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REVIEW ARTICLE

Angiogenesis and lead (Pb): is there a connection?

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ABSTRACT

Lead (Pb) is a toxic heavy metal ubiquitously distributed around the world, especially in industrial areas. Occupational and environmental exposures to Pb have detrimental effects on human health. Pb affects functioning of many systems of the human body, including the cardiovascular system. Angiogenesis, the process of new blood vessel formation, which makes critical contribution throughout life is deranged in various diseases. Excessive angiogenesis may result in different diseases including cancer. On the other spectrum, insufficient angiogenesis is observed in many diseases, such as atherosclerosis, hypertension, and cardiovascular disease. These disorders are also associated with occupational Pb exposure. In this paper, epidemiological and experimental studies are reviewed selectively for evidence in support of this hypothesis, that is, interactions between Pb and angiogenesis. We discuss the evidence for the possible mechanism of Pb impact on concentrations of angiogenic factors. Studies suggested that Pb exposure affects the level of angiogenic factors associated with angiogenesis regulation and promotion. Further research is needed, especially in the mechanisms in which Pb-induced vascular endothelial growth factor (VEGF) disregulation is present. We believe that characterizing the connection between Pb and angiogenesis will provide helpful information for the development of intervention strategies to reduce the adverse effects of Pb exposure.

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1. Introduction

Industrial development increases the threat to human health caused by chemical contamination of the environment. Occupational and environmental exposures to lead (Pb) have detrimental effects on human health. Pb affects functioning of many systems of the human body, including the cardiovascular system (Navas-Acien *et al.* 2007, Cosselman *et al.* 2015). Pb uptake into the cell is affected by the pH changes and the cell type (Simons 1986, Cheong 2004). Pb^{2+} ions can mimic Fe^{2+} and Ca^{2+} to gain access to the intracellular compartment using their transporters (Christy and Rudolfs 2010). Pb toxicity is caused by its high affinity for cysteine –SH group, tyrosine –OH group, lysine $-NH_2$ group, glutamic/aspartic acid carboxylate (COO^-), and phosphate groups in proteins, enzymes, and cell membranes (Sisombath and Jalilehvand 2015). Pb^{2+} has also similar ionic radius (1.19 Å) as Ca^{2+} (1.00 Å) and Zn^{2+} (0.74 Å) and it can displace both Ca^{2+} and Zn^{2+} in proteins (Godwin 2001). Another potential mechanism of Pb toxicity is the ability of Pb to induce oxidative stress.

Angiogenesis, the process of new blood vessel formation, which makes critical contribution throughout life with important role in successful regeneration and growth of new tissues is important for normal functioning of the organism. Excessive angiogenesis may result in different diseases including cancer (Bisht *et al.* 2010). On the other spectrum, insufficient angiogenesis is observed in many diseases, such as atherosclerosis, hypertension, and cardiovascular disease (Khurana *et al.* 2005, Radomska-Leśniewska *et al.* 2016). These disorders are also associated with occupational Pb exposure (Silbergeld *et al.* 2000, Vaziri 2008, Poręba *et al.* 2011, Prokopowicz *et al.* 2017). Several reviews have examined the possible mechanisms relating Pb and cardiovascular alteration (Peters *et al.* 2012, Shinkai and Kaji 2012, Solenkova *et al.* 2014).

In this paper, epidemiological and experimental studies are reviewed selectively for evidence in support of this hypothesis, that is, interactions between Pb and angiogenesis. We discuss the evidence for the possible mechanism of Pb impact on concentrations of angiogenic factors.

1.1. Search strategy

The searching methodology used in this review article included electronic searches which were done in the PubMed database by using key words mentioned in the MeSH regarding the role of Pb in modulation of angiogenesis as well as production of stimulatory or inhibitory factors that impact angiogenesis processes.

2. Pb and endothelial dysfunction – *in vitro* studies

There are only a few *in vitro* studies showing adverse effects of Pb on endothelial cells (EC) and vascular smooth muscle

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cells (VSMC). The endothelium plays a central role in the regulation of vascular function, macromolecular permeability, tissue perfusion, blood fluidity, and numerous other vital functions. Endothelial damage or dysfunction results in atherosclerosis, thrombosis, and tissue injury (Navas-Acien *et al.* 2007, Vaziri 2008, Shinkai and Kaji 2012).

In VSMC, Pb in concentrations 0.5–10 μM had a stimulatory, dose-dependent manner on cells growth and proliferation (Fujiwara 1995). Another *in vitro* studies demonstrated that Pb inhibits the repair of wounded monolayers, reduces proliferation without nonspecific cell damage (Kaji *et al.* 1995, 1997, Kishimoto *et al.* 1995, Ueda *et al.* 1997; Table 1). These results suggest that Pb is potentially involved in the alteration of new blood vessels from preexisting vessels by multiple mechanisms.

3. Pb and selected angiogenic factors

Angiogenesis is regulated by an extensive variety of angiogenic stimulators and inhibitors (Table 2). *In vitro* studies suggest that Pb may modulate angiogenesis *via* induced interleukin 8 (IL-8) gene expression *via* the plasma membrane epidermal growth factor receptor (EGFR) through mitogen activated protein kinases (MAPK) pathway, activator protein 1 (AP-1), and nuclear factor-kappa B (NF-κB) (Figure 1) (Chang *et al.* 2011, Chou *et al.* 2011, Lin *et al.* 2015, Saghiri *et al.* 2016). IL-8 was indicated to promote tumor angiogenesis and invasion *via* inducing angiogenesis and the epithelial–mesenchymal transition of multiple human carcinoma cells (Petzelbauer 1995). Dobrakowski *et al.* (2016a) showed that the level of IL-8 was significantly increased after subchronic and chronic occupational exposure to Pb, by 34% and 40%, respectively. This observation also supports the hypothesis that Pb exposure may indirectly affect angiogenesis.

Vascular endothelial growth factor (VEGF), the key angiogenic growth factor, stimulates proliferation, migration, and tube formation of ECs primarily through the soluble vascular endothelial growth factor receptor-2 (sVEGFR-2; Ushio-Fukai 2006). *In vitro* studies have shown that Pb induces the expression and levels of VEGF in rat spinal cord astrocyte culture with superoxide dismutase-1 G93A mutation (Barbeito *et al.* 2010) and in immortalized human fetal astrocytes (Hossain *et al.* 2000). However, Bouton *et al.* (2001) did not find VEGF in a microarray screen after Pb-exposure on astrocytes. Nevertheless, Kasten-Jolly and Lawrence (2017) demonstrated that low Pb exposure resulted in decreased angiogenesis by increased expression of EVH1 domain-containing protein-1 (Spred-1) in Pb exposed mice. Signal transduction through the VEGF includes Raf and ERK, Spred-1 negatively regulates the ERK pathway by inhibiting the function of Raf.

The analysis for expression of factors associated with early stages of angiogenesis indicated that Pb exposure changed the expression pattern of these factors. The molecular mechanism of these alterations is not clear. Some data suggested

Table 1. Systemic classificatory list of *in vitro* studies reporting the lead impact on endothelial dysfunction.

Cell types	Lead dose (μM)	Main finding	References
Vascular smooth muscle cells	0.5–10	Stimulatory, dose-dependent manner on cells growth and proliferation	Fujiwara (1995)
Aortic endothelial cells	0.5, 1.0, 2.0, or 5.0	Inhibition of the proliferation of cultured cells, without nonspecific cell damage	Kaji *et al.* (1995)
Vascular endothelial cells	10	Alteration of heparan sulfate proteoglycans	Kaji *et al.* (1997)
Vascular endothelial cells	0.3–30.0	Dose-dependently inhibition of the tube formation	Ueda *et al.* (1997)
Vascular endothelial cells	0.1–50.0	Dose-dependently inhibition of the tube formation	Kishimoto *et al.* (1995)

Table 2. Systemic classificatory list of epidemiological and experimental studies reporting the lead impact on selected angiogenic factors.

Epidemiological (Ep) or experimental (Ex) studies	Pb concentration or dose	Main finding	References
Ex: Vascular smooth muscle cell	1 μM	EGFR activation COX-2/cPLA2 expression ↑	Chang *et al.* (2011)
Ex: Gastric carcinoma cells	0.1 μM	IL-8 expression ↑	Lin *et al.* (2015)
Ex: Vascular smooth muscle cells	1 μM	COX-2 expression ↑ EGFR/NF-κB signal transduction pathway ↑	Chou *et al.* (2011)
Ep: Occupational lead exposure	36.6 and 48.7 μg/dl	IL-8 concentration ↑	Dobrakowski *et al.* (2016a, 2016b)
Ex: Rat spinal cord astrocyte	27 μg/dl	VEGF expression ↑	Barbeito *et al.* (2010)
Ex: Human fetal astrocytes	10 μM	VEGF expression ↑ PKC/AP-1/HIF-1 signal transduction pathway ↑	Hossain *et al.* (2000)
Ex: Rat astrocytes	10 μM	VEGF expression –	Bouton *et al.* (2001)
Ex: Pb-exposure mice	Low lead exposure	Spred-1 ↑ VEGF expression ↓	Kasten-Jolly and Lawrence (2017)
Ex: Glia cells	25 μM	COX-2 expression ↑	Wei *et al.* (2014)
Ex: Pb-exposure rats	0.25 mM	NOS ↑	Ramesh and Jadhav (2001)
Ex: Pb-exposure mice	0.1 mM	NOS2 expression ↑ VEGF expression ↑ MAPK signal transduction pathway ↑	Kasten-Jolly *et al.* (2012)
Ex: Pb-exposure rats	25 mg/kg of body weight	HIF-1α concentration ↑ VEGF concentration ↑	Das *et al.* (2015)
Ex: Human breast cancer cell	1 mM	NOS activity ↓	Zhong *et al.* (2014)
Ep: Occupational lead exposure	37.0 μg/dl	sVEGFR-1concentration ↑ FGF-basic concentration ↑	Machoń-Grecka *et al.* (2017)

EGFR: epidermal growth factor receptor; cPLA2: calcium-dependent Phospholipase A2; PKC: protein kinase C; MAPK: mitogen activated protein kinases; AP-1: activator protein 1; NF-κB: nuclear factor-kappa B; VEGF: vascular endothelial growth factor; Spread-1: sprouty-related: EVH1 domain-containing protein 1; COX-2: cyclooxygenase-2; NOS2: nitric oxide synthase 2; HIF-1α: Hypoxia-inducible factor 1-alpha; sVEGFR-1: soluble vascular endothelial growth factor receptor-1; FGF-basic: fibroblast growth factor-basic.

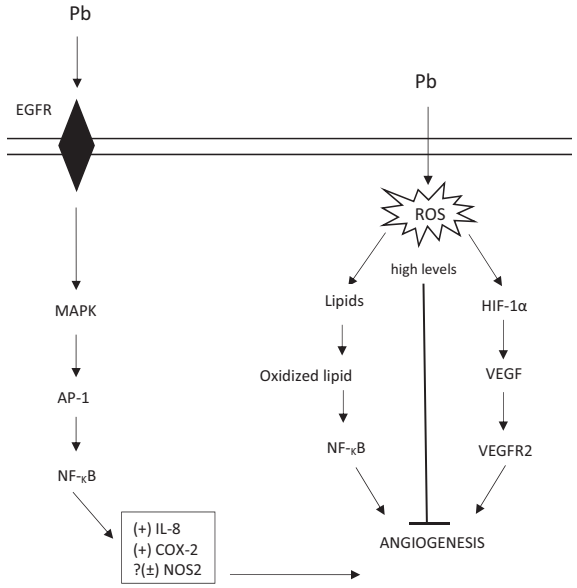

Figure 1. Hypothetical scheme for Pb-modulated angiogenesis. Pb activated the plasma membrane epidermal growth factor receptor (EGFR) through mitogen activated protein kinases (MAPK) pathway, activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), and increased gene expression for Interleukin 8 (IL-8), Cyclooxygenase-2 (COX-2) and Nitric Oxide Synthase 2 (NOS2). Pb stimulated intracellular ROS production. ROS promotes angiogenic responses in various tissues by HIF-1α/VEGF/VEGFR2 signaling pathway or VEGF-independent mechanism *via* lipid oxidation products and nuclear factor-kappa B (NF-κB).

that Pb might have activated transcription of the Cyclooxygenase-2 (COX-2) genes *via* the plasma membrane epidermal growth factor receptor (Figure 1) (Chou *et al.* 2011). COX is the key enzyme required for the conversion of arachidonic acid to prostaglandins. Wei *et al.* (2014) showed the influence of Pb on the induction of COX-2 gene transcription in the mechanism mediated by transcription factors NF-κB, AP-1, and NFAT (nuclear factor of activated T cells). COX-2 is a source of inflammatory mediators and regulates production of angiogenic factors, including VEGF (Kolev *et al.* 2007, Koh *et al.* 2013). COX-2 and its related angiogenic factors may play an important role in promoting morphological change in the microvasculature.

It has been known for many years that subchronic and chronic Pb exposure is able to promote production of proinflammatory mediators and cytokines. Recent studies discussed the possible relationship between expression of the nitric oxide synthase 2 (NOS2) and angiogenesis (Niu 2004, Cheng *et al.* 2014, Lee *et al.* 2016). Some data suggested that Pb exposure causes the up-regulation of NOS2 gene expression (Figure 1) (Ramesh and Jadhav 2001, Kasten-Jolly *et al.* 2012). Moreover, Das *et al.* (2015) showed that both Pb acetate and chronic sustained hypoxia stimulate the production of hypoxia-inducible factor 1-alpha (HIF-1α) transcription factor and VEGF gene expression in hepatic tissue, which are reflected by increased serum HIF-1α and VEGF levels. This alterations were due to changes in the hyper activities of NOS2. However, other studies implied that Pb treatment reduced NOS activity and nitric oxide (NO) production (Zhong *et al.* 2014).

The soluble form of vascular endothelial growth factor receptor-1 (sVEGFR-1) retains its high-affinity binding to VEGF and it is likely to be a negative regulator of VEGF availability by sequestrating the ligand and by forming inactive heterodimers with membrane-bound VEGF receptors (Wierzbowska *et al.* 2003, Duda 2012). Our previous study showed that chronic, occupational Pb exposure (BLL = 37.0 μg/dl) is associated with elevated levels of sVEGFR-1 and fibroblast growth factor-basic (FGF-basic) (Machoń-Grecka *et al.* 2017). However, in the same Pb exposed group we indicated lower levels of leptin (Dobrakowski *et al.* 2017). Both FGF-basic and leptin are positive modulators of angiogenesis (Yamagishi *et al.* 2003, Khurana *et al.* 2005).

4. Oxidative stress due to Pb exposure and angiogenesis

The reactive oxygen species (ROS) can be generated either endogenously, through mitochondrial electron transport chain reactions and nicotinamide adenine dinucleotide phosphate oxidase, or exogenously, resulting from exposure to environmental agents, such as Pb. Previous studies suggested that Pb was known to induce oxidative stress by increasing the production of ROS. Moreover, studies relating the effect of Pb on prooxidant/antioxidant balance represent one of the principal trends in scientific research on Pb toxicology. *In vitro* (Xue *et al.* 2017) and *in vivo* animal studies (Patra *et al.* 2001, Pande and Flora 2002) indicated that Pb induced oxidative damage. This was supported by several human studies (Gurer-Orhan *et al.* 2004, Dobrakowski *et al.* 2016a, 2016b).

There are numbers of compelling studies in which ROS activated angiogenesis *via* two different mechanisms; VEGF-dependent and VEGF-independent mechanism (Radomska-Leśniewska *et al.* 2016). Exogenous ROS stimulates induction of VEGF through HIF-1α–VEGF/VEGFR2 signaling pathway (Ushio-Fukai and Nakamura 2008). The VEGF-independent mechanism mediating proangiogenic function of ROS involves the generation of new lipid oxidation products with proangiogenic activities (Figure 1) (Kim and Byzova 2014).

Results of the recent study show that Pb acetate stimulates the production of ROS, HIF-1α transcription factor, and VEGF gene expression in chronic exposure rats (Das *et al.* 2015). Sun *et al.* (2017) found that HIF-1α gene expression increased after Pb treated in human and mouse-derived primary cells. Other elements such as cobalt or nickel have also been shown to stabilize HIF proteins and promote transcription of HIF-1α-mediated genes (Wang *et al.* 2009).

5. Conclusions

The impact of Pb on angiogenesis is poorly understood. Although pieces of evidence in support of the hypothesis of connection between angiogenesis and Pb are strong. Studies suggested that Pb exposure affects the level of angiogenic factors associated with angiogenesis regulation and promotion. Unfortunately, presented *in vitro* studies have significant limitations resulting from selected Pb doses. Bannon *et al.* (2016) noted that matching target dose to target organ is an

often overlooked aspect of *in vitro* assays. Authors suggest that the Pb dose of 0.1 μM is at the highest end of Pb toxicity, perhaps even lethal. In the discussed *in vitro* studies, the medium Pb does is about 10 μM and it is extremely high, which can significantly affect conclusions about the relationship between Pb and angiogenesis. Cellular stress, mediated by Pb, leads to an adaptive response involving various mechanisms stimulating the early stage of angiogenesis. Further research is needed, especially in mechanisms in which Pb-induced VEGF dysregulation is present. We believe that characterizing the connection between Pb and angiogenesis will provide helpful information for the development of intervention strategies to reduce the adverse effects of Pb exposure.

Disclosure statement

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References

Bannon, D.I., *et al.*, 2016. Open peer review: Matching target dose to target organ [version 2; peer review: 2 approved]. *F1000Research*, 5, 2785.

Barbeito, A.G., *et al.*, 2010. Lead exposure stimulates VEGF expression in the spinal cord ad extends survival in a mouse model of ALS. *Neurobiology of Disease*, 37 (3), 574–580.

Bisht, M., Dhasmana, D.C., and Bist, S.S., 2010. Angiogenesis: future of pharmacological modulation. *Indian Journal of Pharmacology*, 42 (1), 2–8.

Bouton, C.M.L.S., *et al.*, 2001. Microarray analysis of differential gene expression in lead-exposed astrocytes. *Toxicology and Applied Pharmacology*, 176 (1), 34–53.

Chang, W.-C., *et al.*, 2011. Involvement of the epidermal growth factor receptor in Pb2+-induced activation of cPLA2/COX-2 genes and PGE2 production in vascular smooth muscle cells. *Toxicology*, 279 (1–3), 45–53.

Cheng, H., *et al.*, 2014. Nitric oxide in cancer metastasis. *Cancer Letters*, 353 (1), 1–7.

Cheong, J.H., 2004. Different mechanisms mediate uptake of lead in a rat astroglial cell line. *Toxicological Sciences*, 77 (2), 334–340.

Chou, Y.H., *et al.*, 2011. Divalent lead cations induce cyclooxygenase-2 gene expression by epidermal growth factor receptor/nuclear factor-kappa B signaling in A431carcinoma cells. *Toxicology Letters*, 203 (2), 147–153.

Christy, C.B., and Rudolfs, K.Z., 2010. Ionic and molecular mimicry and the transport of metals. *Cellular and Molecular Biology of Metals*, 204 (3), 241–294.

Cosselman, K.E., Navas-Acien, A., and Kaufman, J.D., 2015. Environmental factors in cardiovascular disease. *Nature Reviews Cardiology*, 12 (11), 627–642.

Das, K.K., *et al.*, 2015. α-Tocopherol supplementation prevents lead acetate and hypoxia-induced hepatic dysfunction. *Indian Journal of Pharmacology*, 47 (3), 285–291.

Dobrakowski, M., *et al.*, 2016a. Association between subchronic and chronic lead exposure and levels of antioxidants and chemokines. *International Archives of Occupational and Environmental Health*, 89 (7), 1077–1085.

Dobrakowski, M., *et al.*, 2016b. Glutathione, glutathione-related enzymes, and oxidative stress in individuals with subacute occupational exposure to lead. *Environmental Toxicology and Pharmacology*, 45, 235–240.

Dobrakowski, M., *et al.*, 2017. The influence of chronic and subacute exposure to lead on the levels of prolactin, leptin, osteopontin, and follistatin in humans. *Human and Experimental Toxicology*, 36 (6), 587–593.

Duda, D.G., 2012. Molecular biomarkers of response to antiangiogenic therapy for cancer. *ISRN Cell Biology*, 2012, 1–11.

Fujiwara, Y., 1995. Stimulatory effect of lead on the proliferation of cultured vascular smooth-muscle cells. *Toxicology*, 98 (1–3), 105–110.

Godwin, H.A., 2001. The biological chemistry of lead. *Current Opinion in Chemical Biology*, 5 (2), 223–227.

Gurer-Orhan, H., Sabır, H.U., and Özgüneş, H., 2004. Correlation between clinical indicators of lead poisoning and oxidative stress parameters in controls and lead-exposed workers. *Toxicology*, 195 (2–3), 147–154.

Hossain, M.A., *et al.*, 2000. Induction of vascular endothelial growth factor in human astrocytes by lead. Involvement of a protein kinase C/activator protein-1 complex-dependent and hypoxia-inducible factor 1-independent signaling pathway. *The Journal of Biological Chemistry*, 275 (36), 27874–27882.

Kaji, T., *et al.*, 1995. Inhibitory effect of lead on the proliferation of cultured vascular endothelial cells. *Toxicology*, 95 (1–3), 87–92.

Kaji, T., *et al.*, 1997. Lead-induced alteration of heparan sulfate proteoglycans in cultured vascular endothelial cells. *Toxicology*, 118 (1), 1–10.

Kasten-Jolly, J., *et al.*, 2012. Developmental lead effects on behavior and brain gene expression in male and female BALB/cAnNTac mice. *NeuroToxicology*, 33 (5), 1005–1020.

Kasten-Jolly, J., and Lawrence, D.A., 2017. Sex-specific effects of developmental lead exposure on the immune-neuroendocrine network. *Toxicology and Applied Pharmacology*, 334, 142–157.

Khurana, R., *et al.*, 2005. Role of angiogenesis in cardiovascular disease: a critical appraisal. *Circulation*, 112 (12), 1813–1824.

Kim, Y.-W., and Byzova, T.V., 2014. Oxidative stress in angiogenesis and vascular disease. *Blood*, 123 (5), 625–631.

Kishimoto, T., *et al.*, 1995. Effect of lead on tube formation by cultured human vascular endothelial cells. *Archives of Toxicology*, 69 (10), 718–721.

Koh, Y.W., *et al.*, 2013. Prognostic significance of COX-2 expression and correlation with Bcl-2 and VEGF expression, microvessel density, and clinical variables in classical Hodgkin lymphoma. *The American Journal of Surgical Pathology*, 37 (8), 1242–1251.

Kolev, Y., *et al.*, 2007. Prognostic significance of VEGF expression in correlation with COX-2, microvessel density, and clinicopathological characteristics in human gastric carcinoma. *Annals of Surgical Oncology*, 14 (10), 2738–2747.

Lee, J., *et al.*, 2016. Altered nitric oxide system in cardiovascular and renal diseases. *Chonnam Medical Journal*, 52 (2), 81.

Lin, Y.-C., *et al.*, 2015. Pb^{2+} induced IL-8 gene expression by extracellular signal-regulated kinases and the transcription factor, activator protein 1, in human gastric carcinoma cells. *Environmental Toxicology*, 30 (3), 315–322.

Machoń-Grecka, A., *et al.*, 2017. The influence of occupational chronic lead exposure on the levels of selected pro-inflammatory cytokines and angiogenic factors. *Human and Experimental Toxicology*, (5), 36.

Navas-Acien, A., *et al.*, 2007. Lead exposure and cardiovascular disease – a systematic review. *Environmental Health Perspectives*, 115 (3), 472–482.

Niu, X.-J., 2004. Relationship between inducible nitric oxide synthase expression and angiogenesis in primary gallbladder carcinoma tissue. *World Journal of Gastroenterology*, 10 (5), 725–728.

Pande, M., and Flora, S.J., 2002. Lead induced oxidative damage and its response to combined administration of α-lipoic acid and succimers in rats. *Toxicology*, 177 (2–3), 187–196.

Patra, R., Swarup, D., and Dwivedi, S., 2001. Antioxidant effects of α tocopherol, ascorbic acid and l-methionine on lead induced oxidative stress to the liver, kidney and brain in rats. *Toxicology*, 162 (2), 81–88.

Peters, J.L., *et al.*, 2012. Lead concentrations in relation to multiple biomarkers of cardiovascular disease: the Normative Aging Study. *Environmental Health Perspectives*, 120 (3), 361–366.

Petzelbauer, P., 1995. IL-8 and angiogenesis: evidence that human endothelial cells lack receptors and do not respond to IL-8 in vitro. *Cytokine*, 7 (3), 267–272.

Poręba, R., *et al.*, 2011. Environmental and occupational exposure to lead as a potential risk factor for cardiovascular disease. *Environmental Toxicology and Pharmacology*, 31 (2), 267–277.

Prokopowicz, A., *et al.*, 2017. Effect of occupational exposure to lead on new risk factors for cardiovascular diseases. *Occupational and Environmental Medicine*, 74 (5), 366–373.

Radomska-Leśniewska, D.M., *et al.*, 2016. Reactive oxygen species and synthetic antioxidants as angiogenesis modulators: clinical implications. *Pharmacological Reports*, 68 (2), 462–471.

Ramesh, G.T., and Jadhav, A.L., 2001. Levels of protein kinase C and nitric oxide synthase activity in rats exposed to sub chronic low level lead. *Molecular and Cellular Biochemistry*, 223 (1/2), 27–33.

Saghiri, M.A., *et al.*, 2016. Functional role of inorganic trace elements in angiogenesis part III: (Ti, Li, Ce, As, Hg, Va, Nb and Pb). *Critical Reviews in Oncology/Hematology*, 98, 290–301.

Shinkai, Y., and Kaji, T., 2012. Cellular defense mechanisms against lead toxicity in the vascular system. *Biological and Pharmaceutical Bulletin*, 35 (November), 1885–1891.

Silbergeld, E.K., Waalkes, M., and Rice, J.M., 2000. Lead as a carcinogen: experimental evidence and mechanisms of action. *American Journal of Industrial Medicine*, 38 (3), 316–323.

Simons, T.J., 1986. Passive transport and binding of lead by human red blood cells. *The Journal of Physiology*, 378 (1), 267–286.

Sisombath, N.S., and Jalilehvand, F., 2015. Similarities between N-acetylcysteine and glutathione in binding to lead(II) ions. *Chemical Research in Toxicology*, 28 (12), 2313–2324.

Solenkova, N.V., *et al.*, 2014. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. *American Heart Journal*, 168 (6), 812–822.

Sun, Y., *et al.*, 2017. Lead promotes abnormal angiogenesis induced by CCM3 gene defects via mitochondrial pathway. *Journal of Developmental Origins of Health and Disease*, 9 (2), 182–190.

Ueda, D., *et al.*, 1997. Inhibitory effect of lead on tube formation by cultured human vascular endothelial cells. *Human Cell*, 10 (4), 283–291.

Ushio-Fukai, M., 2006. Redox signaling in angiogenesis: role of NADPH oxidase. *Cardiovascular Research*, 71 (2), 226–235.

Ushio-Fukai, M., and Nakamura, Y., 2008. Reactive oxygen species and angiogenesis: NADPH oxidase as target for cancer therapy. *Cancer Letters*, 266 (1), 37–52.

Vaziri, N.D., 2008. Mechanisms of lead-induced hypertension and cardiovascular disease. *American Journal of Physiology – Heart and Circulatory Physiology*, 295 (2), H454–H465.

Wang, L.-S., *et al.*, 2009. Effect of 1-butyl-3-methylimidazolium tetrafluoroborate on the wheat (*Triticum aestivum* L.) seedlings. *Environmental Toxicology*, 24 (3), 296–303.

Wei, J., *et al.*, 2014. Lead induces COX-2 expression in glial cells in a NFAT-dependent, AP-1/NFκB-independent manner. *Toxicology*, 325, 67–73.

Wierzbowska, A., *et al.*, 2003. Circulating VEGF and its soluble receptors sVEGFR-1 and sVEGFR-2 in patients with acute leukemia. *European Cytokine Network*, 14 (3), 149–153.

Xue, W.-Z., *et al.*, 2017. Kiwifruit alleviates learning and memory deficits induced by Pb through antioxidation and inhibition of microglia activation in vitro and in vivo. *Oxidative Medicine and Cellular Longevity*, 2017, 5645324.

Yamagishi, S., *et al.*, 2003. Pigment epithelium-derived factor inhibits leptin-induced angiogenesis by suppressing vascular endothelial growth factor gene expression through anti-oxidative properties. *Microvascular Research*, 65 (3), 186–190.

Zhong, L., *et al.*, 2014. The cytotoxic effect of the NOS-mediated oxidative stress in MCF-7 cells after $PbCl_2$ exposure. *Environmental Toxicology*, 31 (5), 601–608.