Developmental Neurotoxicity of Lead

Samuel Caito and Michael Aschner

Abstract Lead exposure is a major concern for the developing nervous system. Environmental exposures to lead, predominantly from contaminated water or lead paint chips, account for the majority of exposures to children. In utero and early life exposures to lead have been associated with lower IQ, antisocial and delinquent behaviors, and attention-deficit hyperactivity disorder. In this review, we will discuss sources of developmental lead exposure and mechanisms of lead neurotoxicity. We will highlight both human epidemiological studies showing associations between lead exposure and behavioral abnormalities as well as experimental data from animal studies. Finally, we will discuss the effects of lead on neurological endpoint past childhood, namely, development of Alzheimer's disease in old age.

Keywords Air quality criteria • Behavioral impairments • Permissible exposure limit (PEL) • Encephalopathy • Metalloproteins • Alzheimer's disease

Introduction

Lead is a widely used metal that has a long history of toxicity in humans. It is a very common element in the Earth's crust but not very prevalent on the Earth's surface. Therefore, developmental exposures to lead are the result of industrial processes/products. Lead is not an essential metal, such as iron, cobalt, or copper, as there are no physiological processes in humans that are dependent on lead. Exposure to lead does not confer any benefits and can result in toxicity.

Lead has many uses in industry and consumer products, primarily due to its chemical properties: softness, low melting temperature, malleability, ductility, poor conductivity, and resistance to corrosion and easily combined with other metals to form alloys. Currently lead is used in batteries, ammunition, electrodes for electrolysis, radiation shielding and reactor coolant, semiconductors, polyvinyl chloride (PVC) plastics, and sailing ballasts. However, lead is a persistent contaminant in our

S. Caito • M. Aschner (✉)
Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Ave, Forchheimer Rm 209, Bronx, NY 10461, USA
e-mail: michael.aschner@einstein.yu.edu

M. Aschner and L.G. Costa (eds.), *Neurotoxicity of Metals*, Advances in Neurobiology 18, DOI 10.1007/978-3-319-60189-2_1

environment. It has been estimated that the Greeks and Romans deposited around 400 tons of lead into the environment, which can still be measured in the polar regions of Greenland (Needleman 2004). Lead has been used in the past in pipes, kitchen utensils and tableware, ceramic pigment, cosmetics, and, due to its sweet taste, a wine sweetener. More recently, lead was used in paints, stain glass, book printing, and antiknock agents (Hernberg 2000).

The toxicity of lead has been appreciated since ancient times, with the Greek physician Dioscorides describing how "lead makes the mind give way" and that by the eighteenth century, Benjamin Franklin remarked how he did not understand how lead poisonings could still be occurring (Major 1931). Lead affects every organ system, but the nervous system is the most sensitive. The toxicity of lead has been expertly reviewed extensively (White et al. 2007; Neal and Guilarte 2010; Winneke et al. 1996); herein we give an overview of its effects on the developing nervous system. The US Environmental Protection Agency has performed a series of assessments on the safety of lead concluding that the developing organism is of greatest risk, there is no evident threshold that has been found for lead's effects on the nervous system, and behavioral impairments of developmental exposures persist into childhood and adulthood (US Environmental Protection Agency 1977, 1986, 2006). Blood lead levels are the predominant biomarker used in both human and animal studies, where blood lead levels of 80–100 μg/dl result in encephalopathy, 30–80 μg/dl disrupt cognitive function, and 30–50 μg/dl lower IQ in humans (US Environmental Protection Agency 1986, 2006). Rat and monkey studies have demonstrated that blood lead levels as low as 10 μg/dl can cause neurobehavioral deficits and learning impairments that can persist into adulthood (US Environmental Protection Agency 2006).

The developing brain is susceptible to a variety of toxins, including lead, due to its unique characteristics. The developing brain of children is highly susceptible to lead and more vulnerable than the adult brain. The high susceptibility and vulnerability as compared to adults are due to differences in exposure and toxicokinetics. Children under the age of 5 absorb triple the amount of lead from their GI tract than adults (Chamberlain et al. 1978). Brain development is a long process, with waves of cell division, migration, synaptogenesis, cellular pruning, and myelination. These processes occur at varying rates and persist into childhood. For this reason, lead has been shown to interrupt trimming and pruning of synapses, migration of neurons, and formation of neuron-glia interactions, all of which can result in failure to establish the proper connections between structures and lead to functional deficits. The duration and time of exposure are important determinants to the extent of damage. As different brain areas mature at varying rates, exposure to lead in utero can have different effects on the developing brain than a pediatric exposure.

Environmental exposures to lead have multiple effects on the developing nervous system. Some effects manifest early in an individual's life; however, recent research has associated developmental exposure with lead in the development of neurological and psychological diseases later in life. In this review, we will discuss exposure to lead in children and fetuses, mechanisms of lead toxicity, and effects of lead on cognition, attention, IQ, behavior, and the development of Alzheimer's disease (AD).

Developmental Exposures to Lead

Environmental exposures to lead compromise the major source of lead for developmental exposures in children. Pregnant mothers can be exposed to lead occupationally if they are involved in the manufacture of lead-containing products or battery recycling. Regulations from Occupational Safety and Health Administration (OSHA) have reduced lead exposure in the workplace, setting their permissible exposure limit (PEL) at 30 μg/m^3 averaged over 8 hours and a reduction in the PEL for shifts longer than 8 hours. However, the PEL is set for adults and may not be low enough for fetuses in utero.

Geographic location influences a child's exposure to lead. Lead contaminates the soil and groundwater around sites of its use, including mines, industrial sites, power plants, incinerators, and hazardous waste sites (Mielke and Reagan 1998). Food crops grown in areas of lead contamination will absorb lead from the groundwater and incorporate into the vegetable or fruits. Public drinking water contains only trace levels of lead; however, acidic (soft) water is corrosive to older lead pipes and solder, which results in lead dissolving into the water. This has been observed recently in Flint, Michigan, in 2014 and Washington, D.C., in 2001, where there was a 9.6-fold increase of elevated blood lead levels in children (Edwards et al. 2009).

Living in older homes and low-income urban dwellings that contain lead paint increases one's exposure to lead. Lead paints were desirable for their vibrant colors and durability; however, due to health concerns, leaded paints and dyes have been phased out of use to minimize lead's harmful effect on people. Ingestion of paint chips by children remains a major source of exposure in the United States. Young children are especially prone to hand-to-mouth behavior, which increases the likelihood of children eating lead paint chips. This is of great concern since children under the age of 5 absorb triple the amount of lead in their gastrointestinal tract than adults (Chamberlain et al. 1978). As paint peels and chips, paint can disintegrate into dust along friction surfaces. Lead dusts can be inhaled, and alarmingly it has been shown that particulate lead between 2 and 10 μm does not degrade but remains as a persistent contaminant (Mielke and Reagan 1998; Gasana and Chamorro 2002). The removal of lead from paints and gasoline has caused a remarkable reduction in exposures seen in the United States. In the 1970s, the median blood lead level of preschool children was 15 μg/dl, and 88% of children had a level exceeding 10 μg/dl (Mahaffey et al. 1983), according to the current Centers for Disease Control screening guideline. Presently, the mean blood lead level of preschool children in the United States is less than 2 μg/dl, and less than 2% are above 10 μg/dl (Bellinger and Bellinger 2006).

Children can be exposed to lead from its mother through the placenta in utero or through breast milk. Pregnancy allows for lead being released from bone stores. Studies using lead isotope ratios demonstrated that 80% of lead in fetal cord blood derives from maternal bone stores, whereas 20% derive from the more recent exposure (Gulson et al. 2003). Alcohol consumption late in pregnancy and high blood

pressure have been shown to increase lead deposition from the mother into cord blood, while high hemoglobin content or sickle cell trait is associated with decreased cord blood levels of lead (Harville et al. 2005). Unlike in utero lead exposure, lead exposure through breast milk is more influenced by maternal blood lead concentrations than by maternal bone lead levels (Ettinger et al. 2006).

Neurobehavioral Effects of Lead

Extremely high levels of lead exposure (blood lead levels between 60 and 300 μg/dL) result in encephalopathy in children. Lead encephalopathy can present as hyperirritability, ataxia, convulsions, stupor, coma, and death. Pathologically, it is characterized by endothelial cell swelling and necrosis of the cerebral and cerebellar capillaries, capillary leakage and cerebral edema, loss of neuronal cells, cytoplasmic vacuolization, interstitial edema, and demyelination of nerve fibers. Nonfatal neurobehavioral effects occur at much lower blood lead levels than lead encephalopathy.

Lead exposure has been associated with delinquent behavior, attention deficit hyperactivity disorder (ADHD), and decrements in IQ. The effects of lead on delinquent behavior come from analyses on school-aged children, teenagers, and crime statistics. Bone lead levels have been associated with aggression, attention, and delinquency in children as well as with arrest and adjudication in the juvenile court system (Needleman et al. 2002). Prenatal lead exposure also has a positive correlation with delinquent behavior and drug use as a teenager (Dietrich et al. 2001). It has also been noted that in areas of lead air pollution from gasoline, there is increased incidence of homicides and violent crimes in the Unites States after adjusting for unemployment and percent of population in the high-crime age group (Nevin 2000; Stretesky and Lynch 2001). The mechanism behind lead-induced delinquency is not fully understood. Delinquent behavior in adolescence has been associated with alterations in the hypothalamus pituitary adrenal (HPA) axis (Popma et al. 2006). The HPA axis has been shown to be a target of lead toxicity. In rats exposed to lead either maternally or early in life, there were changes in the functioning of the HPA axis, including altered corticosterone levels (Virgolini et al. 2006; Cory-Slechta et al. 2004). One of the many functions of the HPA axis is to respond to and manage stress; rats exposed to lead had poor stress responses, which were worse in rats exposed to lead and stress (Virgolini et al. 2006).

ADHD is a chronic condition where those affected have difficulty with attention and concentration and are hyperactive and impulsive. An assessment of child behavior by classroom teachers using the Child Behavior Checklist and Disruptive Behavior Disorders Rating Scale of 279 Inuit children aged 11 years in Arctic Quebec found low levels of childhood lead exposure were associated with ADHD behaviors (Boucher et al. 2012). This population was characterized as a predominantly fish-eating population and had significant blood methylmercury levels, which may be a confounder. However, in a case-control study with 71 medically diagnosed

ADHD cases and 58 controls performed near a former lead refinery in Omaha, NE, there was a clear increase in the odds ratio that for each natural log unit of blood lead, there was an odds ratio of 2.52 having ADHD, after adjusting for maternal smoking, socioeconomic status, and environmental smoke exposure (Kim et al. 2013). No similar risk was found for blood mercury or cadmium levels (Kim et al. 2013). Furthermore, a performance and questionnaire study of children in Romania found correlations between blood lead levels, but not mercury or aluminum (Nicolescu et al. 2010). Lead exposure causes similar hyperactive and attention deficits in wild-type rodents (Luo et al. 2014; Sanchez-Martin et al. 2013) or in a genetic rat model prone to neuropsychiatric problems (Ruocco et al. 2015).

Intelligence is negatively affected by lead exposure. The amount of IQ points that are decreased in an individual lead-exposed child is small; however, the troubling effect of lead is on the population as a whole. Lead shifts the population's IQ, leading to fewer individuals in the higher end of the IQ spectrum and more individuals in the lower end. In a study performed from 1978 to 2007, researchers compared blood lead levels in Swedish children ages 7–12, school performance at age 16, and overall IQ at ages 18–19. Over the course of 29 years, there was a statistically significant negative association between school performance, IQ, and blood lead levels below 50 μg/dL. Low exposures of lead (<60 μg/dL blood lead level) early in life cause a decrease in IQ around the time children enter school even though at school age blood lead levels are lower than at the time of exposure (Chen et al. 2005). In a study, 780 children were followed from age 2 to age 7 after being treated for elevated blood lead levels (20–44 μg/dL), and serial IQ tests were administrated, showing decreased IQ, while average lead level at age 7 was 8 μg/dL (Chen et al. 2005). Furthermore, in utero exposures to lead as early as during the first trimester of pregnancy have been associated with decreases in intelligence scores (Hu et al. 2006). Areas of intelligence that have shown decrements include arithmetic skills, reading skills, nonverbal reasoning, reaction time, visual-motor integration, fine motor skills, attention, and short-term memory (White et al. 2007; US Environmental Protection Agency 1977, 1986, 2006). While multiple studies have examined the effects of lead on IQ in various locations around the globe, there are variables that affect the effects of lead. Socioeconomic status, prenatal smoking, maternal age, and prenatal alcohol use exacerbate the effects of lead on IQ (Lanphear et al. 2005).

Molecular Mechanisms of Neurotoxicity

Following inhalation or ingestion, lead enters the bloodstream and will find its way to the brain through both the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier. The endothelial cells in the BBB microvasculature and the choroid plexus cells that comprise the blood-CSF barrier accumulate lead, causing the barriers to become leaky. This can result in increased permeability of the barriers, brain swelling, herniation, ventricular compression, petechial and cerebral hemorrhages, thrombosis, and arteriosclerosis (Zheng et al. 2003). Lead mimics the action

of both iron and calcium, altering these ions' homeostasis and signaling. In the BBB and blood-CSF cells, lead can bind to calcium-dependent protein kinase C (PKC) enzymes, activating the kinases and increasing endothelial permeability (Markovac and Goldstein 1988). Additionally, accumulation of lead by the choroid plexus causes a decrease in transthyretin production (Zheng et al. 1996), disrupting thyroid hormone signaling. The thyroid itself is also targeted by lead and, upon developmental exposure, shows abnormal architecture and decreased functioning (Kumar et al. 2016). Whether the effects on the thyroid are direct actions of lead or indirect due to altered transthyretin production remains to be determined.

Alteration in calcium signaling has important implications on learning and memory deficits in lead-exposed children. Neurotransmitter release through voltage-gated Ca^{2+} channels has been shown to either impede or spontaneously release neurotransmitters (Minnema et al. 1988; Atchison and Narahashi 1984). Cognitive function in rodent studies is usually measured by long-term potentiation (LTP) from hippocampal slices, which require presynaptic glutamate release and subsequent activation of the postsynaptic N-methyl-D-aspartate (NMDA) glutamate receptor (Sui et al. 2000a, b; Altmann et al. 1993). Chronic exposures to lead beginning in utero and continued past weaning as well as transient exposures to lead from in utero to weaning altered presynaptic release of glutamate in the hippocampus (Gilbert et al. 1996, 1999; Lasley et al. 1999). This data suggests that continual presence of lead is not necessary for neurochemical changes but that there is a window of exposure that can produce irreversible deficits. Acute exposures to lead in cell culture or brain tissue homogenates have demonstrated its ability to block the NMDA receptor (Neal et al. 2010; Lasley and Gilbert 1999; Alkondon et al. 1990). Blockade of the NMDA receptor by lead further disrupts calcium signaling. In altering both the presynaptic glutamate release and postsynaptic receptor signaling, lead significantly changes the ways in which the hippocampus produces LTPs. This has implications on memory function, as a neuronal mechanism for memory has different phases of LTPs (short term, intermediate, and long term) (Matthies et al. 1990; Reymann and Frey 2007). Lead exposure results in very long-lasting LTPs, which hinders the formation of short-term and intermediate phases (Gilbert and Mack 1998).

In addition to altering calcium homeostasis, lead can displace metals in metalloproteins and induce oxidative stress. Lead can substitute for physiologic metals in metalloproteins, leading to alteration in protein function. For example, lead binds to the zinc-binding site of the Cys_2/His_2 zinc finger transcription factors TFIIIA and Sp1 (Hanas et al. 1999; Rodgers et al. 2001), the function of which is important for the developing brain. Lead also substitutes for divalent metals present in Cu/Zn superoxide dismutase (SOD), MnSOD, and glutathione peroxidase (GPx) 1 and GPx4, inhibiting these enzymes which are responsible for scavenging reactive oxygen species (ROS). As with many heavy metal exposures, lead can bind to glutathione (GSH) and decrease the reactive thiol pool, increasing the oxidative stress. Disruption of mitochondrial calcium signaling can lead to the generation of ROS and loss of mitochondrial membrane potential, initiate apoptosis, and inhibit the Na^+/K^+ ATPase, decreasing cellular ATP levels (Baranowska-Bosiacka et al. 2011).

Developmental Exposures to Lead and Alzheimer's Disease

While several studies investigate the influence of lead exposure on IQ and cognition in children, developmental lead exposure in rodents and nonhuman primates has shown links to the development of Alzheimer's disease (AD) later in life. Alzheimer's disease is the most common neurodegenerative disease. It is characterized by dementia and loss of cognition, with a brain pathology comprised of proteinaceous plaques comprised of amyloid beta (Aβ). In postmortem human brains of AD patients, lead levels have been measured to be significantly higher in the globus pallidus, dentate gyrus, temporal cortex, and temporal white matter than in control healthy age-matched brains (Haraguchi et al. 2001a, b). An observational study of elderly individuals exposed to multiple heavy metals living near the volcano Etna in Sicily found increased lead in the blood of AD patients than in healthy controls (Giacoppo et al. 2014). Pb exposure increases amyloid precursor protein (APP) mRNA and aggregation of Aβ in rats, amyloidogenesis, and senile plaque deposition and upregulates APP proteins in nonhuman primates exposed to lead as infants (Basha et al. 2005a, b; Wu et al. 2008). After exposing mice to lead during different life span periods, Bihaqi et al. found that a window of vulnerability to lead toxicity exists in the developing brain, where cognitive impairment occurred only in mice exposed to Pb as infants, but not as adults (Bihaqi et al. 2014a). Early life exposure of mice to lead enhances the expression of AD-associated protein tau and alters epigenetic markers associated with the development of AD (Bihaqi et al. 2014b; Masoud et al. 2016). An epigenetic basis for the increased expression of AD-related proteins and cognitive decline is an emerging hypothesis to explain the link between early life exposure to lead and AD. Exposures that occur during fetal or early life stages can produce epigenetic changes in the brain leading reprogramming of genes. In a study of rats exposed in utero or postnatally to Pb, decreased DNA methyltransferase expression was found in the hippocampus of exposed females (Schneider et al. 2013), suggesting that less DNA methylation may be occurring and allowing for genes that are normally repressed to be expressed. Gene expression for DNA methyltransferases in this study was performed at postnatal day 55 (Schneider et al. 2013). Conversely, in a genome-wide expression and methylation profiling experiment carried out in infant Pb-exposed mice aged to postnatal day 700, there was a repression of a set of genes that are normally expressed in aged mice (Dosunmu et al. 2012). These genes were involved in the immune response, metal binding, and metabolism, repression of which due to developmental exposure to Pb compromises the brain's ability to defend against age-related stressors.

Conclusions

Lead is a highly toxic metal that poses great risks to the developing nervous system. Environmental exposures to lead are a major problem for children growing up communities with old homes and water systems, as the recent mass exposure in Flint, Michigan (USA), illustrates. While the effects of lead have been associated with behavioral and cognitive deficits in childhood, we are starting to understand the long-term effects of developmental lead exposure as the population ages.

References

Alkondon M, Costa AC, Radhakrishnan V, Aronstam RS, Albuquerque EX. FEBS Lett. 1990;261(1):124–30.
Altmann L, Weinsberg F, Sveinsson K, Lilienthal H, Wiegand H, Winneke G. Toxicol Lett. 1993;66(1):105–12.
Atchison WD, Narahashi T. Neurotoxicology. 1984;5(3):267–82.
Baranowska-Bosiacka I, Gutowska I, Marchetti C, Rutkowska M, Marchlewicz M, Kolasa A, Prokopowicz A, Wiernicki I, Piotrowska K, Baskiewicz M, Safranow K, Wiszniewska B, Chlubek D. Toxicology. 2011;280(1-2):24–32.
Basha MR, Murali M, Siddiqi HK, Ghosal K, Siddiqi OK, Lashuel HA, Ge YW, Lahiri DK, Zawia NH. FASEB J Off Publ Feder Am Soc Exp Biol. 2005a;19(14):2083–4.
Basha MR, Wei W, Bakheet SA, Benitez N, Siddiqi HK, Ge YW, Lahiri DK, Zawia NH. J Neurosci Off J Soc Neurosci. 2005b;25(4):823–9.
Bellinger DC, Bellinger AM. J Clin Invest. 2006;116(4):853–7.
Bihaqi SW, Bahmani A, Subaiea GM, Zawia NH. Alzheimers Dement. 2014a;10(2):187–95.
Bihaqi SW, Bahmani A, Adem A, Zawia NH. Neurotoxicology. 2014b;44:114–20.
Boucher O, Jacobson SW, Plusquellec P, Dewailly E, Ayotte P, Forget-Dubois N, Jacobson JL, Muckle G. Environ Health Perspect. 2012;120(10):1456–61.
Chamberlain A, Heard C, Little M. Philos Trans R Soc Lond A. 1978;290:557–89.
Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ. Environ Health Perspect. 2005;113(5):597–601.
Cory-Slechta DA, Virgolini MB, Thiruchelvam M, Weston DD, Bauter MR. Environ Health Perspect. 2004;112(6):717–30.
Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL. Neurotoxicol Teratol. 2001;23(6):511–8.
Dosunmu R, Alashwal H, Zawia NH. Mech Ageing Dev. 2012;133(6):435–43.
Edwards M, Triantafyllidou S, Best D. Environ Sci Technol. 2009;43(5):1618–23.
Ettinger AS, Tellez-Rojo MM, Amarasiriwardena C, Peterson KE, Schwartz J, Aro A, Hu H, Hernandez-Avila M. Am J Epidemiol. 2006;163(1):48–56.
Gasana J, Chamorro A. J Expo Anal Environ Epidemiol. 2002;12(4):265–72.
Giacoppo S, Galuppo M, Calabro RS, D'Aleo G, Marra A, Sessa E, Bua DG, Potorti AG, Dugo G, Bramanti P, Mazzon E. Biol Trace Elem Res. 2014;161(2):151–60.
Gilbert ME, Mack CM. Brain Res. 1998;789(1):139–49.
Gilbert ME, Mack CM, Lasley SM. Brain Res. 1996;736(1-2):118–24.
Gilbert ME, Mack CM, Lasley SM. Neurotoxicology. 1999;20:57–70.
Gulson BL, Mizon KJ, Korsch MJ, Palmer JM, Donnelly JB. Sci Total Environ. 2003;303(1–2):79–104.
Hanas JS, Rodgers JS, Bantle JA, Cheng YG. Mol Pharmacol. 1999;56(5):982–8.

Haraguchi T, Ishizu H, Takehisa Y, Kawai K, Yokota O, Terada S, Tsuchiya K, Ikeda K, Morita K, Horike T, Kira S, Kuroda S. Neuroreport. 2001a;12(18):3887–90.
Haraguchi T, Ishizu H, Kawai K, Tanabe Y, Uehira K, Takehisa Y, Terada S, Tsuchiya K, Ikeda K, Kuroda S. Neuroreport. 2001b;12(6):1257–60.
Harville EW, Hertz-Picciotto I, Schramm M, Watt-Morse M, Chantala K, Osterloh J, Parsons PJ, Rogan W. Occup Environ Med. 2005;62(4):263–9.
Hernberg S. Am J Ind Med. 2000;38(3):244–54.
Hu H, Tellez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, Schwartz J, Schnaas L, Mercado-Garcia A, Hernandez-Avila M. Environ Health Perspect. 2006;114(11):1730–5.
Kim S, Arora M, Fernandez C, Landero J, Caruso J, Chen A. Environ Res. 2013;126:105–10.
Kumar BK, Reddy AG, Krishna AV, Quadri SS, Kumar PS. Vet World. 2016;9(2):133–41.
Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Environ Health Perspect. 2005;113(7):894–9.
Lasley SM, Gilbert ME. Toxicol Appl Pharmacol. 1999;159(3):224–33.
Lasley SM, Green MC, Gilbert ME. Neurotoxicology. 1999;20:619–30.
Luo M, Xu Y, Cai R, Tang Y, Ge MM, Liu ZH, Xu L, Hu F, Ruan DY, Wang HL. Toxicol Lett. 2014;225(1):78–85.
Mahaffey KR, Annest JL, Murphy RS. N Engl J Med. 1983;307:573–9.
Major RH. Ann Med Hist. 1931;3:218–27.
Markovac J, Goldstein GW. Nature. 1988;334(6177):71–3.
Masoud AM, Bihaqi SW, Machan JT, Zawia NH, Renehan WE. J Alzheimers Dis. 2016;
Matthies H, Frey U, Reymann K, Krug M, Jork R, Schroeder H. Adv Exp Med Biol. 1990;268:359–68.
Mielke HW, Reagan PL. Environ Health Perspect. 1998;106(Suppl 1):217–29.
Minnema DJ, Michaelson IA, Cooper GP. Toxicol Appl Pharmacol. 1988;92(3):351–7.
Neal AP, Guilarte TR. Mol Neurobiol. 2010;42(3):151–60.
Neal AP, Stansfield KH, Worley PF, Thompson RE, Guilarte TR. Toxicol Sci. 2010;116(1):249–63.
Needleman H. Annu Rev Med. 2004;55:209–22.
Needleman HL, McFarland C, Ness RB, Fienberg SE, Tobin MJ. Neurotoxicol Teratol. 2002;24(6):711–7.
Nevin R. Environ Res. 2000;83(1):1–22.
Nicolescu R, Petcu C, Cordeanu A, Fabritius K, Schlumpf M, Krebs R, Kramer U, Winneke G. Environ Res. 2010;110(5):476–83.
Popma A, Jansen LM, Vermeiren R, Steiner H, Raine A, Van Goozen SH, van Engeland H, Doreleijers TA. Psychoneuroendocrinology. 2006;31(8):948–57.
Reymann KG, Frey JU. Neuropharmacology. 2007;52(1):24–40.
Rodgers JS, Hocker JR, Hanas RJ, Nwosu EC, Hanas JS. Biochem Pharmacol. 2001;61(12):1543–50.
Ruocco LA, Treno C, Gironi Carnevale UA, Arra C, Boatto G, Pagano C, Tino A, Nieddu M, Michel M, Prikulis I, Carboni E, de Souza Silva MA, Huston JP, Sadile AG, Korth C. Amino Acids. 2015;47(3):637–50.
Sanchez-Martin FJ, Fan Y, Lindquist DM, Xia Y, Puga A. PLoS One. 2013;8(11):e80558.
Schneider JS, Kidd SK, Anderson DW. Toxicol Lett. 2013;217(1):75–81.
Stretesky PB, Lynch MJ. Arch Pediatr Adolesc Med. 2001;155(5):579–82.
Sui L, Ruan DY, Ge SY, Meng XM. Neurotoxicol Teratol. 2000a;22(5):741–9.
Sui L, Ge SY, Ruan DY, Chen JT, Xu YZ, Wang M. Neurotoxicol Teratol. 2000b;22(3):381–7.
US Environmental Protection Agency. Air quality criteria for lead. Research Triangle Park: Health Effects Research Laboratory, Criteria and Special Studies Office; 1977.
US Environmental Protection Agency. Air quality criteria for lead, Office of Health and Environmental Assessment. Research Triangle Park: Environmental Criteria and Assessment Office; 1986.

US Environmental Protection Agency. Air quality criteria for lead, vol. I and II of II. Research Triangle Park: National Center for Environmental Assessment – RTP Office; 2006.
Virgolini MB, Bauter MR, Weston DD, Cory-Slechta DA. Neurotoxicology. 2006;27(1):11–21.
White LD, Cory-Slechta DA, Gilbert ME, Tiffany-Castiglioni E, Zawia NH, Virgolini M, Rossi-George A, Lasley SM, Qian YC, Basha MR. Toxicol Appl Pharmacol. 2007;225(1):1–27.
Winneke G, Lilienthal H, Kramer U. Arch Toxicol Suppl. 1996;18:57–70.
Wu J, Basha MR, Brock B, Cox DP, Cardozo-Pelaez F, McPherson CA, Harry J, Rice DC, Maloney B, Chen D, Lahiri DK, Zawia NH. J Neurosci Off J Soc Neurosci. 2008;28(1):3–9.
Zheng W, Shen H, Blaner WS, Zhao Q, Ren X, Graziano JH. Toxicol Appl Pharmacol. 1996;139(2):445–50.
Zheng W, Aschner M, Ghersi-Egea JF. Toxicol Appl Pharmacol. 2003;192(1):1–11.