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Review

Neurotoxicity of low-level lead exposure: History, mechanisms of action, and behavioral effects in humans and preclinical models

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ABSTRACT

Lead is a neurotoxin that produces long-term, perhaps irreversible, effects on health and well-being. This article summarizes clinical and preclinical studies that have employed a variety of research techniques to examine the neurotoxic effects of low levels of lead exposure. A historical perspective is presented, followed by an overview of studies that examined behavioral and cognitive outcomes. In addition, a short summary of potential mechanisms of action is provided with a focus on calcium-dependent processes. The current level of concern, or reference level, set by the CDC is 5 μg/dL of lead in blood and a revision to 3.5 μg/dL has been suggested. However, levels of lead below 3 μg/dL have been shown to produce diminished cognitive function and maladaptive behavior in humans and animal models. Because much of the research has focused on higher concentrations of lead, work on low concentrations is needed to better understand the neurobehavioral effects and mechanisms of action of this neurotoxic metal.

1. Introduction

Lead is a naturally occurring heavy metal that has been used since ancient times for its malleability, low melting point, high resistance to corrosion, and versatility (Gilfillan, 1965; Lewis, 1985; Markowitz and Rosner, 2003; Needleman, 1991; Woolley, 1984). Despite its toxicity, lead remains ubiquitous in modern life [Table 1]. Even after the closing of the last lead smelter in 2013, the U.S. ranks as a major global producer of lead over the last 20 years, only third to China and Australia (see U.S. Geological Survey, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016) [Fig. 1]. Modern uses of lead include leaded batteries, which have accounted for over 85% of lead production in the United States from 2005 to the present (see U.S. Geological Survey, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016). Several occupations remain at high risk for lead exposure, including workers who engage in the demolition of older buildings (ATSDR, 2007). In addition to the continued mining of lead and manufacturing of leaded products, the U.S. imports items with elevated lead levels, some of which are intended for use by children (CPSIA, 2012).

Lead does not degrade once mobilized. Consequently, significant health risks persist due to residual lead particles released into the environment decades ago (Canfield et al., 2003; Mielke et al., 1999). Leaded paint continues to be a problem because of deteriorating older buildings and lead-based vehicle exhaust from decades ago. Approximately 24 million homes have hazardous levels of lead-based paint or dust, and low-income families are eight times more likely to be at risk (HUD, n.d.; Raymond and Brown, 2015) [see Table 1 for a short history of lead, including bans and regulations]. Leaded particles from these sources and others settle into the soil and resurface with rainfall and construction.

In addition to leaded paint, leaded plumbing remains a modern problem. Under suboptimal conditions, older plumbing leaches lead into the water system (Tiemann, 2017). The recent incidence in Flint, Michigan was primarily due to improperly treated water from a new source causing lead to leach from water pipes and to contaminate the water supply (DeWitt, 2017; Young, 2017) [see Table 1 for a brief history of lead]. The concentration of lead in the water reached as high as 13,200 parts per billion (ppb), while the level of concern set by the Environmental Protection Agency (EPA) is 15 ppb (Torrice, 2016). Flint is not an anomaly (Pell and Schneyer, 2016). Lead is a modern problem that poses health risks and is easily transferred from the mother's bloodstream to the fetus, thus transcending generations (Detroit Department of Health and Wellness Promotion, 2005; Gardella, 2001; Gulson et al., 1997; Silbergeld, 1991; Téllez-Rojo et al., 2004; Weizsaecker, 2003).

An individual's lead burden is often measured by lead found in blood. The reference value, which is currently 5 μg/dL, is set according

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Table 1
Milestones in the history of lead.

Year	Event	Reference
6500 B.C.	First evidence of lead mine dates back to this period in Turkey	Bochynska, 2013; Needleman, 1991
3000 B.C.	Chinese used lead to manufacture coins	Schafer, 1956
2000 B.C.	Spanish used lead to manufacture coins Egyptians used lead as pigment in cosmetics	Walter et al., 1999; Woolley, 1984
500 B.C.- 300 A.D.	Romans used lead in cookware, food, and other applications	Needleman, 1991
200 B.C.	Nicander, a Greek physician-poet, offered an early description of lead poisoning	Needleman, 2009
< 100 A.D.	Dioscorides, the physician to the Roman Emperor Nero, asserted that "lead makes the mind give way," providing one of the first direct medical diagnoses of lead poisoning	Needleman, 1991; Woolley, 1984
1621	Lead first mined and smelted in the U.S. for production of bullets	Swiggett, 1917
1804	First white lead factory in the U.S.	Kessler, 2014
1891	National Lead Company is incorporated	Kessler, 2014
1897	Jefferis Turner, Queensland Australia pediatrician, diagnosed lead poisoning in children	Rosner et al., 2005
1904	Lockhart Gibson, American clinician, was attributed with the first scientific studies linking lead-based paint to neurotoxicity in children	Rosner et al., 2005; Gibson, 1904
1909	France, Belgium, and Austria were among the first countries to ban or restrict white lead from interior paint	Markowitz & Rosner, 2000
1918	Lead Industries Association promoted lead for use in children's products with a "Cater to the Children" campaign featuring the Dutch Boy	Markowitz & Rosner, 2000, 2003
1921	Edward Cornish, president of the Lead Industries Association, acknowleded in a letter to Harvard that "lead is a poison"	Markowitz & Rosner, 2000
1922	League of Nations banned white-lead interior paint and limited lead in exterior paint.	Gilbert & Weiss, 2006; Markowitz & Rosner, 2003
1922	Thomas Midgley Jr., first developed tetraethyl lead gasoline as an anti-knock compound	Kitman, 2000
1922	William Mansfield Clark of the Public Health Service warns against use of tetraethyl, calling it a "serious menace to the public health"	Kitman, 2000; Nriagu, 1990
1923	13 to 15 deaths and over 300 men suffered mental health issues in three GM automobile plants due to working with tetraethyl lead	Needleman, 1991
1936	U.S. increased production of leaded gasoline; 90% of gasoline sold in the U.S. contained tetraethyl lead	Nriagu, 1990
1955	Voluntary standard adopted to limit lead in paint to 1% by weight in the U.S.	Markowitz & Rosner, 2000
1971	Lead-Based Paint Poisoning Prevention Act passed to begin eliminating lead in paint in the U.S.	MMWR, 2012 www.hud.gov/sites/documents/20258_legislativehistory.pdf
1973	Environmental Protection Agency (EPA) calls for a phasing out of lead in gasoline	EPA (1996) https://archive.epa.gov/epa/aboutepa/epa-takes-final-step-phaseout-leaded-gasoline.html
1976	Toxic Substances Control Act enacted by EPA	EPA (n.d.) https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act
1978	Consumer Product Safety Commission (CPSC) enacted in the U.S. to ban white lead paint from indoor, residential use over 50 years after the ban is recommended by the League of Nations	MMWR, 2012 www.hud.gov/sites/documents/20258_legislativehistory.pdf
1986	Leaded material banned from the installation and repair of public water systems in both residential and non-residential facilities by the Safe Drinking Water Act (SDWA) [Proposition 65]	EPA (n.d.) www.epa.gov/dwstandardsregulations/use-lead-free-pipes-fittings-fixtures-solder-and-flux-drinking-water
1992	Title X of the Housing and Community Development Act enacted—Residential Lead-Based Paint Hazard Reduction Act	MMWR, 2012 www.hud.gov/sites/documents/20258_legislativehistory.pdf
1994	Third National Health and Nutrition Examination Survey (NHANES-III) study showed that U.S. blood lead levels declined by 78% from 1976-1991	MMWR, 1994 www.cdc.gov/mmwr/preview/mmwrhtml/00032080.htm
1995	U.S. banned use of lead in sealing canned foods	MMWR, 2012
1996	Clean Air Act banned sale of leaded fuel for use in on-road vehicles in a final step to phaseout tetraethyl from gasoline	EPA, 1996
1996	World Bank called for a worldwide phaseout of leaded gasoline and called lead one of the most serious health threats to large populations	Lovei, 1996
1999	U.S. Department of Housing and Urban Development (HUD) enacted Lead-Safe Housing Rule	Federal Register, 2001
2001	Lead dust and soil hazard standards are set	Federal Register, 2001
2000	42 countries phased out lead from petrol	Bulletin of the World Health Organization, 2002
2007	CPSC recalled 2 million toy units due to excessive levels of lead in paint and Mattel and Fisher Price were fined $23 million for violations	CPSC, 2009
2010	Healthy People 2020—Centers for Disease Control and Prevention (CDC) proposed health objectives to be achieved by the reduction of lead	CDC (n.d.)www.cdc.gov/nceh/lead/publications/10_217029A_Walker_HealthyHomesBooklet_101310_updated_WithCovers.pdf
2011	CPSC decreased the limit of lead by weight allowed in a product marketed toward children from 600 parts per million to 300 parts per million (ppm) in 2009 and to 100 ppm in 2011	CPSIA, 2012
2011	Reduction of Lead in Drinking Water Act lowered lead content in pipes and plumbing fixtures from 8% to .25% by weight	HUD, 2014
2014	Paint companies in California ordered to pay $1.15 billion for selling leaded paint against regulations	Kessler, 2014
2014	Flint Michigan's water system was contaminated by improperly treated water that caused leaching of lead from old plumbing.	DeWitt, 2017; EPA, 2016; Pell & Schneyer, 2016; Torrice, 2016

to the level of lead in blood in the highest 2.5% of children tested in the CDC National Health and Nutrition Examination Survey (NHANES) and is expected to be revised every four years using the two most recent NHANES surveys (CDC, 2017). Thus, the CDC level of concern is not based on toxicity as established by the scientific and medical literature. According to the latest NHANES data, the new 97.5th percentile of

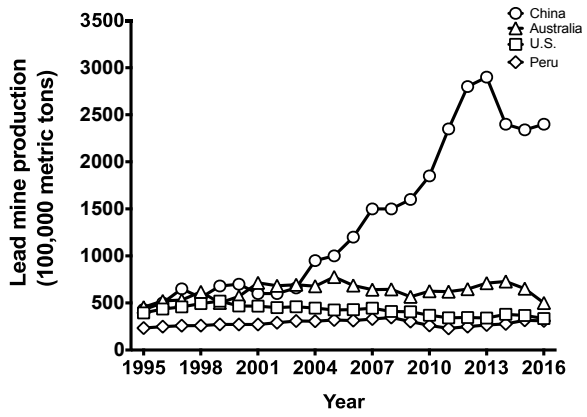

Fig. 1. World mine production of lead by year in 100,000 metric tons. The U.S. is third in the world production of lead behind China and Australia. Lead production in the U.S. has only minimally decreased over the decades in spite of the known harmful effects of lead.

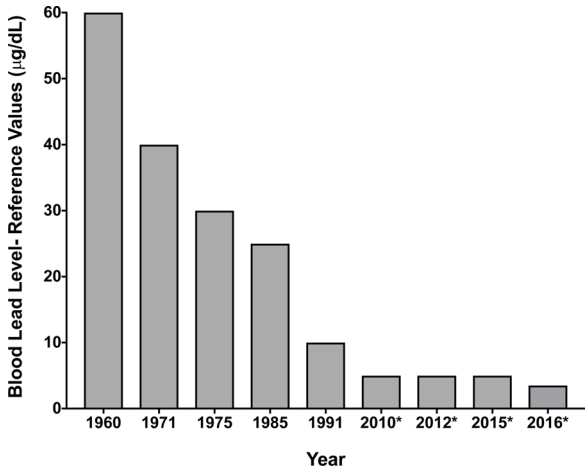

Fig. 2. Blood lead levels determined to be levels of concern, or reference values, by the Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP), a Centers for Disease Control and Prevention (CDC) workgroup. In 2010, the reference value was decreased to 5 μg/dL only for pregnant women, followed by a similar decrease in 2012 to include children. By 2015, the decrease also applied to adults. In 2016, a suggested decrease to 3.5 μg/dL was based on the latest National Health and Nutrition Examination Survey (NHANES) data outlining the current 97.5th percentile of blood lead levels in children.

blood lead levels in this age group recommends a revision of the reference level down to 3.5 μg/dL (Tsoi et al., 2016) [see Fig. 2]. This level of concern is down from 60 μg/dL in the 1960s to 10 μg/dL in 2015 (ATSDR, 2017; CDC, 2005, 2010a,b, 2017; Gilbert and Weiss, 2006; National Research Council, 1993) [see Fig. 2]). Blood lead levels are a good indicator of recent lead exposure due to a 30-day half-life. Bone lead levels are a better indicator of lifetime lead burden due to longer half-lives of 8–20 years and up to 50 years for trabecular/patella bone (e.g. knee cap) and cortical bone (e.g. tibia), respectively (Barry and Mossman, 1970; Farooqui et al., 2011; Hu, 1998; Hu et al., 1989, 1991; Kim et al., 1997; Wilker et al., 2011).

Though lead affects people of all races and socioeconomic backgrounds, there is a disproportionate lead burden placed on minority groups and lower income households (Glass et al., 2009; Lanphear et al., 2002; Mielke et al., 1999; Zierold et al., 2007). The highest percentage of children with blood lead levels greater than 5 μg/dL are non-Hispanic African-American children (46.8%), followed by Mexican-American children (27.9%), and non-Hispanic Caucasian children (18.7%) (Bernard and McGeehin, 2003).

The purpose of the current paper is to provide an overview of lead's neurotoxicity and mechanisms of action. This review is not intended to be comprehensive, but instead will highlight critical work in the field and offer recommendations for future research. Importantly, the evidence suggests that there are health consequences in humans and animal models at very low blood lead levels, below the concentration currently established by the CDC as a reference level.

2. Cognitive and behavioral effects of lead in humans

2.1. Cognitive effects in children

Effects of lead on cognition have long been known to occur at blood levels of 10 μg/dL and above. However, data suggest that significant effects are evident at levels below 5 μg/dL. Table 2 summarizes key studies on the cognitive and behavioral impacts of low blood lead levels in humans below 5 μg/dL and Table 3 summarizes those between 5 and 10 μg/dL. In children, blood lead levels below 5 μg/dL are associated with impulsivity and impairments in verbal processing, non-verbal reasoning, reading and arithmetic, as well as low scores in an array of achievement tests (Canfield et al., 2003; Chiodo et al., 2004; Lanphear et al., 2000). Attention is compromised at levels below 3 μg/dL in children as measured by simple reaction time, teacher report forms, and neuropsychological tests (Chiodo et al., 2004; Després et al., 2005; Min et al., 2007). These results are not surprising. In a longitudinal study decrements in IQ scores were more pronounced at blood lead levels below 10 μg/dL than above this level (Canfield et al., 2003). For example, in a large longitudinal study 1333 children were followed from birth or infancy until 5–10 years of age. Children with blood lead levels below 7.5 μg/dL showed a steeper decline in IQ for a given increase in lead concentration than children with lead levels higher than 7.5 μg/dL (Lanphear et al., 2005). These studies lend support for larger IQ decrements at lower blood lead levels.

In other studies, blood concentrations at or below 10 μg/dL produced neurophysiological and neurobehavioral deficits that could affect academic outcomes, including distractibility, memory deficits, decreased verbal and quantitative scores, impaired visual-motor coordination, and longer reaction times (Bellinger et al., 1991, 1992; Canfield et al., 2003; Chiodo et al., 2004; Dietrich et al., 1993; Jusko et al., 2008; Lanphear et al., 2000; Min et al., 2007; Needleman et al., 1990; Reuben et al., 2017; Stiles and Bellinger, 1993; Surkan et al., 2007).

In an 11-year longitudinal study of children starting at 2 years of age, high dentin lead levels closely predicted future high school graduation drop-out rates, lower class standing, greater absenteeism, impaired reading skills, and deficits in vocabulary, fine motor skills, reaction time, and hand-eye coordination (Needleman et al., 1990). Lead exposure, as quantified through blood, dentin, or bone, is strongly associated with educational achievement outcomes, such as IQ tests, reading and arithmetic tests, tests of attention, short-term memory, verbal and non-verbal reasoning; these deficits are observed even after adjusting for socioeconomic status, mother's age at the time of the child's birth, the reference caregiver's educational level and IQ (Bellinger et al., 1992; Braun et al., 2008; Canfield et al., 2003; Lanphear et al., 2000, 2005; Min et al., 2007; Needleman, 1979; Needleman et al., 1990, 1996; Stiles and Bellinger, 1993).

The impacts of lead on cognition were recently examined in another longitudinal study. A prospective cohort study of 1007 New Zealanders found that blood lead levels taken at 11 years of age (Mean: 10.99 μg/dL) accounted for lower cognitive function and a decline in socioeconomic mobility at 38 years of age (Reuben et al., 2017). Declines in IQ as measured by WAIS-IV full-scale, perceptual reasoning, and working memory at 38 years of age were associated with blood lead levels at 11 years of age. IQ verbal comprehension showed less of an association and processing speed at 38 years of age was not associated with earlier blood lead levels (Reuben et al., 2017).

Table 2
Human < 5 μg/dL. Summary of key studies in humans outlining the neurodevelopmental, cognitive, and achievement outcomes of blood lead levels below 5 μg/dL reported at $p < .05$. Excludes studies not explicitly reporting blood lead levels. Blood lead levels are listed as averages, unless otherwise noted, and appear as reported in respective studies. The most conservative adjusted statistical outcomes available are presented. Inclusion/exclusion criteria were established to determine study selection.[a]

< 5 μg/dL, Human

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
I. Verbal processing/memory					
Color Naming Task; Information Processing Speed	NS	< 3.0 μg/dL	n = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Color Naming Task; Information Processing Speed	Deficits	< 5.0 μg/dL			
WRAML; Verbal Memory Index	NS	3–4.0 μg/dL	n = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
II. Intelligence scale/achievement test					
WISC-III, Full-scale	NS	< 5.0 μg/dL	n = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
WISC-III, Full-scale	NS	3–4.0 μg/dL	n = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
WISC-IV, Short form & WIAT-II	Deficits	0.4–3.47 μg/dL	n = 150 Cross-sectional; case control Regression-based path analysis No reference group	8–17 yrs	Nigg et al., 2008
WISC-III, Performance	NS	< 3.0 μg/dL	n = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
WISC-III, Performance	Deficits	< 5.0 μg/dL			
Stanford-Binet; Intelligence Scale	Deficits	< 5.0 μg/dL	n = 172 Longitudinal Nonlinear mixed model No reference group	24 mos & 120 mos	Canfield et al., 2003
WISC-R, Block Design	NS	< 5.0 μg/dL	n = 4853 Cross-sectional, NHANES-III Regression analysis using quartiles No reference group	6–16 yrs	Lanphear et al., 2000
WISC-III, Block Design	NS	< 3.0 μg/dL	n = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
WISC-III, Block Design	Deficits	< 5.0 μg/dL			
WISC-III Block Design	NS	3–4.0 μg/dL	n = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
WRAT-R; Reading Subset	Deficits	< 5.0 μg/dL	n = 4853 Cross-sectional, NHANES-III Regression analysis using quartiles No reference group	6–16 yrs	Lanphear et al., 2000
WIAT, Reading Composite	NS	3–4.0 μg/dL	n = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
WRAT, Arithmetic	Deficits	< 5.0 μg/dL	n = 4853 Cross-sectional, NHANES-III Regression analysis using quartiles No reference group	6–16 yrs	Lanphear et al., 2000

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Table 2 (*continued*)

< 5 μg/dL, Human

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
WISC-III, Arithmetic	NS	3–4.0 μg/dL	*n* = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
III. Attention					
Child Behavior Checklist-Attention Teacher Report Form	Deficits	< 3.0 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Child Behavior Checklist-Attention Teacher Report Form	NS	< 5.0 μg/dL			
Barkley Inattention	Deficits	< 3.0 μg/dL			
Barkley Off-Task	NS	< 3.0 μg/dL			
Barkley Off-Task	Deficits	< 5.0 μg/dL			
Continuous Performance Test-Sustained Attention	NS	< 5.0 μg/dL			
Mental Rotation; Reaction Time	NS	< 5.0 μg/dL			
Catsys System; Reaction Time	Deficits	< 3.0 μg/dL	*n* = 110 Longitudinal Regression analysis No reference group	Birth & 4–6 yrs	Després et al., 2005
IV. Impulsivity/perseverative errors/cognitive flexibility					
Stop Signal Reaction Time Task	Deficits	0.4–3.4 μg/dL	*n* = 150 Cross-sectional; Case–control Regression-based path analysis No reference group	8–17 yrs	Nigg et al., 2008
Wisconsin Card Sorting Task	NS	3–4.0 μg/dL	*n* = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
Matching Familiar Figures; Match to Sample	NS	< 3.0 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Matching Familiar Figures; Match to Sample	Deficits	< 5.0 μg/dL			
V. Withdrawn					
Child Behavior Checklist-Withdrawn Teacher Report Form	Deficits	< 3.0 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Child Behavior Checklist-Withdrawn Teacher Report Form	NS	< 5.0 μg/dL			
VI. Short-term memory/working memory					
WISC-R; Digit Span	NS	< 5.0 μg/dL	*n* = 4853 Cross-sectional, NHANES-III Regression analysis using quartiles No reference group	6–16 yrs	Lanphear et al., 2000
WISC-III, Digit Span; Backwards	NS	< 3.0 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Sternberg Short-Term Memory Task; Processing Speed	Deficits	< 3.0 μg/dL			
WISC-III, Digit Span; Backwards	Deficits	< 5.0 μg/dL			
Seashore Rhythm Test; Auditory Working Memory	Deficits	< 5.0 μg/dL			
WISC-III, Digit Span	Deficits	3–4.0 μg/dL	*n* = 389 One test point 1–2 μg/dL, reference group	3–4 yrs	Surkan et al., 2007

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Table 2 (*continued*)

< 5 μg/dL, Human

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
VII. Visual-motor					
Beery Visual-Motor Integration	NS	< 3.0 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Beery Visual-Motor Integration	Deficits	< 5.0 μg/dL			
Bruininks-Oseretsky; Visual-Motor Control	NS	Neonatal Day 10: 4.8 μg/dL	One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
VIII. Dexterity/balance					
Catsys System; Balance	Deficits	4.1 μg/dL	*n* = 110 Longitudinal Regression analysis No reference group	Birth & 4–6 yrs	Després et al., 2005
Catsys System; Pointing Movements	Deficits				
IX. ADHD					
DSM-IV Criteria for ADHD	Association	1st tertile: 0.2–0.8 μg/dL 2nd tertile: 0.9–1.3 μg/dL 3rd tertile: > 1.3 μg/dL	*n* = 2588 Cross-sectional; NHANES (2001–2004) Regression analysis using tertiles No reference group	8–15 yrs	Froehlich et al., 2009
DSM-IV Criteria for ADHD-Combined	Association	3.4 μg/dL	*n* = 150 Cross-sectional; Case–control Regression-based path analysis No reference group	8–17 yrs	Nigg et al., 2008
DSM-IV Criteria for ADHD, Hyperactivity-Impulsivity Symptoms	Association				
DSM-IV Criteria for ADHD, Inattention-Disorganized Symptoms	NS				
DSM-IV Criteria for ADHD-Combined	Association	0.3–2.2 μg/dL	*n* = 150 Cross-sectional; Case–control Regression-based path analysis No reference group	6–17 yrs	Nigg et al., 2010
DSM-IV Criteria for ADHD-Predominantly Inattentive	NS				
DSM-IV Parent Report of Child's ADHD Symptoms (KSADS); Hyperactivity-Impulsivity	Association				
DSM-IV Parent Report of Child's ADHD Symptoms (KSADS); Inattention	NS				
DSM-IV Parent Report of Child's Cognition & Hyperactivity-Impulsivity (Conners)	Association				
DSM-IV Teacher Report of Child; ADHD Rating Scale & Inattention or Hyperactivity-Impulsivity	NS				
DSM-IV Teacher Report of Child's Cognition (Conners)	Association				
DSM-IV Teacher Report of Child's Hyperactivity & Impulsivity (Conners)	NS				
DSM-IV criteria for ADHD & ADHD-Combined	Increased incidence	1st tertile: 0.2–0.8 μg/dL 2nd tertile: 0.9–1.3 μg/dL 3rd tertile: > 1.3 μg/dL	*n* = 2588 Cross-sectional, NHANES (2001–2004) Regression analysis using tertiles No reference group	8–15 yrs	Froehlich et al., 2009
ADHD Assessed By Parent-Reported Medical Diagnosis of ADHD for Child & Child's Current Use of Stimulant Medication Use	Increased incidence (4.5-fold)	Lowest quintile (< 0.7 μg/dL) vs Highest quintile (2–5.0 μg/dL)	*n* = 4704 Cross-sectional, NHANES (1999–2002) Dose response measure 0.7 μg/dL or less, reference group	4–15 yrs	Braun et al., 2006

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Table 2 (*continued*)

< 5 μg/dL, Human					
Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
X. Conduct disorder					
DSM-IV Criteria for Conduct Disorder	Increased incidence	1st quartile: 0.2–0.7 μg/dL 2nd quartile: 0.8–1.0 μg/dL 3rd quartile: 1.1–1.4 μg/dL 4th quartile: 1.5–10 μg/dL	*n* = 3081 Cross-sectional, NHANES (2001–2004) Regression analysis using quartiles No reference group	8–15 yrs	Braun et al., 2008

Abbreviations: ADHD = attention deficit hyperactivity disorder; DSM-IV = diagnostic and statistical manual of mental disorder; KSADS = kiddie schedule for affective disorders and schizophrenia; mos = months; NHANES III = National Health and Nutrition Examination Survey III Version; NHANES (2001–2004) = National Health and Nutrition Examination Survey 2001–2004 Version; NS = not significant; WIAT = Wechsler Individual Achievement Test; WIAT-II = Wechsler Individual Achievement Test II Version; WISC-III = Wechsler Intelligence Scale for Children III Version; WISC-IV = Wechsler Intelligence Scale for Children IV Version; WISC-R = Wechsler Intelligence Scale for Children-Revised; WRAML = wide range assessment of memory and learning; WRAT = wide range achievement test; WRAT-R = wide range achievement test revised; yrs = years.

[a] Inclusion and exclusion criteria for tables: Tables 2–6 summarize some key studies in the field. A Pubmed search was conducted using the phrase "low-level lead exposure." Studies were included in the tables if they were performed in the United States and examined blood lead levels < 10 μg/dL for humans, < 15 μg/dL for rodents and < 20 μg/dL for monkeys. Representative studies were included in cases where one author or group of authors conducted multiple studies using a similar paradigm over the years. Only outcomes for doses that yielded blood lead levels in the corresponding ranges were included (i.e. studies were excluded if regression analyses included blood lead levels outside of the set limits). Studies were excluded if blood lead levels were not explicitly reported. Studies were also excluded if peak levels or steady state levels were above the range indicated for each respective table. In human work, the most conservative statistical outcomes for each study were reported after adjusting for possible covariates such as sex, age, race, birth weight, iron status, maternal age at child's birth, maternal education level, primary caregiver's IQ, household income, medication used in the previous month, and other variables.

2.2. Behavioral effects in children and young adults

In addition to producing cognitive deficits, lead can affect educational achievement by increasing behavioral problems that run counter to academic success. Lead exposure during infancy has long been linked to violent, disruptive, and unpredictable behavior that contributes to academic failure and school dismissal (Byers and Lord, 1943). Dentin lead levels in children have been correlated with maladaptive classroom behavior, as reported by teachers (Needleman, 1979). In addition to teacher and parent reports, self-reports have correlated K-shell X-ray fluorescence (KXRF) measures of lead in tibia with aggression, attention, and delinquency in boys aged 7–11. KXRF is a reliable and non-invasive method used to measure long-term lead stores (Hu et al., 1991). Adolescents between the ages of 12–18 who were found guilty of committing a delinquent act were four times more likely to have elevated bone lead concentrations in tibia than a comparable non-delinquent group (Needleman et al., 1996). In a prospective, longitudinal study, prenatal exposure to lead was associated with increased parent reports of antisocial behavior in adolescent children and postnatal exposure was associated with the adolescents' self-reported delinquent acts (Dietrich et al., 2001). In this study, 92% of the participants were African-American, 74% were of low socioeconomic status, and parental IQ was low, perhaps limiting generalizability; however, this study demonstrated that given a fairly homogenous population, lead levels are associated with delinquent behavior (Dietrich et al., 2001). In a cross-sectional study of 15–24 year olds, those with blood lead levels between 1.5 and 10 μg/dL were over 8 times more likely to meet the DSM-IV criteria for conduct disorder when compared to those in the lowest detectable range of less than .7 μg/dL (though the number of cases in each group was small) (Braun et al., 2008).

An examination of trends in lead contamination and delinquent behavior further supports a relationship between these two factors. After a delinquency rate that consistently increased over the years in the United States, a 13% decrease was observed in 2010 that is attributed to the phasing out of lead in gasoline years earlier (Department of Justice, 2012; FBI, 2011). The phasing out was not uniform across cities and, in fact, the lead burden remains variable throughout the nation. This variability can be used to calculate the effects of lead on delinquent behavior by comparing the lead burden in specific areas. The reduction in lead exposure in the 1970s may have contributed to a drop in violent crime in the 1990s when those people would have reached adolescence; these findings remain after controlling for several environmental, social, and economic factors (Jaeok et al., 2016; Nevin, 2000). The relationship between lead burden and crime trends remains on a global scale. One study estimated that 63–93% of the variability in international crime trends is explained by preschool blood lead levels from 19 years earlier (Nevin, 2007).

Behavioral parallels between children with attention deficit hyperactivity disorder (ADHD) and those exposed to lead are notable (Nigg et al., 2008; Rice, 2000). Children with ADHD and those exposed to lead exhibit pronounced impairments on discrimination reversal tasks such as the Wisconsin Card Sorting Test, spatial delayed alternation, go-no-go task, distractibility task and serial reaction tasks (e.g. review by Winneke, 2011). These effects are evident when blood lead levels are below 10 μg/dL, whereas comparably low levels of other toxic heavy metals, such as mercury and aluminum are not associated with ADHD-like effects (Ha et al., 2009; Nicolescu et al., 2010). Consistent with these findings, blood lead levels below 5 μg/dL are associated with combined hyperactive-inattentive ADHD symptoms, as described in the DSM-IV. This remains true even after co-varying for family income (Chiodo et al., 2007) and gender (Nigg et al., 2008). Lead levels below 5 μg/dL are associated with a more than 2-fold increased risk of diagnosis of ADHD when compared to children with undetectable levels of lead (Froehlich et al., 2009) [see Table 2]. Consistent with the increased rate of ADHD that is reported in males versus females, Denno observed that lead poisoning was the most significant predictor of delinquent and criminal behavior in males, but not in females (1984). These studies provide growing evidence that some diagnoses of ADHD may stem from the behavioral consequences of environmental lead exposure.

2.3. Cognitive and behavioral effects in the elderly

In addition to lead effects in the young, lead that accumulates over a

Table 3
Human 5–10 μg/dL. Summary of key studies in humans outlining the neurodevelopmental, cognitive, and achievement outcomes of blood lead levels between 5 and 10 μg/dL reported at $p < .05$. Excludes studies not explicitly reporting blood lead levels. Blood lead levels are listed as averages, unless otherwise noted, and appear as reported in respective studies. The most conservative adjusted statistical outcomes available are presented. Inclusion/exclusion criteria were established to determine study selection.[a]

5–10 μg/dL, Human

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
I. Reading					
WRAT-R; Reading Subset	Deficits	7.5–10.0 μg/dL	$n = 4853$ Cross-sectional, NHANES-III Multiple linear regression No reference group	6–16 yrs	Lanphear et al., 2000
WIAT; Reading Composite	Deficits	5–10.0 μg/dL	$n = 389$ One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
II. Verbal processing/memory					
WRAML; Verbal Memory Index	Deficits	5–10.0 μg/dL	$n = 389$ One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
Color Naming Task; Information Processing Speed	NS	< 7.5 μg/dL	$n = 237$ One test point Multiple regression using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
III. Intelligence scale/achievement test					
WISC-III, Full-scale & Performance	Deficits	< 7.5 μg/dL	$n = 237$ One test point Multiple regression using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
WISC-III, Full-scale & Performance	Deficits	5–10.0 μg/dL	$n = 389$ One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
WISC-R, Full-scale	Deficits	6.3–6.5 μg/dL	$n = 148$ Longitudinal Multiple regression No reference group	Association between 24 mos & 57 mos or 10 yrs	Bellinger et al., 1992
Full-scale	NS	6.3–7.8 μg/dL	Longitudinal	Association between 6, 12, or 18 mos & either 57 mos or 10 yrs	
WIAT Listening Comprehension	Deficits	5–10.0 μg/dL	$n = 389$ One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
K-TEA, Battery Composite Score	Deficits	6.3–6.5 μg/dL	$n = 148$ Longitudinal Multiple regression No reference group	Association between 24 mos & 57 mos; 24 mos & 10 yrs	Bellinger et al., 1992
K-TEA, Battery Composite Score	NS	6.3–7.8 μg/dL	Longitudinal	Association between 6, 12, or 18 mos & either 57 mos or 10 yrs	
Stanford-Binet Intelligence Scale, Composite Score	Deficits	7.4 μg/dL (36 mos) 7.7 μg/dL (60 mos)	$n = 172$ Longitudinal Nonlinear mixed model No reference group	36 mos 60 mos	Canfield et al., 2003
WISC-III, Verbal	Deficits	5–10.0 μg/dL	$n = 389$ One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
WISC-R, Verbal	Deficits	6.3–6.5 μg/dL	$n = 148$ Longitudinal Multiple regression No reference group	Association between 24 mos & 57 mos or 10 yrs	Bellinger et al., 1992
WISC-R, Verbal	NS	6.3–7.8 μg/dL	$n = 169$ Longitudinal Multiple regression No reference group	Association between 6, 12, or 18 mos & either 57 mos or 10 yrs	

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Table 3 (*continued*)

5–10 μg/dL, Human

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
WISC-R, Block Design	Deficits	7.5–10.0 μg/dL	*n* = 4853 Cross-sectional, NHANES-III Multiple linear regression using quartiles No reference group	6–16 yrs	Lanphear et al., 2000
WISC-III, Block Design	Deficits	< 10.0 μg/dL			
WRAT, Arithmetic	Deficits	7.5–10.0 μg/dL			
WIAT, Math Composite	Deficits	5–10.0 μg/dL	*n* = 389 One test point 1–2 μg/dL, reference group	6–10 yrs	Surkan et al., 2007
IV. Cognition					
McCarthy Scales of Children's Abilities General Cognitive Index; Verbal Subscale	NS	6.4–6.8 μg/dL	*n* = 170 Longitudinal Regression analysis No reference group	24 mos or 57 mos	Bellinger et al., 1991
McCarthy Scale of Children's Abilities; General Cognitive Index-Quantitative Subscale	NS	6.4–6.8 μg/dL	*n* = 170 Longitudinal Regression analysis No reference group	24 mos or 57 mos	Bellinger et al., 1991
McCarthy Scale of Children's Abilities; General Cognitive Index Perceptual-Performance Subscale	Deficits	6.4– 6.8 μg/dL	*n* = 170 Longitudinal Regression analysis No reference group	24 mos or 57 mos	Bellinger et al., 1991
McCarthy Scale of Children's Abilities; General Cognitive Index Motor Subscale	NS				
McCarthy Scale of Children's Abilities; General Cognitive Index Memory Subscale	NS				
V. Attention					
Child Behavior Checklist-Attention Teacher Report Form	NS	< 10.0 μg/dL	*n* = 237 One test point Multiple regression using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Child Behavior Checklist-Attention Teacher Report Form	NS	< 7.5 μg/dL			
Barkley Off Task	NS	< 7.5 μg/dL			
Barkley Off Task	Deficits	< 10.0 μg/dL			
Continuous Performance Test; Sustained Attention	NS	< 10.0 μg/dL			
Mental Rotation; Reaction Time	Deficits	< 7.5 μg/dL			
VI. Withdrawn					
Child Behavior Checklist-Withdrawn Teacher Report Form	Deficits	< 7.5 μg/dL	*n* = 237 One test point Multiple regression using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Child Behavior Checklist-Withdrawn Teacher Report Form	NS	< 10.0 μg/dL			
VII. Short-term memory/working memory					
Seashore Rhythm Test; Auditory Working Memory	NS	< 7.5 μg/dL	*n* = 237 One test point Regression analysis using quartiles No reference group	7.5 yrs	Chiodo et al., 2004
Seashore Rhythm Test; Auditory Working Memory	Deficits	< 10.0 μg/dL			
VIII. Visual-Motor					
Bruininks-Oseretsky; Visual-Motor Control	NS	Neonatal: 8.4 μg/dL 72 mos: 10.1 μg/dL	*n* = 245 Longitudinal Regression analysis No reference groupjs	Neonatal Day 10 association at 72 mos	Dietrich et al., 1993
Bruininks-Oseretsky; Visual-Motor Control	Deficits	Neonatal: 8.4 μg/dL 72 mos: 10.1 μg/dL	*n* = 245 Longitudinal Regression analysis No reference group	72 mos	Dietrich et al., 1993

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Table 3 (*continued*)

5–10 μg/dL, Human					
Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Design	Age of testing	Reference
IX. Dexterity/balance					
Bruininks-Oseretsky; Upper Limb Speed & Dexterity	Deficits	Neonatal: 8.4 μg/dL 72 mos: 10.1 μg/dL	*n* = 245 Longitudinal Regression analysis No reference group	Neonatal Day 10 association at 72 mos	Dietrich et al., 1993
Bruininks-Oseretsky; Fine Motor Composite	Deficits				
Bruininks-Oseretsky; Bilateral Coordination	NS				
Bruininks-Oseretsky; Upper Limb Speed & Dexterity	Deficits	72 mos: 10.1 μg/dL	*n* = 245 Longitudinal Regression analysis No reference group	72 mos	Dietrich et al., 1993
Bruininks-Oseretsky; Fine Motor Composite	Deficits				
Bruininks-Oseretsky; Bilateral Coordination	Deficits				
X. ADHD					
DSM-IV Criteria for ADHD	Association	1st tertile: 0.2–0.8 μg/dL 2nd tertile: 0.9–1.3 μg/dL 3rd tertile: > 1.3 μg/dL	*n* = 2588 Cross-sectional, NHANES (2001–2004) Logistic regression No reference group	8–15 yrs	Froehlich et al., 2009
XI. Conduct disorder					
DSM-IV Criteria for Conduct Disorder	Association	1st quartile: 0.2–0.7 μg/dL 2nd quartile: 0.8–1.0 μg/dL 3rd quartile: 1.1–1.4 μg/dL 4th quartile: 1.5–10 μg/dL	*n* = 3081 Cross-sectional, NHANES (2001–2004) No reference group	8–15 yrs	Braun et al., 2008

Abbreviations: ADHD = attention deficit hyperactivity disorder; DSM-IV = Diagnostic and Statistical Manual of Mental Disorder IV Version; K-TEA = Kaufman Test of Educational Achievement; mos = months; NS = not significant; NHANES (2001–2004) = National Health and Nutrition Examination Survey 2001–2004 Version; NHANES III = National Health and Nutrition Examination Survey III Version; WAIS-IV = Wechsler Adult Intelligence Scale IV Version; WIAT = Wechsler Individual Achievement Test; WISC-III = Wechsler Intelligence Scale for Children III Version; WISC-R = Wechsler Intelligence Scale for Children Revised; WRAML = wide range assessment of memory and learning; WRAT = wide range achievement test; yrs = years.

[a] Inclusion and exclusion criteria for tables: Tables 2–6 summarize some key studies in the field. A Pubmed search was conducted using the phrase "low-level lead exposure." Studies were included in the tables if they were performed in the United States and examined blood lead levels < 10 μg/dL for humans, < 15 μg/dL for rodents and < 20 μg/dL for monkeys. Representative studies were included in cases where one author or group of authors conducted multiple studies using a similar paradigm over the years. Only outcomes for doses that yielded blood lead levels in the corresponding ranges were included (i.e. studies were excluded if regression analyses included blood lead levels outside of the set limits). Studies were excluded if blood lead levels were not explicitly reported. Studies were also excluded if peak levels or steady state levels were above the range indicated for each respective table. In human work, the most conservative statistical outcomes for each study were reported after adjusting for possible covariates such as sex, age, race, birth weight, iron status, maternal age at child's birth, maternal education level, primary caregiver's IQ, household income, medication used in the previous month, and other variables.

lifetime produces negative cognitive consequences in the elderly. In older individuals, lead stored in bone is released due to osteoporosis that occurs during decalcification (Rosin, 2009). Studies corroborate that lead exposure early in life produces latent cognitive effects that emerge later in life in the form of Alzheimer's disease. Shih et al. (2006) reported that older adults with blood lead levels averaging 3.46 μg/dL had much higher cumulative levels of lead in tibia, averaging 18.7 μg/g. Importantly, tibia lead levels, but not blood lead levels, were significantly correlated with decreases in a wide range of cognitive tasks including language, processing speed, eye-hand coordination, executive functioning, verbal memory and learning, visual memory, and visuo-construction. Though blood lead levels were low, the steady state and peak blood lead levels were not reported and presumably were high in order to produce the elevated levels of lead in bone. These studies suggest that lead impacts cognition later in life although results are mixed and ultimate susceptibility may be due to epigenetics and other factors (Basha and Reddy, 2010; Basha et al., 2005; Stewart et al., 2002, 2006; van Wijngaarden et al., 2009; Wu et al., 2008; Zawia and Basha, 2005).

Parkinson's disease is another concern in the aging population that can be affected by lead exposure. Long-term occupational exposure to a combination of lead and copper (Gorell et al., 1999, 2004), or lead and iron (Gorell et al., 1999) increases the risk for Parkinson's disease by twofold as assessed by retrospective, self-report measures. Objective measures such as K-shell X-ray fluorescence (KXRF) also correlate long-term lead exposure with Parkinson's disease (Coon et al., 2006; Weisskopf et al., 2010). Furthermore, Parkinson's disease is associated with KXRF measures of lead levels in cortical bone (e.g. tibia) where the half-life of lead is 20–30 years, but not in trabecular/patella bone (e.g. knee cap) where the half-life is 8 years (Weisskopf et al., 2010).

2.4. Gross brain structure in humans

A prospective, longitudinal study identified brain correlates of youth lead exposure. Children's blood lead levels were compared to morphometric brain images (obtained via MRI) when those same children reached 19 through 24 years of age (Cecil et al., 2008). A lead-induced, dose-dependent decline in the volume of gray matter in various areas of the prefrontal cortex was reported, including in the ventrolateral prefrontal cortex and anterior cingulate cortex in men; as well

Table 4
Animals < 5 μg/dL. Summary of key studies in rodents outlining neurodevelopmental and cognitive outcomes of blood lead levels below 5 μg/dL reported at $p < .05$. Excludes studies where peak levels were above 5 μg/dL. Excludes studies not explicitly reporting blood lead levels. Blood lead levels are presented as averages, unless otherwise noted, and appear as reported in respective studies. Inclusion/exclusion criteria were established to determine study selection.[a]

< 5 μg/dL, Animals – rodents

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL), strain, species, & sex	Exposure protocol	Age of testing	Reference
I. Exploratory activity					
Rearing During Spatial Memory Retrieval; Object-in-Place Task	Increased rearing in male & females	3.3 μg/dL C57BL/6J Mice Males & Females	0 ppm *n* = 18 (10 Males; 8 Females) 30 ppm *n* = 16 (6 Male; 10 Female) Via lactation & drinking water PND 0-PND 28	PND 28	Sobin et al., 2017
Distance Traveled & Time Immobile During Spatial Memory Retrieval; Object-in-Place Task	NS				
Rearing During Object Memory Retrieval; Object-in-Place Task	Increased rearing in male & females				
Distance Traveled & Time Immobile during Object Memory Retrieval; Object-in-Place Task	NS				
II. Associative learning					
Acquisition-Trace Fear Conditioning	NS	5.65 μg/dL Long Evans Rats Males	0 ppm & 150 ppm *n* = 32 (16 Males; 16 Females, per group) Via food Gestation to PND 21	PND 55	Verma and Schneider, 2017
Acquisition-Trace Fear Conditioning	NS	4.38 μg/dL Long Evans Rats Females			
Acquisition-Trace Fear Conditioning	NS	5.42 μg/dL Sprague Dawley Rats Males	0 ppm & 150 ppm *n* = 36 (18 Males; 18 Females, per group) Via food Gestation to PND 21		
Acquisition-Trace Fear Conditioning	NS	4.52 μg/dL Sprague Dawley Rats Females			
Acquisition-Trace Fear Conditioning	NS	5.95 μg/dL Long Evans Rats Males	0 ppm & 150 ppm *n* = 32 (16 Males; 16 Females, per group) Via food PND 1–PND 21		
Acquisition-Trace Fear Conditioning	NS	5.38 μg/dL Long Evans Rats Females			
Acquisition-Trace Fear Conditioning	NS	5.45 μg/dL Sprague Dawley Rats Males	0 ppm & 150 ppm *n* = 36 (18 Males; 18 Females) Via food PND 1–PND 21		
Acquisition-Trace Fear Conditioning	NS	5.06 μg/dL Sprague Dawley Rats Females			
III. Memory					
Memory Retention-Trace Fear Conditioning	Deficits	Long Evans Rats Males	0 ppm & 150 ppm *n* = 32 (16 Males; 16 Females, per group) Via food Gestation to PND 21	PND 55	Verma and Schneider, 2017
Memory Retention-Trace Fear Conditioning	NS	Long Evans Rats Females			

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Table 4 (*continued*)

< 5 μg/dL, Animals – rodents					
Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL), strain, species, & sex	Exposure protocol	Age of testing	Reference
Memory Retention-Trace Fear Conditioning	NS	Sprague Dawley Rats Males	0 ppm & 150 ppm *n* = 36 (18 Males; 18 Females, per group) Via food Gestation to PND 21		
Memory Retention-Trace Fear Conditioning	NS	Sprague Dawley Rats Females			
Memory Retention-Trace Fear Conditioning	NS	Long Evans Rats Males	0 ppm & 150 ppm *n* = 32 (16 Males; 16 Females, per group Via food PND 1–PND 21		
Memory Retention-Trace Fear Conditioning	Deficits	Long Evans Rats Females			
Memory Retention-Trace Fear Conditioning	NS	Sprague Dawley Rats Males	0 ppm & 150 ppm *n* = 36 (18 Males; 18 Females) Via food PND 1–PND 21		
Memory Retention-Trace Fear Conditioning	NS	Sprague Dawley Rats Females			
Spatial Memory Retrieval, Object-in-Place Task	NS	0 ppm 0.2 μg/dL 30 ppm 3.3 μg/dL C57BL/6J Mice Males & Females (*Note*: BBLs were averaged from four previously published studies.)	0 ppm *n* = 18 (10 Males; 8 Females) 30 ppm *n* = 16 (6 Male; 10 Female) Via lactation & drinking water PND 0–PND 28	PND 28	Sobin et al., 2017
Object Memory Retrieval, Object-in-Place Task	NS				

Abbreviations: BLL = blood lead level; NS = not significant; PND = postnatal day; PPM = parts per million.

[a] Inclusion and exclusion criteria for tables: Tables 2–6 summarize some key studies in the field. A Pubmed search was conducted using the phrase "low-level lead exposure." Studies were included in the tables if they were performed in the United States and examined blood lead levels < 10 μg/dL for humans, < 15 μg/dL for rodents and < 20 μg/dL for monkeys. Representative studies were included in cases where one author or group of authors conducted multiple studies using a similar paradigm over the years. Only outcomes for doses that yielded blood lead levels in the corresponding ranges were included (i.e. studies were excluded if regression analyses included blood lead levels outside of the set limits). Studies were excluded if blood lead levels were not explicitly reported. Studies were also excluded if peak levels or steady state levels were above the range indicated for each respective table. In human work, the most conservative statistical outcomes for each study were reported after adjusting for possible covariates such as sex, age, race, birth weight, iron status, maternal age at child's birth, maternal education level, primary caregiver's IQ, household income, medication used in the previous month, and other variables.

as in the inferior parietal lobe in women. These regions of the prefrontal cortex are associated with executive function, higher order thinking, decision-making, inhibitory control, mood regulation and fine motor control. Decreased functioning of these regions could lead to impulsive, aggressive, or violent behavior. In this study, males were more susceptible to lead-induced deficits given the same concentrations of lead and similar demographic factors to females. Perhaps not coincidentally, males are more prone to antisocial behavior. This study was conducted in economically impoverished areas of Cincinnati. While the socioeconomic and geographic homogeneity of the group may decrease generalizability, it provides a control for these two important factors and further supports the conclusion that dose-dependent lead levels are the reason for the observed morphological changes. Moreover, it is reasonable to suggest that neuroanatomical changes, such as these, contribute to cognitive and behavioral problems.

3. Cognitive, behavioral and environmental effects in animal models

3.1. Cross-species comparison

Animal models help clarify the consequences of lead exposure in a controlled laboratory setting. Neurodevelopmental, cognitive, and learning deficits following lead exposure are similar in humans, primates, and rodents (Davis et al., 1990; Winder et al., 1983). Extrapolation from animal studies to humans is possible even though cross-species comparisons are complicated by differences in absorption, distribution, metabolism, and excretion. Physiologically-based pharmacokinetic (PBPK) models, for example, are successfully used to extrapolate information from animals to humans (Ginsberg et al., 2004).

Similarities in neurotoxic effects are evident across species despite pharmacokinetic differences. This is the case even though blood lead levels in small mammals are higher than in humans due to a faster metabolic rate in smaller organisms that affects gastrointestinal absorption and elimination of the metal. Summaries of neurodevelopmental, cognitive, and learning outcomes are outlined according to blood lead levels in Tables 4 and 5 for rodents (< 5 μg/dL and 5–20 μg/dL, respectively), and Table 6 for non-human primates (< 20 μg/dL).

3.2. Cognitive and behavioral effects in animals

In humans and animals lead exposure affects cognitive measures, such as learning and memory. Rodents exhibit memory impairments at blood lead levels as low as 3.58 μg/dL (Wang et al., 2012),

Table 5
Animals 5–20 μg/dL. Summary of key studies in rodents outlining neurodevelopmental and cognitive outcomes of blood lead levels between 5 and 20 μg/dL reported at $p < .05$. Excludes studies where peak levels were above 20 μg/dL. Excludes studies not explicitly reporting blood lead levels. Blood lead levels are presented as averages, unless otherwise noted, and appear as reported in respective studies. Inclusion/exclusion criteria were established to determine study selection.[a]

5–20 μg/dL, Animals – rodents

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL), strain, species, & sex	Exposure protocol	Age of testing	Reference
I. Exploratory activity					
Unbaited Nose Poke Task	Decreased exploratory activity	0.2–15 μg/dL C57BL/6J Mice Males & Females	0 ppm *n* = 19 (8 Males; 11 Females) 30 ppm *n* = 26 (16 Males; 10 Females) 230 ppm *n* = 16 (12 Males; 4 Females) Via lactation & drinking water PND 0–28 (offspring tested) Regression analysis	PND 28	Flores-Montoya and Sobin, 2015
Open Field, Number of Quadrant Crosses	NS				
Rotarod	NS				
Total Exploration Time During Novel Odor Recognition Task for males, but not females	NS	0.02–20.31 μg/dL C57BL/6J Mice Males & Females	0 ppm *n* = 10 (8 Males; 2 Females) 30 ppm *n* = 10 (5 Males; 5 Females) 330 ppm *n* = 13 (7 Males; 6 Females) Via lactation & drinking water PND 0– 28 (offspring tested) Regression analysis		Flores-Montoya et al., 2015
Open Field, Activity Counts	Decreased activity	< 10 μg/dL, P C57BL/6 Mice Males	0 ppm & 27 ppm (*n* = 6–8 Males; 6–8 Females, per group) Via lactation & drinking water; Dam's lead exposure: 14 days prenatal-PND 10 (offspring tested)	1 yr	Leasure et al., 2008
Open Field, Activity Counts	NS	< 10 μg/dL, P C57BL/6J Mice Females			
II. Global locomotor					
Amphetamine-Induced Motor Activity	Increased drug-induced locomotor activity	< 10 μg/dL, P C57BL/6J Mice Males	0 ppm & 27 ppm (*n* = 6–9 Males; 6–9 Females, per group) Via lactation and drinking water; Dam's lead exposure: 14 days prenatal-PND 10 (offspring tested)	1 yr	Leasure et al., 2008
Amphetamine-Induced Motor Activity	NS	< 10 μg/dL, P C57BL/6J Mice Female			
Running Wheel Activity	NS	< 10 μg/dL, P C57BL/6J Mice Male	*n* = 6 (Male)		
III. Motor coordination					
Rotarod	Deficits	< 10 μg/dL, P C57BL/6J Mice Male			
Rotarod	NS	< 10 μg/dL, P C57BL/6J Mice Female			

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Table 5 (*continued*)

5–20 μg/dL, Animals – rodents

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL), strain, species, & sex	Exposure protocol	Age of testing	Reference
IV. Odor recognition					
Novel Odor Recognition Task	Preference for familiar over novel odor	0.02–20.31 μg/dL C57BL/6J Mice Male	0 ppm *n* = 10 (8 Males; 2 Females) 30 ppm *n* = 10 (5 Males; 5 Females) & 330 ppm *n* = 13 (7 Males; 6 Females) Via lactation & drinking water PND 0–28 (offspring tested)	PND 28	Flores-Montoya et al., 2015
Novel Odor Recognition Task	NS	0.02–20.31 μg/dL C57BL/6J Mice Female			
V. Cognitive flexibility					
Delayed Spatial Alternation	Deficits	19 μg/dl, SS Long-Evans Rats Male	0 ppm & 75 ppm *n* = 15 per group (Male) Via drinking water PND 25-through testing	22 weeks	Alber and Strupp, 1996
Cued Alternation Spatial Alternation	NS NS				
VI. Delay of reinforcement/impulsivity					
Fixed-Ratio Waiting-for-Reward Schedule of Reinforcement (FR50)	Deficits	10.8 μg/dL, SS Long-Evans Rats Male	0 ppm & 50 ppm *n* = 12 per group (Male) Via drinking water PND 21 through testing	PND 60	Brockel and Cory-Slechta, 1998
Fixed Interval Schedule-Controlled (FI 1 Minute)	NS	11.4 μg/dL, SS Long-Evans Rats Male	0 ppm & 50 ppm *n* = 10 per group (Male) Via drinking water PND 21 through testing	PND 21 through testing	Cory-Slechta et al., 2002
Fixed Interval Schedule-Controlled (FI 1 Minute)	NS	7.2 μg/dL, SS Long-Evans Rats Male	0 ppm *n* = 13 50 ppm *n* = 14 (Male) Via drinking water PND 21 through testing	PND 21 through testing	Cory-Slechta et al., 1998
Fixed Interval Schedule-Controlled (FI 1 Minute)	NS	15.9 μg/dL Fischer-344 Rats Male	0 ppm & 50 ppm *n* = 16 per group (Male) Via drinking water from arrival through testing	16 mos old at arrival. Testing began after 6th mos of exposure through testing	Cory-Slechta and Pokora, 1991
Fixed Interval Schedule-Controlled (FI 1 Minute)	NS Deficits NS	PND 21: 11.3 μg/dL PND 8 months: 17.1 μg/dL PND 16 months: 18.3 μg/dL Fischer-344 Rats Male	2 mg/kg/day in 5 mos PND 21: *n* = 30 PND 8 mos: *n* = 34 PND 16 mos: *n* = 42 (Male) Via drinking tube from arrival through testing	PND 21, 8 mos. 16 mos at arrival. Testing began after 2.5 mos of lead exposure	
Variable Interval Schedule-Controlled (F1 Minute)	NS NS NS	PND 21: 11.3 μg/dL PND 8 months: 17.1 μg/dL PND 16 months: 18.3 μg/dL Fischer-344 Rats Male			
Fixed Interval Schedule-Controlled (FI 1 Minute)	Deficits	15–20 μg/dL Long-Evans Rats Male	0 ppm & 25 ppm *n* = 12 per group (Male) Via drinking water PND 21 through testing	PND 50	Cory-Slechta et al., 1985

(*continued on next page*)

Table 5 (*continued*)

5–20 μg/dL, Animals – rodents					
Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL), strain, species, & sex	Exposure protocol	Age of testing	Reference
Fixed Interval Schedule-Controlled (FI 1 Minute)	Deficits	< 20 μg/dL Long-Evans Rats Male	0 ppm & 50 ppm *n* = 6 per group (Male) Via drinking water PND 21–PND 178 or PND 20–PND 335	PND 55	Cory-Slechta et al., 1983
Fixed Interval Schedule-Controlled (FI 1 Minute)	Deficits	< 10 μg/dL Sprague-Dawley Rats Male	0 ppm *n* = 8 50 ppm *n* = 11 (Male) Via drinking water from PND 21 through testing	PND 55	Cory-Slechta and Thompson, 1979

Abbreviations: mos = months; NS = not Significant; P = peak; PND = postnatal day; PPM = parts per million; SS = steady state; yr = year.

[a] Inclusion and exclusion criteria for tables: Tables 2–6 summarize some key studies in the field. A Pubmed search was conducted using the phrase "low-level lead exposure." Studies were included in the tables if they were performed in the United States and examined blood lead levels < 10 μg/dL for humans, < 15 μg/dL for rodents and < 20 μg/dL for monkeys. Representative studies were included in cases where one author or group of authors conducted multiple studies using a similar paradigm over the years. Only outcomes for doses that yielded blood lead levels in the corresponding ranges were included (i.e. studies were excluded if regression analyses included blood lead levels outside of the set limits). Studies were excluded if blood lead levels were not explicitly reported. Studies were also excluded if peak levels or steady state levels were above the range indicated for each respective table. In human work, the most conservative statistical outcomes for each study were reported after adjusting for possible covariates such as sex, age, race, birth weight, iron status, maternal age at child's birth, maternal education level, primary caregiver's IQ, household income, medication used in the previous month, and other variables.

discrimination tasks and increased distractibility at 15 μg/dL (Rice, 1985), and delayed spatial cognitive flexibility at 19 μg/dL (Alber and Strupp, 1996). Other characteristics of lead-exposed animals include perseveration of incorrect responses, impulsivity, increased rates of operant responding, and problems handling delays of reinforcement at, or below, 10 μg/dL (Brockel and Cory-Slechta, 1998; Cory-Slechta and Thompson, 1979), or below 20 μg/dL (Cory-Slechta et al., 1983, 1985) [see Tables 4 and 5, respectively]. Tasks that require higher-level learning reveal greater impairment than simpler, lower-level learning tasks (EPA, 2006; White et al., 2007).

In addition to cognitive deficits, locomotor effects are evident in rodents at blood lead levels below 10 μg/dL. Alterations include increased rearing during spatial memory retrieval at 3.3 μg/dL (Sobin et al., 2017) and decreased exploratory behavior at blood lead levels below 10 μg/dL in mice (Flores-Montoya and Sobin, 2015; Leasure et al., 2008). Likewise, a reduction of exploratory behavior on an open field task and motor coordination on a rotarod are observed in rats administered lead at concentrations that yield blood lead levels in this range (Sabbar et al., 2012). These motor impairments accompany noradrenaline depletion and changes in the firing rate in the subthalamic nucleus while dopamine levels in the striatum remain unchanged (Sabbar et al., 2012). Interestingly, animals with lower blood lead levels (< 10 μg/dL) than those with higher blood lead levels (24–27 μg/dL) show the greatest decreases in horizontal and vertical exploratory activity, amphetamine-induced increases in locomotion, and lack of motor coordination that is male-specific (Leasure et al., 2008).

3.2.1. Alteration of drug responses in animals

Lead targets the frontal cortex, nucleus accumbens, dorsal striatum, and hippocampus with dopaminergic and glutamatergic changes in these regions that vary by dose, age, and duration of exposure as suggested by autoradiography receptor binding studies (Cory-Slechta, 1997; Cory-Slechta et al., 1993, 1997, 1998; Jett and Guilarte, 1995; Listos et al., 2013). Animals exposed to lead postweaning acquire drug discrimination more rapidly to SKF38393 (D_1 agonist), quinpirole (D_2 agonist), cocaine, apomorphine, and amphetamine suggesting a supersensitivity of the dopaminergic system. Similarly, increased sensitivity of the glutamatergic system in lead-exposed animals is evidenced by faster acquisition of a drug discrimination task when substituting NMDA for quinpirole in animals exposed to lead at postweaning (Cory-Slechta and Widzowski, 1991). Alternatively, hypoglutamatergic effects or no effects in animals exposed to lead at postweaning have also been reported along with glutamatergic sensitivity only in animals exposed to lead early in development (Cory-Slechta et al., 1997; Jett and Guilarte, 1995).

Age-dependent differences extend to drug self-administration in animals exposed to lead. While perinatal lead exposure increases sensitivity to dopaminergic systems producing hypersensitivity to cocaine, adult exposure to lead produces hyposensitivity to the same drug. Animals perinatally exposed to lead show sustained self-administration of cocaine at doses too low to sustain responding in control animals, exhibit a higher return to drug-seeking (relapse) at lower doses of a cocaine priming injection (Nation et al., 2004), and a higher rate of acquisition of cocaine self-administration (Rocha et al., 2005). Alternatively, animals exposed to lead in adulthood show an attenuated sensitization to the locomotor-stimulating properties of chronic cocaine (Nation et al., 1996) and the impact of cocaine on schedule-controlled operant responding is reduced when lead is presented in adulthood (Burkey et al., 1997).

These differences are consistent with other studies in which directionally opposite behavioral effects are observed depending on whether lead exposure occurs perinatally or postweaning (Areola and Jadhav, 2001; Pokora et al., 1996; Widzowski et al., 1994). Curiously, while perinatal lead exposure increases cocaine reward, it attenuates methamphetamine self-administration in a progressive ratio task, perhaps due to differences in the involvement of specific neurotransmitter systems (Rocha et al., 2008).

Age-dependent effects of lead exposure also apply to opiates suggesting interactions between the heavy metal and the opiate system. Specifically, exposure to lead during adulthood produces reduced locomotor activity in response to morphine while perinatal lead exposure

Table 6
Cynomolgus Monkeys. Summary of key studies in monkeys outlining neurodevelopmental and cognitive outcomes of blood lead levels below 20 μg/dL reported at $p < .05$. Excludes studies where peak levels were above 20 μg/dL. Excludes studies not explicitly reporting blood lead levels. Blood lead levels are presented as averages, unless otherwise noted, and appear as reported in respective studies. Inclusion/exclusion criteria were established to determine study selection.[a]

< 20 μg/dL, Cynomolgous monkeys

Test	Outcome (using adjusted scores when available)	Mean blood lead level (μg/dL)	Exposure protocol	Age of testing	Reference
I. Attention/impulsivity/discrimination task					
Discrimination task spatial discrimination; no irrelevant cues	NS	15.4 μg/dL, SS 10.9 μg/dL, P Controls: 3 μg/dL (*Note*: Controls had BLLs between 2.9 & 3.5 μg/dL perhaps masking an effect at the low level of lead tested)	0 μg/kg/day (n = 3 Males; n = 3 Females) 50 μg/kg/day (4 = Males; 4 = Females) Experimenter administered PND 0 through testing	9–10 yrs	Gilbert and Rice, 1987
Irrelevant form cues	NS	15 μg/dl, P 11 μg/dl, SS	0 μg/kg/day (n = 4 Males; n = 3 Females) 50 μg/kg/day (n = 4 Males; n = 4 Females) Experimenter administered PND 0 through testing	3–4 yrs	Rice, 1985
Irrelevant form & color cues	NS				
Acquisition of nonspatial form discrimination	NS				
Acquisition of nonspatial color discrimination with irrelevant form cues	NS				
Acquisition of nonspatial form discrimination with irrelevant color cues	NS				
Spatial form discrimination	Deficits				
Nonspatial color discrimination with irrelevant form cues	Deficits				
Nonspatial form discrimination with irrelevant color cues	Deficits				
Delayed alternation	Deficits				
II. Delay of reinforcement					
Differential reinforcement of low rate (DRL varied between 5 and 30 s)	NS	15.4 μg/dL, SS 10.9 μg/dL, P Controls: 3 μg/dL (*Note*: Controls had high levels of lead, perhaps masking an effect of the low level of lead tested)	0 μg/kg/day (n = 4 Males; n = 3 Females) 50 μg/kg/day (n = 4 Males; n = 4 Females) Experimenter administered PND 0 through testing	3 yrs	Rice and Gilbert, 1985
III. Memory					
Acquisition of alternation tasks	NS	15.4 μg/dl, P 10.9 μg/dl, SS	0 μg/kg/day (n = 4 Males; n = 3 Females) 50 μg/kg/day (n = 4 Males; n = 4 Females) Experimenter administered PND 0 through testing	7–8 yrs	Rice and Karpinski, 1988
Acquisition of delayed alternation	Deficits				

Abbreviations: BLL = blood lead level; NS = not significant; P = peak; PND = postnatal day; SS = steady state; YRS = years.

[a] Inclusion and exclusion criteria for tables: Tables 2–6 summarize some key studies in the field. A Pubmed search was conducted using the phrase "low-level lead exposure." Studies were included in the tables if they were performed in the United States and examined blood lead levels < 10 μg/dL for humans, < 15 μg/dL for rodents and < 20 μg/dL for monkeys. Representative studies were included in cases where one author or group of authors conducted multiple studies using a similar paradigm over the years. Only outcomes for doses that yielded blood lead levels in the corresponding ranges were included (i.e. studies were excluded if regression analyses included blood lead levels outside of the set limits). Studies were excluded if blood lead levels were not explicitly reported. Studies were also excluded if peak levels or steady state levels were above the range indicated for each respective table. In human work, the most conservative statistical outcomes for each study were reported after adjusting for possible covariates such as sex, age, race, birth weight, iron status, maternal age at child's birth, maternal education level, primary caregiver's IQ, household income, medication used in the previous month, and other variables.

produces an enhanced locomotor response (Miller et al., 2000), a downward vertical shift in a heroin dose-effect curve, and lower break points for heroin self-administration in a progressive ratio task (Rocha et al., 2004). A decreased sensitivity to morphine following lead exposure could contribute to use of the drug in larger quantities to get the same effect. Lead effects are age-dependent and the directional effects are drug-class dependent.

Studying lead effects on the responses to psychoactive drugs provides insights into the mechanisms of action of the heavy metal by pointing toward neurotransmitters and receptors that may be affected. Learning how lead modifies neurochemical systems that underlie the effects of psychoactive drugs has implications for substance abuse, addiction, and psychiatric and neurological disorders (Braun et al., 2008; Byers and Lord, 1943; Canfield et al., 2003; Cecil et al., 2008; Coon et al., 2006; Cory-Slechta et al., 1997; Jones and Miller, 2008; Jusko et al., 2008; Lanphear et al., 2000; Nation et al., 2004; Needleman et al., 1990; Reuben et al., 2017; Rocha et al., 2005; van Wijngaarden et al., 2009, 2011; Weisskopf et al., 2010; Clifford et al., 2011).

3.3. Environmental effects in animals

Research in animal models has revealed that environmental factors profoundly impact the severity of lead neurotoxicity. For example, Schneider et al. (2001) observed that an enriched environment consisting of playmates or novel objects could mitigate lead-induced deficits. Immediately after weaning, rat pups were put in either impoverished or enriched environments. Lead-exposed rats raised in an enriched environment performed similarly to control animals not exposed to lead, whereas lead-exposed animals reared in impoverished environments showed decreases in spatial ability in a Morris water maze relative to controls. Although the levels of lead in blood were relatively high (average: 26–34 μg/dL), the impact of environmental manipulation was striking. Similarly, Guilarte et al. (2003) found that lead-induced deficits were reversed by an enriched environment. Lead-exposed animals that were raised in isolation showed disruption of spatial learning and altered NMDA receptor gene expression, while those that were raised under social and environmental enrichment did not (average: 31.9 μg/dL blood lead). The translational implications of these studies are substantial, suggesting that even when lead burdens are elevated, environmental manipulations are enough to either mitigate or exacerbate lead-induced learning deficits (Schneider et al., 2001).

3.4. Summary

Low blood lead levels produce cognitive and behavioral effects in animal models; however, animal studies examining blood lead levels below 5 μg/dL are limited. To our knowledge, only three animal studies have been rigorously conducted and explicitly report blood lead levels below 5 μg/dL (Sobin et al., 2017; Verma and Schneider, 2017; Wang et al., 2012). Each of these studies found deficits. Other studies claim to use low levels of lead but include methods that initially introduce high peak levels of lead to dams and then study the offspring, expose animals to high peak levels of lead and then take blood samples after blood lead levels decline, or report deficits when comparing doses of lead below 5 μg/dL to high doses of lead, instead of comparing them to a control group with no detectable levels of lead. In other studies, blood lead levels are not measured at critical points during testing but are taken at the end of testing, thus missing the peak and steady state levels. In yet other studies, bone, dentin, or brain lead levels are reported but blood lead levels are absent, thus making comparisons difficult between the more traditional studies that report blood lead levels. This is further a problem because blood lead levels are a measure of current lead exposure and are not necessarily associated with bone lead levels that are a measure of lifetime lead exposure. In some instances, no lead levels are reported after a lead exposure regimen. Previously reported blood lead levels using similar dosing regimens are sometimes used to estimate blood lead levels for animals in the current study. Of note, thirty years ago it was common for control groups in animal studies to have blood lead levels as high as 3 μg/dL (Gilbert and Rice, 1987; Rice and Gilbert, 1985). These are levels that we now suspect produce cognitive and behavioral deficits. It is essential that animal studies examine lower blood lead levels in a highly controlled manner in order to better inform human findings and to better understand the threshold range for effects on the brain and behavior.

4. Mechanisms of action: calcium dynamics

The mechanisms by which lead disrupts the brain and behavior are complex and poorly understood. Nonetheless, cellular and molecular work has resulted in a growing understanding of the effects of lead on brain function. Of particular importance are the effects of lead on calcium-dependent cellular processes. Calcium is a critical ion in neuronal function, including cell growth and differentiation, neurotransmitter release, and intracellular biochemical cascades.

Lead and calcium are divalent cations of similar size and ionic charge. The ability of lead to mimic or inhibit calcium-mediated effects is central to its biological and behavioral effects. Unlike calcium, which is a highly regulated ligand in the body, lead is an unregulated heavy metal. Lead binds to sites at which calcium acts and enters the cell through calcium channels, thus displacing, inhibiting, substituting, and/or activating calcium-dependent processes (Bridges and Zalups, 2005; Habermann et al., 1983; Kerper and Hinkle, 1997; Pounds, 1984). Given the ubiquity of calcium in cellular signaling, and the critical role of the spatial and temporal patterning of calcium signals in cell function, disruption of calcium-dependent processes can have profound cellular consequences (Berridge et al., 2000, 2003; Bootman, 2012; Bootman et al., 2001, 2002; Florea et al., 2013). The effects of lead on neuronal calcium dynamics help to explain many far-reaching changes in brain function and behavior.

Below are short descriptions of some of the more well-known cellular actions of lead, including effects on NMDA receptors, presynaptic intracellular signaling proteins, mitochondria, and non-neuronal brain cells (for a more complete summary of targets involved in lead toxicity see CDC, 2005).

4.1. NMDA receptors

Lead is a non-competitive, *N*-Methyl-D-aspartate receptor (NMDA-R) antagonist. NMDA-Rs are ionotropic receptors that are activated by the neurotransmitter glutamate, and are involved in many processes, including neural development, neuronal plasticity, learning and memory, and long-term potentiation (a physiological correlate of learning) (Cohn and Cory-Slechta, 1994; Cory-Slechta et al., 1997; Gilbert and Lasley, 2007; Hori et al., 1993; Hubbs-Tait et al., 2005; Nihei and Guilarte, 2001). Activation of NMDA-Rs by glutamate produces an influx of calcium through a ligand-gated ion channel, which can produce an excitatory post-synaptic potential, as well as strongly influence neuronal function by activating calcium-dependent second messenger cascades.

By blocking postsynaptic NMDA-Rs, lead inhibits activity-dependent calcium influx, which in turn can disrupt NMDA receptor-dependent developmental processes, neural plasticity, learning and memory, and long-term potentiation (LTP). Chronic, developmental lead exposure increases the threshold for induction of LTP at a wide range of lead concentrations and this is associated with impaired learning and memory (Cohn et al., 1993; Jett and Guilarte, 1995; Lasley and Gilbert, 2000, 2002; Lasley et al., 2001; Luo et al., 2011; Ma et al., 1997; Nihei and Guilarte, 2001; Ruan et al., 1998). Disruption of LTP and learning may be related to NMDA receptor blockade or other downstream effects of lead on calcium-dependent processes (Hori et al., 1993; Hussain et al., 2000).

Another consequence of NMDA receptor blockade is apoptosis, programmed cell death produced by a well-characterized biochemical cascade that leads to disruptions in normal brain development (Anastasio et al., 2009; Hansen et al., 2004; Ikonomidou et al., 1999; Léveillé et al., 2010; Lyall et al., 2009; Yuede et al., 2010). Apoptosis is normally involved in pruning unneeded connections and 'sculpting' the brain during development. However, under certain conditions pathological apoptosis can occur. Developmental exposure to lead has also been found to produce apoptosis and disrupt brain development at low concentrations in both mammalian and zebrafish models via blockade of NMDA receptors (Dou and Zhang, 2011; Dribben et al., 2011; Liu et al., 2010).

Given the critical role of NMDA receptors in a variety of neural and behavioral processes, and the ability of lead to block NMDA receptors, these receptors are essential to a complete understanding of the effects of lead on the brain and behavior.

4.2. Calmodulin

Another target of lead is calmodulin (CaM), or "calcium-modulated protein," a major calcium-activated intracellular protein (Heizmann and Hunziker, 1991). Calmodulin is important in many neuronal processes, including transduction of calcium signaling, regulation of neurotransmitter receptors and ion channels, and neuronal plasticity (McCue et al., 2010; Sandhir and Gill, 1994). Calmodulin has four binding sites at which calcium is the natural ligand. When calcium is bound at all four sites, calmodulin is functionally active (Costa, 1998).

At physiologically-relevant levels, lead binds with greater affinity than calcium to calmodulin and activates the protein (Fullmer et al., 1985; Habermann et al., 1983; Sandhir and Gill, 1994; Shirran and Barran, 2009). When this occurs, calmodulin is activated in a non-physiological manner. Calmodulin signaling becomes tonically activated and stimulus-independent. Given the broad role of calmodulin in calcium signaling, unregulated calmodulin activation can have many consequences, ranging from disruption of calmodulin-dependent signal transduction to interference with calmodulin-dependent learning and memory (Goldstein, 1993; Goldstein and Ar, 1983; Habermann et al., 1983; Sandhir and Gill, 1994).

4.3. Protein kinase C

Protein Kinase C (PKC) is a calcium- and phospholipid-dependent, intracellular signaling enzyme that is involved in a variety of cellular functions (Markovac and Goldstein, 1988). PKC phosphorylates proteins via the transfer of phosphate from ATP. PKC-mediated phosphorylation of transport proteins is important for the regulation of cellular growth and differentiation. PKC is also implicated in cytoskeletal function and signal transduction (Pears, 1995), and plays a role in learning and memory (Van der Zee et al., 1992; Xu et al., 2014).

At a clinically-relevant, picomolar concentration, lead substitutes for calcium in the activation of PKC, increasing intracellular calcium and interfering with neurotransmitter release (Goldstein, 1993). Specifically, at the synaptotagmin site, lead mimics and competes for calcium and does so with greater affinity than calcium (Bouton et al., 2001). Prolonged lead-induced increases of PKC activity produce a compensatory decrease in activity perhaps by downregulation or decreased efficacy of calcium activity (EPA, 2006). PKC is important for calcium-mediated LTP; in fact, PKC inhibitors, such as polymyxin B block the induction and maintenance of calcium-induced LTP (Cheng et al., 1994). Lead-induced impairment of learning and memory processes is thought to be due, at least in part, to disruption of normal PKC functioning. In addition, lead effects on PKC activity impact cell division, neuronal communication, neural plasticity, and structural organization of the cytoskeleton (Bressler et al., 1999; EPA, 2006), as well as cellular proliferation and differentiation (Markovac and Goldstein, 1988).

4.4. Neurotransmitter release

Under normal circumstances, depolarization of neurons leads to the opening of voltage-gated calcium channels, which allows for influx of calcium into the presynaptic terminal. Calcium then activates a cascade of enzymes, which promotes fusion of the synaptic vesicle to the cell membrane and neurotransmitter release. Lead has converging effects on neurotransmitter release, binding to voltage-gated calcium channels and reducing the influx of calcium. In addition, lead competes with calcium for its binding sites on multiple proteins involved in neurotransmitter release, including calmodulin, CaM kinase II (CaMKII), and synaptotagmin (Bouton et al., 2001; Kern et al., 2000; Westerink et al., 2002). Together, these actions result in reduced neurotransmitter release at the presynaptic terminal. For example, nanomolar concentrations of lead have been found to inhibit neuronal release of glutamate and GABA (Braga et al., 1999). Disruption of normal neurotransmitter release can have a variety of consequences for the brain and behavior, depending on the specific neurotransmitter and its location in the brain.

4.5. Mitochondria

Mitochondria are organelles responsible for cellular respiration and energy production and, thus, are known as the powerhouses of eukaryotic cells. In addition to other functions, mitochondria store unbound calcium that regulates essential cellular activities such as cellular differentiation, neurogenesis, apoptosis, and signaling. Mitochondria can be found in dendrites and axon terminals where they are associated with the synthesis, storage, release, and reuptake of neurotransmitters.

Lead accumulates in mitochondria leading to oxidative stress and degradation of energy metabolism (Lidsky and Schneider, 2003; Silbergeld et al., 1980). Mitochondrial efflux of both calcium and lead occurs through a calcium uniporter (Chavez et al., 1987; Kamer and Mootha, 2015; Pounds, 1984). Lead competitively inhibits the energy-dependent intake of calcium into the mitochondrial matrix at the calcium uniporter, depleting necessary mitochondrial calcium stores (Galeotti et al., 1983; Goldstein, 1977; Holtzman et al., 1978; Parr and Harris, 1976; Pounds, 1984). Depletion of mitochondrial calcium stores is implicated in lead-induced apoptosis (Kapoor and van Rossum, 1984) and excitotoxicity (Beal et al., 1993; Lidsky and Schneider, 2003) as well as oxidation of pyridine nucleotides, and a decay in membrane potential (Chavez et al., 1987; Kapoor and van Rossum, 1984). Lead depletion of mitochondria-generated ATP energy metabolism also contributes to disruption of neuronal function (Rafałowska et al., 1996).

4.6. Non-neuronal CNS targets

Although much of the research on lead neurotoxicity has focused on neuronal cells, attention has also been given to non-neuronal brain cells. Glial cells, for example, help protect the central nervous system against toxicants and provide support to neurons.

Astroglia are a type of glial cell that provide neurons with physical structure, necessary nutrients, chemicals, and clear debris. Astroglia sequester lead, exerting neuroprotectant effects in the short term (Holtzman et al., 1987; Tiffany-Castiglioni et al., 1986, 1989). However, after chronic or elevated blood lead burdens, astroglia gradually release sequestered lead, contributing to the neuronal effects of lead. The precise mechanism by which lead accumulates in astroglia is not completely understood; however, the transport site shares properties akin to an anion-dependent transporter and a divalent metal transporter 1 (DMT1) (Cheong et al., 2004). The mode of entry may include voltage-dependent calcium channels that are activated by depletion of intracellular calcium stores (Kerper and Hinkle, 1997). Via PKC activity, lead inhibits astroglia-induced microvessel formation and function that increases the permeability of the blood brain barrier to toxicants, particularly in the developing fetus and in young children. The

increased absorption of toxicants into the brain increases the vulnerability to neurobehavioral deficits (Laterra et al., 1992).

Oligodendroglia are another type of glial cell. These are responsible for the production and maintenance of a protective myelin sheath that insulates axons (Tiffany-Castiglioni, 1993; Tiffany-Castiglioni et al., 1986). Oligodendroglia are believed to be the most lead-sensitive cell type in the brain (Tiffany-Castiglioni, 1993; Tiffany-Castiglioni et al., 1986). Lead can cause either hypomyelination or demyelination depending on concentration (Goyer, 1993; Krigman et al., 1974; Tennekoon et al., 1979; Toews et al., 1983). Lead produces a delay in the differentiation of oligodendroglia that may indirectly cause myelin damage, possibly as a result of impaired axonal growth and survival (Deng et al., 2001; Laterra et al., 1992; Tennekoon et al., 1979). Lead also interrupts the developmental maturation of oligodendrocytes by interfering with galactolipid metabolic enzymes (Deng et al., 2001). In addition, oligodendrocyte progenitors are vulnerable to low levels of lead exposure, while mature oligodendroglia are relatively resistant, suggesting a complex interaction (Deng et al., 2001).

4.7. Summary

Considerable progress has been made on the cellular mechanisms that mediate lead neurotoxicity and the resulting consequences for neuropathology, psychopathology, and behavior. However, many pioneering studies on the mechanisms of action of lead explored relatively high lead concentrations in vitro, but did not examine lower concentrations. It is possible that low levels of lead target a narrower range of cellular processes than higher levels. It would therefore be revealing to examine the targets of lead in vitro at concentrations that reflect blood levels below 5 μg/dL in vivo. It is possible that at these lower concentrations a clearer picture of the targets responsible for problems that arise from low-level lead exposure will be revealed.

5. Conclusions

Research on humans and in animal models has yet to determine a level of lead that is without neurobehavioral consequences. The CDC set 10 μg/dL as the reference level in 1991 and this was recently reduced to 5 μg/dL (ATSDR, 2017; CDC, 2005, 2017, 2018; Gilbert and Weiss, 2006; National Research Council, 1993). The reference level is now recommended to decrease to 3.5 μg/dL based on the most current NHANES data (Tsoi et al., 2016). However, levels as low as 2.5 μg/dL have been found to produce diminished cognitive function and maladaptive behavior in humans. Attention deficit hyperactivity disorder, Alzheimer's disease, Parkinson's disease and even criminal behavior have been associated with lead exposure. Of concern, there is an unequal lead burden placed on low-income and minority groups, contributing to income- and race-based health disparities. While the number of children with blood lead levels above the reference level has declined over the years following bans on leaded gasoline and leaded paint, considerable exposure continues to occur due to lead remaining in the environment from centuries of production and continued mining. Once lead is in the environment it does not dissipate.

The compilation of scientific research presented in this review argues that significant cognitive and behavioral consequences are evident at what previously were considered very low levels of lead. More controlled studies on low levels of lead would improve our understanding of the neurobehavioral consequences and mechanisms of action at these lower levels. Current human research has few prospective, longitudinal designs with lead measurements taken at critical points in development to provide us with an understanding of how early lead exposure could produce long-term effects on neuropsychological tests, health, and other outcomes. Studies on lead would also benefit from taking bone lead levels, in addition to blood lead levels. Bone lead levels are normally reserved for the elderly population, but may reveal important information about the lead burden across all ages because of its longer half-life (8–50 years, depending on bone type) compared to the half-life of lead in blood (30 days).

Likewise, more research using highly controlled animal studies is needed to better understand the neurobehavioral consequences and mechanisms of action of lower levels of lead. The current animal research has not adequately studied the impact of very low levels of lead. As with human studies, many animal studies rely on regression analyses across a range of blood lead concentrations that include high levels of lead. As an alternative, studies that compare low levels of lead directly with controls would help provide a threshold of effect for lead-induced deficits. Also, much of the animal work on lead is missing steady state or peak lead levels and often includes only one measurement at the end of the study. Some studies fail to report lead measurements, relying on previous lead levels reported by their group given similar dosing regimes. As with the clinical population, animal models will be improved by testing bone lead levels at critical points due to the longer half-life compared to blood lead levels.

With regard to policy implications, a clear understanding of the threshold for lead neurotoxicity would be a significant benefit to human health and well-being. Further research would allow for evidence-based guidance for health officials and federal agencies. This, in turn, would promote increased health and well-being by raising consumer awareness, improving environmental safety practices, and optimizing efforts to protect populations who are most vulnerable.

Conflicts of interest

None declared.

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