

The review by Shih et al. was very different from the prior four reviews (Shih et al., 2007). These authors only included studies that measured both recent and cumulative dose. Thus, only two of the 20 papers in Shih et al. had been included in a prior review. This review included papers that studied subjects with current occupational exposure, past occupational exposure, and only environmental exposure to lead, and many were population-based studies, minimizing the possible selection bias of earlier studies, as well as including study participants

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across the entire dose-effect range for both blood lead and bone lead. Shih et al. also included four large longitudinal studies with good follow-up rates, also unique to this review. Furthermore, whereas none of the prior reviews had any papers that reported on 450 or more subjects, the Shih et al. review included 10 such papers, indicating that more recent studies were much more adequately powered. The median sample size (of only exposed subjects in occupational studies or all subjects in environmental studies) was 257 and a total of 7615 study participants were reported on. Because of large differences across studies in design, target population, source of lead exposure, and other key features, no pooled estimates of effect were reported.

Author conclusions. Ehle and McKee concluded that the literature did not allow inferences about the cognitive effects of lead exposure in adults (Ehle and McKee, 1990). Balbus-Kornfeld et al. concluded that the literature did not allow inferences about the effects of cumulative dose in adults (Balbus-Kornfeld et al., 1995). Meyer-Baron and Seeber concluded that the literature did allow inferences and that a blood lead concentration of 70 μg/dL could not be considered a safe limit (Meyer-Baron and Seeber, 2000). Goodman et al., in a study eventually determined to have been funded by the lead industry (Schwartz, Stewart & Hu, 2002; Seeber and Meyer-Baron, 2003), concluded that the literature did not allow inferences about the neurobehavioral effects of exposure to 'moderate' blood lead levels (Goodman et al., 2002). Shih et al. concluded that '... at exposure levels encountered after environmental exposure, associations with biomarkers of cumulative dose (mainly lead in tibia) were stronger and more consistent than were associations with blood lead. Similarly, in studies of former workers with past occupational lead exposure, associations were also stronger and more consistent with cumulative dose than with recent dose (in blood). In contrast, in studies of currently exposed workers, associations are generally more apparent with blood lead; we speculate that the acute effects of recent dose may mask the chronic effects of cumulative dose' (Shih et al., 2007).

Summary evaluation of literature. Early studies were characterized by small sample sizes, reliance on blood lead levels as the sole dose measure, possible selection bias, highly varying cognitive test batteries, and other methodological challenges such as different approaches to confounding and modelling. The Shih et al. review included more large studies, more well-designed studies that minimized sources of bias, and more study subjects (Shih et al., 2007). We are most convinced by the studies in this review and support its overall conclusions (however, note that one of us is a co-author on the review and six of our papers are included in the review).

In summary, lead is associated with decrements in neurobehavioral test scores as a function of both recent and cumulative dose in both cross-sectional and longitudinal analyses. The magnitude of the lead associations across studies is moderate to large; for example, in one study, an increase along the interquartile range of tibia lead was equivalent in its association with cognitive test scores across all seven domains with which both age and tibia lead were associated with a median increase of 3.1 years of age at baseline (ranging from 2.2 to 6.1 years) (Shih et al., 2006). Associations differ across studies depending on current exposure status, level of current dose, level of cumulative dose, and whether analysis is focused on current test scores or declines in test scores over time. The literature supports the conclusion that there is a strong and consistent association between lead dose and cognitive function, of a magnitude that is important at both the individual and population levels, and the body of evidence, including from longitudinal studies, animal toxicological studies, and mechanistic studies, supports the inference that this association is highly biologically plausible and likely to be causal.

Does lead cause psychiatric symptoms or psychiatric outcomes after adult exposure?

The relations of lead with psychiatric symptoms and psychiatric outcomes have been under-studied, despite ample evidence that lead affects the brain and the growing interest in the relation between the environment and psychiatric disease. Shih et al. reported that there is a moderate level of evidence for an association between psychiatric symptoms and lead dose (Shih et al., 2007). The associations appear to be confined to high levels of current occupational lead exposure (i.e., high current blood lead levels), or with cumulative dose in environmentally-exposed adults. Several studies have reported that elevated blood lead levels in adults are associated with depression, anxiety, irritability, and anger. For instance, at least three studies (Baker, Feldman, White, & Harley, 1983; Lindgren, Masten, Tiburzi, Ford, & Bleecker, 1999; Maizlish, Parra, & Feo, 1995) have used the Profile of Mood States (McNair, Lorr, & Droppelman, 1971). One cross-sectional study of 107 lead workers reported higher levels of depression, confusion, anger, fatigue, and tension among those with blood levels greater than 40 μg/dL (Baker et al., 1983). Another study reported that a cumulative dose estimate based on IBL was associated with tension, anxiety, hostility, and depression after occupational exposure (Lindgren et al., 1999).

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In occupationally-exposed South Korean lead workers (Schwartz et al., 2001), tibia lead was significantly associated with more depressive symptoms measured by the Center for Epidemiologic Studies Depression scale (Radloff, 1977). Rhodes et al. reported associations of 'modest' levels of blood, tibia, and patella lead with an increased risk of anxiety and depression in elderly men (Rhodes, Spiro, Aro, & Hu, 2003) using the Brief Symptom Inventory (Derogatis and Melisaratos, 1983).

Psychiatric symptoms may share the same neural substrates with components of cognition, and thus may be important to late-life cognitive function. Late-life depression is also associated with the risk of AD and a faster rate of cognitive decline (Wilson et al., 2002). Whether lead first causes cognitive dysfunction or depression, and then the other follows, is not clearly known, but it would seem clear that each are likely part of the adverse effect of lead on the adult brain. It is also possible that the inter-relations among lead dose, cognitive dysfunction, and depression may offer opportunities for intervention.

Finally, other recent studies raise additional concerns. For example, Opler et al. concluded, after extrapolation from maternal serum δ-aminolevulinic acid levels, that blood lead levels above 15 μg/dL were associated with an increased risk of schizophrenia spectrum disorder (Opler et al., 2004). This finding suggests that the risk associated with early life lead exposure could extend into later life, as schizophrenia mainly presents during the second decade of life and later (Opler et al., 2004). This association could be explained by hypoactivity of the *N*-methyl-d-aspartate subtype (NMDAR) of glutamatergic receptors (Guilarte, 2004), which is potently inhibited by lead. Despite the fact that these findings may be related to non-adult lead exposure it highlights the need for better research to examine associations between cumulative lead dose and adult psychiatric outcomes.

Are the long-term effects of adult lead exposure function-specific in the brain?

Lead can affect the brain in numerous ways, including the possibility of deposition or retention in selected brain regions (e.g., hippocampus and limbic system, prefrontal cortex, and cerebellum) (Finkelstein, Markowitz, & Rosen, 1998). It would not be surprising, therefore, to see that specific functions are affected by lead. However, as we have noted, numerous factors influence the ability to measure the effect that lead has on the brain and whether this effect is specific to one or several cognitive domains. While lead may initially cause persistent deficits to specific functions, progression (e.g., through a dying-back process) could result in pervasive changes affecting many more brain functions over time.

Nine studies (in 20 papers) obtained measures of cumulative dose, current dose, and cognitive function. These nine studies are diverse in terms of source of exposure (i.e., two environmental, seven occupational), current occupational exposure status (five current, two past), sample size (four with fewer than 70 exposed versus five with more than 400 exposed), and test batteries. Taken together, measures of cumulative lead dose were associated with decrements in function in a wide diversity of domains. The two studies of environmental lead exposure differ substantially. Tibia lead was associated with decrements in pattern composition performance in the Normative Aging Study (mean age 69 years, 100% male) versus all seven cognitive domains in the BMS (mean age 59 years, 35% male). Age- and gender-specific effects could account for the difference. Among the occupational studies, cumulative dose was most often associated with decrements in verbal or visual memory, executive function, and attention. Not surprisingly, the most consistent associations for these domains are observed in the three large occupational studies (two current exposed, one past exposure). Less consistent associations were observed for visuospatial function and motor-related functions (e.g., visuomotor, manual dexterity, psychomotor).

Is there evidence that adult lead exposure affects brain structures?

Exposure to neurotoxicants could result in changes to dendritic density, reduced myelination, reduced cell density due to neuronal apoptosis, or other persistent changes supported by experimental evidence. There are numerous mechanisms of action (e.g., oxidative stress, damage to mitochondria, altered neurotransmitter storage and release) that could mediate these changes. As we have noted, there is extensive evidence that adult lead exposure results in cognitive deficits. Little is known, however, about how this occurs and whether there are structural changes in the brain associated with cumulative dose. While magnetic resonance imaging (MRI) data have been collected in several case series of lead-exposed individuals or very small occupational groups, only one study has examined the relation between cumulative dose and brain structure.

In our longitudinal study of former organolead workers exposed to both organic and inorganic lead, we obtained MRIs on 532 individuals (Stewart et al., 2006). We examined white matter (WM) lesions as well as grey (GM) and WM

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volumes of lobar regions and a subset of specific structures that were selected *a priori*. WM lesions were graded using the Cardiovascular Health Study ten-point scale (Fried et al., 1991), and 36% of subjects had WM lesion grades of one or greater. Increasing WM lesion grade was directly related to tibia lead levels ($p = 0.004$). The adjusted odds ratio for moving from the lower to the upper end of the inter-quartile range of tibia lead (i.e., from 12.3 to 31.6 μg Pb/g) was 2.21 for lesions of grade five or greater.

In separate analysis, we evaluated associations of tibia lead with brain volumes using both a regions-of-interest (ROI) and voxel-by-voxel approaches. In both analyses, higher tibia lead was associated with decreases in structural volumes. This finding paralleled what we observed for measures of cognitive function. In the ROI-based approach, statistically significant associations ($p < 0.05$) were observed for volumes of total brain, frontal and total GM, parietal WM, cingulate gyrus, and insula. The voxel-by-voxel analysis verified these results. Thus, in this relatively young cohort – over 60% were less than 60 years of age – with past exposure, cumulative lead dose was associated with substantial decreases in brain volumes, a finding consistent with our prior evidence on tibia lead and cognitive function. Both WM and GM were affected. However, we cannot state for certain that the structural effects we have observed are due to inorganic lead because these former workers had past exposure to both organic and inorganic lead.

Is the affect of adult lead exposure on the brain persistent or progressive?

There is compelling evidence that the effects of adult lead exposure on the brain results in persistent effects. While we suspect progressive effects also occur, obtaining convincing evidence poses unique challenges. We define persistent to mean that the effect of lead is not reversible. Remarkably, the question of persistence has challenged investigators for years, largely because, as noted, most studies of adult lead exposure have focused on workers with current exposure and did not obtain measures to separate the acute effects of lead from chronic longer-term effects. More importantly, the notion of persistence could not be evaluated until measures of cumulative dose or exposure were used in studies. In cross-sectional studies, persistence is inherent to the finding of a relation between cumulative lead dose and cognitive function and necessarily implies that some portion of the effect of past exposure to lead was not reversible. As we have noted, a number of the previously cited studies (Table I) offer compelling evidence that lead causes persistent changes to cognitive function.

Demonstrating that lead causes progressive change is more challenging and relatively few studies can begin to address this question. By progression we mean that the initial effect of a unit of lead dose is propagated, first leading to a persistent change and then ongoing change for some defined period of time thereafter in the absence of ongoing exposure. Progression can occur in a number of ways. Lead that remains in the brain for long periods of time can act as a chronic stimulus, activating ongoing pathophysiologic processes. Even if lead is eventually eliminated from the brain, it can cause a cascade of molecular changes that continue for some time after its elimination. Finally, if lead results in neuronal cell death, a dying-back can unfold and eventually result in death of other neurons. Progression is convincingly demonstrated in longitudinal studies of populations with past exposure; if change (decline) in cognitive function is associated with past cumulative dose, it is *prima facie* evidence of progression, as it indicates that a process of decline in function continues to unfold even in the absence of continued exposure and that the process is dose-dependent.

Only three studies have reported on populations in which exposure to lead ceased and where repeated measures of cognitive function were obtained after exposure ceased; two are studies of environmental exposure and one is the above-noted study of former organolead workers. In the BMS there was a weak association between tibia lead and declines in cognitive domain scores over time (currently unpublished data). This finding was in contrast to relatively strong associations observed at cross-section. The contrast between the cross-sectional and longitudinal analysis may suggest that the effect of cumulative lead dose in this population may be persistent, but perhaps not progressive. Alternatively, it may simply mean that a longer time period of observation is required to measure progression, as cognitive function in 'cross-sectional' analysis represented the cumulative change over time since first exposure, but in the longitudinal analysis in the BMS, change was only evaluated over 28 months. More convincing evidence of progression can be derived from the former organolead workers study, where, on average, repeated measures of cognitive function were obtained more than 15 years after exposure ceased. In this cohort, tibia lead was associated with longitudinal decline in verbal memory and learning, visual memory, and executive function (Schwartz et al., 2000).

Links et al. formalized a test of progression using data from the study of organolead workers (Links, Schwartz, Simon, Bandeen-Roche, & Stewart, 2001). Applying linear systems theory, they evaluated

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longitudinal change in cognitive function in relation to blood lead, tibia lead, and estimated area-under-the-curve of tibia lead versus time, and concluded that progressive changes had to account for some portion of the observed associations. That is, in these former workers, current blood lead levels were low and brain lead levels were thus presumed to be low, so lead must have gained access to the brain decades ago, caused lesions, and the functional effects of these lesions were progressive over the ensuing time period.

Since all older Americans were exposed to lead as children, how do we know the culprit is adult lead exposure, not early life exposure?

Environmental exposure to lead began to increase in the 1920s with the introduction of organic lead into gasoline. Environmental contamination was at its worst between 1950 and the early 1970s, after which lead was eliminated from gasoline. After this time, blood lead levels in Americans eventually dropped, on average, by 90%. While individuals who are between 35 and 55 years of age in 2006 had the worst exposure during the perinatal and early childhood period, any individual born between 1920 and 1970 was exposed during this time period as well as later in life. There are some animal studies that can also be brought to bear on this question. For example, chronic lead exposure has been reported to reduce adult neurogenesis in the dentate gyrus of the hippocampal formation in rats (Gilbert, Kelly, Samsam, & Goodman, 2005). This lead-caused reduction in the capacity for structural plasticity in the adult hippocampus (decreased survival of newly generated neurons) did not occur after only early life exposure to lead, but rather required exposure into later life. However, at this time it must be concluded that it is possible that cognitive effects observed today in studies of older adults with environmental lead exposures could be due to exposures that occurred in early life.

What is the mechanism of lead toxicity in the brain?

Weiss (2000) has written that toxicants could influence brain function in later life by three main mechanisms (Weiss, 2000): interference with brain development, leaving a legacy of diminished cognitive reserve, which would only become apparent decades later when age-related declines in the substrate of cognitive reserve become apparent; a direct neurotoxic effect at all ages; or a direct neurotoxic effect on the aging nervous system because of its reduced capacity to withstand toxic challenges.

There are a myriad of mechanisms that could mediate the neurotoxic effects of lead, including loss of neurons, vascular injury, reduced blood-brain barrier function (Zheng, 2001), oxidative damage, DNA damage (Fishel, Vasko, & Kelley, 2006), and programmed cell death (Krantic, Mechawar, Reix, & Quirion, 2005). Lead mimics calcium in many biochemical pathways which are very important to many aspects of brain function. Evidence suggests that on most protein targets the affinity of calcium-binding sites is greater for lead than for calcium, and lead is known to modify the activity of many calcium-binding sites. Because it can also non-specifically bind carboxyl and sulfhydryl groups of proteins, numerous structural or functional proteins can be altered. Several specific mechanisms are noteworthy because of their fundamental role in neuronal cell function. Inorganic lead activates calmodulin, a major calcium-binding protein in the brain, which in turn may influence many other cellular processes and calcium-dependent enzymes, including protein kinase C (Markovac and Goldstein, 1988), calcium/calmodulin dependent protein kinase II, and the phosphatase calcineurin (Sola, Barron, Tusell, & Serratosa, 2001). In addition, lead may affect proteins involved in voltage-gated calcium channels, calcium-activated potassium channels, ligand-gated ion channels, and $\alpha 7$ nicotinic acetylcholine receptors (Braga, Pereira, Mike, & Albuquerque, 2004; Guilarte, 1997; Marchioro, Swanson, Aracava, & Albuquerque, 1996; Mike, Pereira, & Albuquerque, 2000; Suszkiw, 2004), proteins known to be important to normal cognitive function and neuronal response to changes in intracellular calcium concentration (Sola et al., 2001). Lead can also influence Ca^{2+}-ATPase, which plays an important role in regulation of 'resting' intracellular free calcium ion concentration; in culture, nanomolar concentrations of lead decreased resting intracellular free calcium concentrations (Ferguson, Kern, & Audesirk, 2000). Lead appears to affect virtually every neurotransmitter system, with consistent evidence of neurotoxicity for the glutaminergic, dopaminergic, and cholinergic systems (ATSDR, 1999), the possible product of agonism or antagonism of calcium-regulated signalling. Finally, several calcium-regulated signalling pathways may also have a role in amyloid beta-induced synaptic dysfunction (Xie, 2004).

In animal toxicology studies, low to moderate lead levels (mean blood lead level of 18 μg/dL) induced the activation of several nuclear transcription factors in rat brain, including NF-κB, activator protein-1 (AP-1), c-Jun N-terminal kinase (JNK), mitogen-activated protein kinase kinase (MAPKK), and caspases (Ramesh, Manna, Aggarwal, & Jadhav, 2001). These multiple effects could certainly contribute to or be part of the mechanism of the

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neurotoxic effects of lead. Of particular relevance, caspase-associated apoptotic pathways and loss of synaptic circuitry have been implicated as a mechanism in AD (LeBlanc, 2005) and schizophrenia (Glantz, Gilmore, Lieberman, & Jarskog, 2006).

Does lead exposure explain disparities by race/ethnicity or socioeconomic status (SES) in cognitive function in adults?

It is well known that blood lead is associated with race/ethnicity and socioeconomic status, with substantially higher levels among African-Americans, Hispanics, and individuals in lower SES groups. It is also known that African-Americans and persons of low SES have lower cognitive test scores and varying risks of AD (Gurland et al., 1999; Schwartz et al., 2004; Tang et al., 2001). Could differences in recent or cumulative lead dose explain these disparities? We know that early life lead exposure reduces attained IQ; cumulative lead dose measured in adults is associated with cognitive dysfunction and decline in function over time; and blood lead levels were higher in African-Americans for decades. However, relatively little is known about whether these different observations are causally linked, as few studies have explicitly examined the relation between cumulative environmental doses and cognitive function in relation to race/ethnicity or SES.

Lin et al. (2004) reported on lead biomarker levels in 69 African-American volunteers in Boston, with a mean age of approximately 50 years; mean (SD) blood (μg/dL), tibia (μg/g), and patella lead (μg/g) levels were 3.0 (2.3), 12.9 (11.2), and 14.6 (15.4), respectively, levels that were not appreciably different from non-concurrent data obtained from whites in the same areas (Lin et al., 2004). In contrast, in the BMS, among 612 whites and 474 African-Americans aged 50 to 70 years randomly selected from study neighbourhoods in Baltimore City, there were no significant differences in current blood lead levels but large differences in tibia lead levels (Martin et al., 2006). The mean tibia lead levels in whites and blacks were 16.7 and 21.8 μg/g, respectively ($p < 0.05$), that is, African-Americans had tibia lead levels, on average, that were 31% higher than in whites. The race/ethnic difference in bone lead may in fact be under-estimated, as whites have a higher risk of bone demineralization with age than do African-Americans, and such bone mineral loss could lead to an over-estimate of bone lead concentration in whites (because the denominator of the bone lead concentration in μg lead per gram bone mineral is under-estimated in persons who have some bone mineral loss). Thus, in this first population-based study of tibia lead levels in older urban residents, there were large differences in cumulative lead dose by race/ethnicity. However, as has been recently discussed (Weiss and Bellinger, 2006), it can be extremely difficult to separate the effects of certain risk factors that are 'chained together' like low SES, poor neighbourhoods, race/ethnicity, and high body lead burdens, so the portion due to cumulative lead dose remains undefined.

Do the findings on lead and cognitive function have any relevance to the epidemiology of Alzheimer's disease (AD)?

A number of studies have provided varying levels of evidence that risk of chronic diseases (e.g., different forms of cancer, Parkinson's disease, kidney disease) is associated with past exposure to environmental or occupational toxicants. Often evidence that links such exposure to diseases first emerges from case-control studies, sometimes followed by retrospective studies of occupational groups. Establishing such a link with AD poses logistical and data collection challenges since very large studies are required to obtain a reasonable number of new onset cases of AD. In the absence of such a study, there are other sources of evidence to consider regarding the link between lead exposure and AD.

As we have noted, progressive declines in cognitive function may be associated with past lead exposure. If progression is occurring, it may lead to pervasive changes, affecting widely distributed neural networks involved in the integration of functions. More specifically, as previously discussed, our MRI findings of lesions to cortical association areas (i.e., para-limbic structures) would be consistent with our finding that the strongest associations with tibia lead were observed for verbal memory and learning, visual memory, and executive function. This finding is noteworthy as myelination appears to continue into later life (Bartzokis, 2004) in cortico-cortical association areas (e.g., inferior temporal, prefrontal, and temporoparietal regions) (Bartzokis, 2004; Braak and Del Tredici, 2004). Interestingly, these regions include cells with long but small caliber projections that may be particularly sensitive to the effects of exogenous insults (Scahill et al., 2003). The specificity of relation between tibia lead and selected brain regions in our study of former organolead workers is consistent with the notion that lead could promote or accelerate an age-associated region-specific neurodegenerative process in a locus relevant to dementing illnesses like AD (Braak and Del Tredici, 2004; Scahill et al., 2003).

We recently reported additional evidence that lead influences an AD-like pathophysiologic process. An interesting point is that for ubiquitous toxicants such as lead, true underlying gene-environment interaction could appear to be a genetic main effect in

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epidemiologic studies (Prince, 1998). We found evidence of effect modification by the apolipoprotein E (*APOE*)-ε4 allele on relations of tibia lead with neurobehavioral test scores in our study of former organolead workers (Stewart, Schwartz, Simon, Kelsey, & Todd, 2002). This provides some evidence for what Prince suggested, that the association of *APOE* with cognitive outcomes may actually be due to gene-environment interaction, but it appeared as a genetic main effect because of the ubiquitous nature of lead exposure. Recent studies have also linked lead to amyotrophic lateral sclerosis (Kamel et al., 2002) and Parkinson's disease (Gorell et al., 1997, 1999). Taken together, these clues are enticing.

Other linkages between AD pathology and lead have been increasingly recognized. For example, at nanomolar concentrations, lead increases the aggregation and sedimentation of amyloid beta *in vitro* (Basha et al., 2005; Davey and Breen, 1998). Amyloid plaques consist of 39 to 42 amino acid peptides (the 40 residue peptide is designated of $A\beta_{1\text{-}40}$); this aggregation appeared to have some specificity, as lead promoted aggregation of $A\beta_{1\text{-}40}$, while several other metals did not, and lead did not promote aggregation of other 'control' proteins such as bovine serum albumin. Furthermore, lead selectively accumulates in the protein fractions from both cortical GM and subcortical WM in patients with AD (Momcilovic et al., 2001). There are thus a number of interesting parallels between AD and the brain effects of lead exposure (Table II).

If lead affects cognitive function, are there any treatment options?

What is perhaps most stunning, regarding a chemical – lead – that has been used by humans for over 2000 years, and quite extensively so over the past 150 years, and whose myriad serious health effects have been documented for almost as long, is that there has never been a randomized trial of any treatment intervention in adults. Nonetheless, several treatment options have emerged.

Chelating agents – mainly EDTA (ethylene diamine tetraacetic acid) administered by vein and DMSA (dimercaptosuccinic acid) by mouth – remove lead from soft tissue and other lead stores and enhance urinary excretion, have largely been used to treat lead workers with high blood lead levels (some clinicians treat over 50 μg/dL while others not until over 80 μg/dL) and current symptoms attributable to lead (e.g., colic, joint pain, irritability, encephalopathy) (Kosnett et al., 2007). Blood lead levels can be rapidly lowered with these agents. Anecdotal reports suggest that acutely lead-poisoned individuals can have relief of the most severe symptoms with this treatment (Kosnett et al., 2007). However, if bone lead stores are high, blood lead levels can return over weeks to months to pre-chelation levels, requiring repeated courses of chelation. EDTA is generally administered as 2 grams per day for up to five days, while DMSA is administered as 10 mg per kg three times a day for five days followed by 10 mg per kg twice per day for 14 more days. These courses are repeated every four to eight weeks, as needed, to reach treatment goals, which is often relief of symptoms or a target blood lead level.

While chelation can rapidly lower blood lead levels, levels will decline on their own without chelation, although much more slowly. Chelating agents may actually alter the distribution of lead in adverse ways, for example, by redistributing lead from bone stores to brain (Cory-Slechta, 1988; Cory-Slechta, Weiss, & Cox, 1987). In clinical practice, we have believed that it is better to rapidly enhance the excretion of lead because in this way it is prevented from depositing in bone and becoming part of long-term body burden. Second, because there have never been any randomized trials of chelation or other therapeutic interventions, we do not know if chelation for blood lead at any level can prevent

Table II. Evidence for suggestive links between Alzheimer's disease and lead exposure from human, animal, and *in vitro* studies.

Characteristic	Alzheimer's disease	Lead exposure
Linked to aging	Yes	'Accelerated aging'
Anatomical correlates	Starts in specific areas	Deposits in same areas?
Early memory loss	Yes	Yes
Brain atrophy	Yes	Yes
Neuritic plaques	Yes	Increases amyloid β aggregation
Neurofibrillary tangles	Yes	Increases phosphorylation of tau
APOE connection	A risk factor for	An effect modifier of
White matter links	Yes (Braak and Del Tredici, 2004)	Increased prevalence and severity
Mild cognitive impairment (MCI) links	A risk factor	A possible association with (unpublished data from our Baltimore Memory Study)
Links to caspases	Yes (LeBlanc, 2005)	Yes (Ramesh et al., 2001)

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the long-term sequelae of lead dose, such as cognitive dysfunction and decline (Schwartz et al., 2005; Schwartz et al., 2001; Schwartz et al., 2000; Stewart et al., 1999), renal insufficiency (Weaver et al., 2003), hypertension (Martin et al., 2006), and cardiovascular mortality (Lustberg and Silbergeld, 2002). Finally, and very importantly, we want to emphasize that none of the writing in this section is meant to encourage the practice being commonly encountered in mainly non-traditional clinical practice of offering chelation, on non-standard and lower dose protocols, to subjects with low to moderate blood lead levels (i.e., blood lead levels of 5 to 30 μg/dL). An increasing recent concern is the practice of using hair lead to document 'elevated' lead levels (Frisch and Schwartz, 2002), then using low-dose, mainly oral, chelating agents over long periods of time to treat patients with non-specific symptoms such as memory 'fog' and other cognitive complaints, fatigue, low energy, achiness, and other mild somatic symptoms. There is no evidence that such treatment offers patients any benefit.

Calcium supplementation has also been discussed as a possible treatment intervention. Calcium supplementation can possibly decrease intestinal absorption of lead, decrease the deposition of lead in bone, and decrease the release of lead from bone over time (Bogden et al., 1992; Bogden et al., 1991; Bogden et al., 1995; Fullmer, 1995). While these toxicokinetic changes would seem to be of potential therapeutic benefit in the long-term prevention of lead-related health effects, to our knowledge, no randomized trials have investigated calcium supplementation approaches to prevent lead-related cognitive dysfunction and decline in adults.

A final possible treatment intervention hinges on the relations between lead dose, cognitive dysfunction, and depression or other psychiatric symptoms. Although it would seem plausible that treatment of depression could mitigate lead-related cognitive effects, to our knowledge, anti-depressants have never been evaluated for this purpose.

Are there any preventive interventions that are available to prevent lead-related cognitive decline as people age?

Lead has been extensively eliminated from most new uses in commercial and consumer products, so primary prevention, the minimization of future lead dose, has been largely addressed for the general population. Lead is still present in many work places, so occupational exposures are still commonly encountered. The standards of the US Occupational Health and Safety Administration (OSHA) allow blood lead levels as high as 40 μg/dL for a working lifetime (40 years), so this would result in a CBLI of 1,600 μg-years per dL. Using data from the studies previously mentioned that have examined relations between tibia lead and CBLI, this would result in a tibia lead level of 80 to 160 μg lead per gram bone mineral. These are very high regulatory allowances for recent and cumulative lead dose. These regulatory limits will not prevent lead-related cognitive dysfunction and decline in workers with occupational lead exposure. Primary prevention must be a focus of efforts to revise the OSHA lead standards.

However, as previously mentioned, most of the concern about lead that has been discussed in this review is lead exposure that has occurred over the past five decades, resulting in high lifetime cumulative lead doses and high current body burdens of lead in the majority of older Americans. This lead dose is likely to cause lead-related cognitive decline as these people age, and as this may be a progressive effect of cumulative dose, it is occurring at a time when lead levels in blood and brain are likely to be low. Thus, chelation is very unlikely to offer any benefit for prevention, because this cognitive dysfunction and decline is probably due to lead's effects on the brain decades ago, not currently. No studies have evaluated what can be done to prevent this expected lead-related cognitive dysfunction and/or decline. Thus, we discuss some ideas for potential interventions but none of these have been studied to date.

One interesting intervention strategy hinges on a number of recent observations concerning the interaction of enrichment or deficits in the psychosocial environment with lead exposure in causing decrements in cognitive function. One study has reported that environmental enrichment reversed the cognitive and molecular deficits induced by developmental lead exposure in rats (Guilarte, Toscano, McGlothan, & Weaver, 2003). Other studies have evaluated the interaction between 'environmental stress' and lead exposure on behavioural outcomes in rodents (Cory-Slechta, Virgolini, Thiruchelvam, Weston, & Bauter, 2004; Virgolini, Bauter, Weston, & Cory-Slechta, 2006; Virgolini et al., 2005; Virgolini, Volosin, Fulginiti, & Cancela, 2004). Finally, we have observed in the BMS that living in a neighbourhood with higher levels of psychosocial hazards (methods for neighbourhood psychosocial hazards scale in Glass et al., 2006) interacted with cumulative lead dose in associations with cognitive dysfunction. That is, the association of tibia lead levels with cognitive test scores was worse across quartiles of the neighbourhoods psychosocial hazards scale (manuscript in preparation). These data suggest that environmental psychosocial conditions may make individuals more susceptible to the influence of lead dose on cognitive function. If these observations are confirmed, it may suggest an opportunity for prevention of lead-related

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cognitive effects: environmental enrichment or improvement of neighbourhood psychosocial conditions.

Conclusions and recommendations

The legacy of occupational and environmental lead exposure on cognitive function and decline will be with us for decades to come, as Americans currently in their 50s, 60s, and 70s, with their high cumulative lead doses, age. Much is still not understood, such as whether inorganic lead exposure alone, especially after environmental exposure, can cause the structural changes in the brain that have been reported in former organolead manufacturing workers. An increasing number of mechanistic and epidemiologic studies highlight interesting possible links between lead exposure and AD, and this should motivate rigorous population-based studies of the relation of cumulative lead dose with AD risk. Finally, studies are needed to evaluate interventions to prevent lead-related cognitive decline with aging, as no such studies have ever been conducted.

Take-home points

- Lead is a ubiquitous neurotoxicant that contributes to cognitive dysfunction and decline in older adults
- The magnitude of the effect due to lead is substantial, on a par with decrements in cognitive function explained by aging; lead may thus be associated with accelerated aging in the brain

Future directions

- Well-designed studies measuring cumulative lead dose should evaluate associations with Alzheimer's disease risk
- Intervention studies should evaluate whether the longitudinal decline associated with cumulative lead dose can be prevented

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