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【实验研究】

急性和亚急性铅染毒后小鼠体内铅分布特征

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摘要:

[目的] 探讨急性和亚急性染毒不同剂量醋酸铅对小鼠体内铅分布的影响。

[方法] 本研究包括急性和亚急性铅染毒实验。急性实验:将15只ICR雄性小鼠随机分为对照组、低铅组和高铅组,每组5只。低铅组、高铅组小鼠分别经腹腔单次给予醋酸铅溶液(25和100 mg/kg),对照组给予等容积生理盐水,染毒24 h后处死并收集生物样本。亚急性实验:将30只ICR雄性小鼠随机分为对照组(反渗透水)、低铅组(250 mg/L醋酸铅溶液)和高铅组(2 500 mg/L醋酸铅溶液),每组10只。经饮水染毒28 d后处死并收集生物样本。两项实验均收集小鼠血清、血细胞、睾丸、心脏、肝脏、肺、肾和大脑,称量脏器重量,离心收集血清,并把所有样品液氮速冻后放入-80℃冰箱保存待用。用石墨炉原子吸收分光光度计检测样品铅含量。用方差分析、秩和检验进行统计学分析。

[结果] 急性铅染毒实验结果显示,与对照组相比,低剂量和高剂量铅处理明显升高小鼠血清(7.7、32.2倍)、血细胞(4.4、7.0倍)、肺脏(21.8、43.3倍)、肝脏(75.0、230.2倍)、肾脏(14.3、40.3倍)和睾丸(13.0、20.3倍)铅含量($P<0.05$);高剂量铅处理还进一步升高小鼠心脏铅含量(0.9倍,$P<0.05$),但高剂量铅处理未引起大脑铅含量改变($P>0.05$);不同剂量铅处理未引起小鼠体重改变($P>0.05$);仅低剂量铅处理引起肺体比下降($P<0.05$)。亚急性铅染毒实验结果表明,与对照组相比,经饮水暴露低剂量和高剂量铅升高小鼠肺脏(1.7、3.0倍)、肝脏(51.4、107.5倍)、肾脏(4.7、19.7倍)和大脑(1.9、7.2倍)铅含量($P<0.05$);高剂量铅染毒还升高小鼠血清(0.4倍)、血细胞(5.3倍)、心脏(2.3倍)和睾丸(2.0倍)组织中铅含量($P<0.05$),引起小鼠饮水量下降($P<0.05$),但对小鼠体重和进食量均无影响($P>0.05$);低剂量铅染毒升高心脏脏体比($P<0.05$),而高剂量铅染毒却降低肝脏脏体比($P<0.05$)。

[结论] 在本实验研究条件下,急性和亚急性铅染毒均引起小鼠肺脏、肝脏和肾脏铅蓄积,且急性铅处理还引起小鼠睾丸铅蓄积,亚急性铅染毒还引起大脑铅蓄积。

关键词: 铅;小鼠;肝脏;肺脏;肾脏;大脑;心脏

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Lead distribution characteristics in mice after acute and subacute exposures to lead *FENG Yu-jie, WANG Yu-feng, WANG Guo-chen, LI Jun, XU De-xiang, WANG Hua (Department of Toxicology, School of Public Health, Anhui Medical University, Hefei, Anhui 230032, China). Address correspondence to WANG Hua, E-mail: wanghuadev@126.com* *· The authors declare they have no actual or potential competing financial interests.*

Abstract:

[Objective] To investigate the effects of acute and subacute exposures to different doses of lead acetate on lead distribution in mice.

[Methods] This study included acute and subacute lead exposure experiments. As for the acute lead exposure experiment, fifteen male ICR mice were randomly divided into control group, low-lead group, and high-lead group, with five mice in each group. The low-lead group and the high-lead group were given lead acetate solution (25 and 100 mg/kg) through intraperitoneal injection, while the control group was injected with equal volume of normal saline. All mice were sacrificed to collect samples at 24 h after exposure. As for the subacute lead exposure experiment, thirty male ICR mice were randomized into control group (reverse osmosis water), low-lead group (250 mg/L lead acetate solution), and high-lead group (2 500 mg/L lead acetate solution), with 10 mice in each group. Samples were collected after the mice were exposed to lead through drinking water for 28 d. For the two experiments, samples

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of serum, blood cells, testis, heart, liver, lung, kidney, and brain were collected from mice, and organ weights were measured. All samples were fast frozen in liquid nitrogen and stored in a −80℃ refrigerator for later detection. Graphite furnace atomic absorption spectrophotometry was used to measure lead concentration in all samples. Analysis of variance and rank test were used to analyze the experimental data.

[Results] The results from the acute lead exposure experiment showed that the low-dose and the high-dose lead treatment significantly increased lead levels in serum (by 7.7 and 32.2 times), blood cells (by 4.4 and 7.0 times), lung (by 21.8 and 43.3 times), liver (by 75.0 and 230.2 times), kidney (by 14.3 and 40.3 times), and testis (by 13.0 and 20.3 times) of mice as compared to the controls, respectively ($P<0.05$). The high-dose lead treatment further increased lead levels in heart (by 0.9 times, $P<0.05$) of mice, but did not cause obvious changes in lead levels in brain ($P>0.05$). Different doses of lead treatment did not result in body weight changes in the mice ($P>0.05$). Only the low-dose lead treatment caused a decrease in the ratio of lung to body weight ($P<0.05$). The results from the subacute lead exposure experiment showed that the lead levels in lung (by 1.7 and 3.0 times), liver (by 51.4 and 107.5 times), kidney (by 4.7 and 19.7 times), and brain (by 1.9 and 7.2 times) of mice was increased by low-dose and high-dose lead exposure via drinking water as compared to the controls, respectively. The high-dose lead exposure also significantly elevated the levels of lead in serum (by 0.4 times), blood cells (by 5.3 times), heart (by 2.3 times), and testis (by 2.0 times) of mice, reduced the drinking water consumption of mice ($P<0.05$), but had no effect on body weight and diet intake. The low-dose lead exposure increased the ratio of heart to body weight ($P<0.05$), whereas the high-dose lead exposure reduced the ratio of liver to body weight ($P<0.05$).

[Conclusion] Under the experimental conditions, both acute and subacute lead exposures cause accumulation of lead in lung, liver, and kidney of mice. Moreover, acute lead treatment induces lead accumulation in mouse testes, and subacute lead exposure results in lead accumulation in mouse brain.

Keywords: lead; mouse; liver; lung; kidney; brain; heart

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铅是一种环境有毒重金属，已被广泛用于煤、汽油、油漆和铅管道等工业[1]。全国土壤污染状况调查公报显示，中国土壤总的点位超标率达16.1%，以无机污染为主，其中铅污染居于第五位[2]。人类主要通过接触铅污染空气、水和食物以及职业接触等方式暴露于铅[3-4]。急性铅中毒易引起腹泻、呕吐、抽搐、昏迷甚至死亡[5]。长期低水平铅暴露引起机体铅蓄积，并诱发机体心血管、胃肠道、血液系统、神经、肾脏和生殖系统等损害效应[6]。部分人群资料显示，人群铅暴露明显升高心血管疾病或慢性肾脏疾病的发生风险[7-8]。最近研究还发现，孕期母体铅暴露水平分别与不良出生结局和儿童身心健康损害发生有关[9-11]。

过去研究更多关注急性铅染毒对某一脏器或系统的损害作用及其可能机制。本研究系统探讨单次较高剂量铅染毒和较长期低浓度铅染毒对小鼠体内铅蓄积和脏器重量的影响。前者是经腹腔单次给予小鼠两种剂量铅(25和100 mg/kg)，为今后探讨毒性机制奠定基础；后者是小鼠较长期饮用两种剂量铅溶液(250和2 500 mg/L)，模拟人群实际暴露情况，为最终确认铅的主要靶器官及后续研究提供参考。

1　材料与方法

1.1　主要试剂与器材

醋酸铅、优级纯硝酸和30%过氧化氢(国药集团化学试剂有限公司，中国)。TAS-990型原子吸收分光光度计、铅阴极灯和恒温平台石墨管(北京普析通用仪器有限责任公司，中国)。

1.2　动物来源和喂养

45只清洁级ICR雄性小鼠(8周龄，32~35 g)购于北京维通利华实验动物有限公司，许可证号：SCXK(京)2016-0006。正式实验前小鼠适应性喂养1周，自由饮水和进食，动物房12 h/12 h明暗光照、温度20~25℃、湿度45%~60%。本研究所涉及的动物实验均遵循了单位和国家有关实验动物管理和使用的规定。

1.3　急性铅染毒实验

15只小鼠被随机分入对照组、低铅组和高铅组，每组5只。低铅组和高铅组小鼠分别单次经腹腔给予醋酸铅溶液(25和100 mg/kg)[12-13]，对照组腹腔给予等容积生理盐水。染毒24 h后剖杀小鼠，收集血清和血细胞，留取小鼠大脑、心脏、肺、睾丸、肝脏和肾脏，脏器称重后液氮速冻，再置于−80℃冰箱保存待用。计算各脏器脏体比，即脏器重量与体重之比。

所有样品均用石墨炉原子吸收分光光度法检测样品铅含量。

1.4 亚急性铅染毒实验

30只小鼠被随机分为对照组、低铅组和高铅组,每组10只,分别经饮水给予反渗透水、250 mg/L醋酸铅溶液和2 500 mg/L醋酸铅溶液[14-15]。用去离子水和60 mg/mL醋酸铅原液配制相应剂量的醋酸铅溶液。每周称量小鼠体重并记录。染毒28 d后,称量小鼠体重并取眼血后,剖杀小鼠,取其睾丸、心脏、肝、肺、肾、脑,称重后液氮速冻,再置于-80℃冰箱保存待用。计算各脏器脏体比,即脏器重量与体重之比。所有样品均用石墨炉原子吸收分光光度法检测样品铅含量。

1.5 石墨炉原子吸收分光光度法测定样品铅含量

1.5.1 组织硝化 将小烧杯经15%硝酸溶液浸泡24 h后,用三蒸水清洗并烤干备用。精确称取肝脏0.06 g(0.05~0.2 g)放入烧杯,尽量保持每个样品间误差不超过0.005 g。同时做2~3个空白对照。新鲜配制HNO_3:H_2O_2=2:1混合硝化液,加入烧杯(每个3 mL,漫过组织),用锡箔纸封住烧杯口防止污染。硝化至溶液澄清透明(中间务必摇晃混匀几次,加快硝化)。样品硝化完全后,置于温控电热板上加热驱酸(150~200℃),至湿盐状态(溶液体积应小于0.2 mL),稍微冷却后,加入1 mL水,再蒸发至湿盐状态。待完全冷却后,加入2 mL的1%HNO_3溶液定容,以备用于后续检测。

1.5.2 铅含量测定 实验前打开TAS-990型石墨炉原子吸收分光光度计充分预热,打开检测软件设置相关参数,选择铅灯为工作灯和预热灯。分析线(波长283.31 nm)寻峰,氘灯扣背景,自动能量平衡,开氩气,经过相应温度和时间的干燥、灰化、原子化、清洗等过程,对石墨炉进行不少于2次的空烧后校零。先测配置的标准液作出标准曲线,然后测定样品溶液。根据标准曲线计算样品的铅含量进行数据分析。

1.6 统计学分析

所有实验数据均录入Excel文档,计量资料用均数 ± 标准误($\bar{x} \pm S_b$)表示,数据采用SPSS 16.0软件进行分析。依据方差齐性检验结果,多组间比较用方差分析(ANOVA)或Kruskal-Wallis H秩和检验分析,用Bonferroni校正或Tamhane's *T2*进行两组间比较。检验水准α=0.05。

2 结果

2.1 急性铅染毒实验结果

2.1.1 小鼠的一般情况和脏体比 在急性铅染毒实验中,各组小鼠于铅染毒前后均未观察到毛发蓬松、活动减少等中毒体征。表1结果显示,铅染毒前后各组小鼠体重无变化。与对照组相比,低铅组小鼠肺体比降低($P<0.05$),而急性铅染毒对小鼠大脑、心脏、肝脏、肾脏和睾丸的脏体比均无影响。

表1 急性铅染毒小鼠体重变化、脏器脏体比和铅分布情况(n=5, $\bar{x} \pm S_b$)

组别	体重(g)		脏体比(%)					
	染毒前	剖杀前	脑体比	心体比	肺体比	肝体比	肾体比	睾体比
对照组	40.48 ± 1.95	39.94 ± 1.80	1.07 ± 0.07	0.57 ± 0.02	0.57 ± 0.03	4.71 ± 0.32	1.64 ± 0.16	0.55 ± 0.03
低铅组	41.24 ± 1.51	40.26 ± 1.38	0.98 ± 0.04	0.53 ± 0.05	0.49 ± 0.02*	4.82 ± 0.13	1.52 ± 0.05	0.61 ± 0.03
高铅组	40.30 ± 1.52	41.00 ± 1.54	1.05 ± 0.06	0.53 ± 0.04	0.62 ± 0.05	4.41 ± 0.11	1.63 ± 0.08	0.63 ± 0.04

[注]*:与对照组比较,P<0.05。

2.1.2 小鼠体内铅蓄积情况 表2结果表明,低剂量铅处理组小鼠血清、血细胞、肺、肝脏、肾脏和睾丸铅水平较对照组均上升($P<0.05$),高剂量铅处理组小鼠血清、血细胞、心脏、肺、肝脏、肾脏和睾丸铅水平较对照组也上升($P<0.05$)。进一步分析结果表明,高铅组小鼠血清、血细胞、心脏、肝脏和肾脏铅含量较低铅组均升高($P<0.05$)。然而,铅处理组小鼠大脑铅水平与对照组小鼠差异无统计学意义。

表2 急性铅染毒小鼠体内铅分布(n=5, $\bar{x} \pm S_b$)

组别	血清铅(μg/L)	血细胞铅(μg/g)	大脑铅(μg/g)	心脏铅(μg/g)	肺脏铅(μg/g)	肝脏铅(μg/g)	肾脏铅(μg/g)	睾丸铅(μg/g)
对照组	2.55 ± 1.78	0.32 ± 0.15	0.28 ± 0.06	0.61 ± 0.08	0.08 ± 0.06	0.18 ± 0.24	0.25 ± 0.07	0.20 ± 0.02
低铅组	22.06 ± 7.51*	1.72 ± 0.20**	0.33 ± 0.11	0.73 ± 0.07	1.82 ± 0.60*	13.68 ± 2.88**	3.82 ± 0.35**	2.80 ± 0.57*
高铅组	84.65 ± 26.74*#	2.57 ± 0.31**#	0.35 ± 0.05	1.15 ± 0.11**##	3.54 ± 0.75**	41.62 ± 7.74**##	10.33 ± 1.96**##	4.25 ± 0.83**

[注]与对照组比较,*:P<0.05;**:P<0.01。与低铅组比较,#:P<0.05;##:P<0.01。

2.2　亚急性铅染毒实验结果

2.2.1　小鼠进食和饮水情况　表3结果显示，各组间小鼠进食量无差异。与对照组比较，高铅组小鼠饮水量均降低($P<0.05$)。低铅组小鼠每日铅染毒量与28 d铅染毒总量分别为3.0、84.0 mg/只，而高铅组小鼠每日铅染毒量与28 d铅染毒总量分别为23.4、655.2 mg/只。

表3　亚急性铅染毒小鼠饮水、进食和铅染毒情况(n=10, $\bar{x}\pm S_b$)

组别	每日进食量(g/只)	每日饮水量(mL/只)	每日铅染毒量(mg/只)	28 d铅染毒总量(mg/只)
对照组	7.0±0.1	12.7±0.6	—	—
低铅组	6.9±0.1	11.9±0.9	3.0±0.2	84.0
高铅组	7.2±0.1	9.4±0.3**	23.4±0.6	655.2

[注]**：与对照组比较，$P<0.01$。

2.2.2　小鼠体重变化　本次实验中，随着铅染毒时间延长，各组小鼠体重均呈增长趋势，但在不同染毒时间各组间小鼠体重差异均无统计学意义，染毒4周后，各组小鼠的体重增长量之间差异也无统计学意义(F=0.89, P=0.42)。见图1。

2.2.3　小鼠脏体比　分析结果显示，三组小鼠心脏脏体比(H=8.28, P=0.02)和肝脏脏体比(H=10.13, $P<0.01$)之间差异有统计学意义。两两比较分析结果显示，低铅组小鼠心脏脏体比较对照组升高12.96%，而高铅组小鼠心脏脏体比较低铅组降低13.11%；高铅组小鼠肝脏脏体比较对照组降低11.22%。见表4。

2.2.4　小鼠体内铅蓄积情况　表5结果显示，低铅组中小鼠血清、血细胞、心脏、睾丸中铅含量与对照组比较差异均无统计学意义，但大脑、肺脏、肝脏和肾脏中铅水平均升高($P<0.05$)，而高铅组中小鼠各组织铅含量与对照组比较其差异均有统计学意义($P<0.05$)。与低剂量组比较，高剂量组小鼠血清、血细胞、脑、心脏、肝脏和肾脏中铅含量均升高($P<0.05$)。

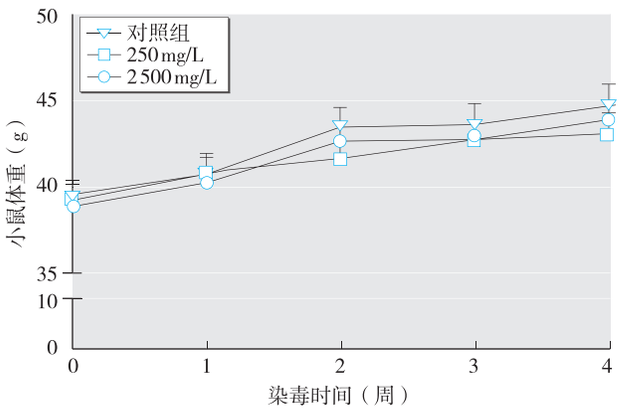

图1　亚急性铅染毒对小鼠体重的影响(n=10, $\bar{x}\pm S_b$)

表4　亚急性铅染毒小鼠不同脏器脏体比(%, n=10, $\bar{x}\pm S_b$)

组别	脑体比	心体比	肺体比	肝体比	肾体比	睾体比
对照组	0.99±0.03	0.54±0.02	0.63±0.03	5.08±0.13	1.60±0.04	0.64±0.03
低铅组	1.01±0.03	0.61±0.02*	0.55±0.02	4.78±0.12	1.72±0.06	0.61±0.02
高铅组	1.04±0.03	0.53±0.02#	0.57±0.02	4.51±0.07**	1.57±0.07	0.62±0.04

[注]与对照组比较，*：$P<0.05$；**：$P<0.01$。#：与低铅组比较，$P<0.05$。

表5　亚急性铅染毒小鼠体内铅分布情况(n=10, $\bar{x}\pm S_b$)

组别	血清铅(μg/L)	血细胞铅(μg/g)	大脑铅(μg/g)	心脏铅(μg/g)	肺脏铅(μg/g)	肝脏铅(μg/g)	肾脏铅(μg/g)	睾丸铅(μg/g)
对照组	28.81±1.71	0.16±0.06	0.13±0.03	0.09±0.02	0.22±0.05	0.08±0.02	0.69±0.18	0.10±0.05
低铅组	31.55±1.39	0.43±0.08	0.38±0.04**	0.18±0.02	0.60±0.09**	4.19±0.26**	3.94±0.16**	0.17±0.04
高铅组	40.07±2.12**##	1.01±0.17**##	1.07±0.05**##	0.30±0.04**##	0.87±0.08**	8.68±0.74**##	14.30±0.94**##	0.30±0.04**

[注]与对照组比较，*：$P<0.05$；**：$P<0.01$。##：与低铅组比较，$P<0.01$。

3　讨论

本研究中急性铅染毒实验结果表明，不同剂量铅处理未引起小鼠体重改变，仅低剂量铅处理引起肺体比下降；亚急性铅染毒实验结果显示，高剂量铅染毒引起小鼠饮水量下降，但对小鼠体重和进食量均无影响；低剂量铅染毒升高心脏脏体比，而高剂量铅染毒却降低小鼠肝脏脏体比。

急性铅染毒常见于职业性铅中毒或人为投毒，其中毒表现包括呕吐、头痛、腹痛、肌肉痛、痉挛、昏迷等症状[6]。职业性铅暴露工人的血铅水平约(386.73±177.93)μg/L(17~1 060 μg/L)[4]。有研究发现，急性染毒醋酸铅(25 mg/kg腹腔染毒)能增加大鼠血铅(60 μg/L)和肾脏铅(3 μg/g)水平[12]，而肾脏的铅水平约上升15倍。这与本次实验低剂量铅染毒结果相符。也有研究发现，睾丸、肝脏和肾脏是铅和镉急性和亚急性联合暴露的靶器官[16]；急性铅暴露能引起肝脏和睾丸的结构和功能障碍[17-18]。而本次急性铅染毒实验结果也提示，肝脏、睾丸、肾脏是急性铅染毒后铅在体内蓄积的主要器官。但急性铅染毒实验中样本量较少，还需要进一步研究加以证实。

亚急性铅染毒多见于一般人群，表现为较长期接触较低水平的铅，出现神经系统、造血系统、心血管

系统、生殖系统、肾脏和骨健康等损害[6, 19-22]。中国0~18岁男性和女性人群的中位血铅水平分别为48.8、46.1 μg/L[14]。大鼠经腹腔注射醋酸铅(20 mg/kg)20 d后,测得其血液、肝脏、肾脏和脑中均有蓄积[17];4周内经腹腔注射氯化铅导致小鼠肝脏和肾脏铅水平分别达到50~260、30~110 μg/g[23]。当通过腹腔或口服途径给予相同量的醋酸铅(约200 mg/L)时,肺中溶菌酶活性降低,肺中铅含量也明显增加,分别为(0.64±0.15)、(22.28±10.1)μg/g[24]。这些研究中脏器的铅蓄积量与本次亚急性铅染毒实验结果有所区别,可能是铅的染毒方式、剂量和时间以及实验动物种属方面的差异导致。但是,亚急性铅染毒后,铅在肝脏、肾脏、大脑和肺等器官内蓄积的现象与本次实验结果相符。

本次急性和亚急性铅染毒实验还发现,铅在小鼠肝脏和肾脏中的脏器蓄积量最高。有研究发现,机体吸收的铅主要通过尿液和胆汁排出体外[25];经饮水暴露醋酸铅(50 mg/L)6周后,测得大鼠体内脏器铅总蓄积量为377.7 μg,其中肝脏和肾脏为主要蓄积器官,所占比例分别为74.2%和24.7%[26]。铅在血液中的循环量大于在肌肉中的残留量,表明铅的分布可能与血铅浓度和器官血液循环量有关,而肝肾中的血流量较高[27-28]。金属硫蛋白是一种低分子质量蛋白,富含半胱氨酸残基并且与重金属具有高亲和力,这种蛋白质对保护金属稳态和解毒具有重要作用[29]。铅和镉的联合暴露能增加肝肾中金属硫蛋白及其mRNA的表达量[30]。这些结果表明,机体在短期内接受接较高剂量的铅暴露后,在肝脏和肾脏有较高的铅蓄积,可能与铅的解毒与排泄途径有关。

综上,在本实验研究条件下,急性和亚急性铅染毒均引起小鼠肝脏、肺脏和肾脏铅蓄积,急性铅处理还引起小鼠睾丸铅蓄积,亚急性铅染毒还引起大脑铅蓄积。这些结果为今后探讨铅的靶器官毒性作用及其机制奠定了基础。

参考文献

[1] KALIA K, FLORA S J. Strategies for safe and effective therapeutic measures for chronic arsenic and lead poisoning [J]. J Occup Health, 2005, 47(1): 1-21.

[2] 环境保护部, 国土资源部. 全国土壤污染状况调查公报 [R/OL]. [2018-07-01]. http://www.gov.cn/foot/site1/20140417/782bcb88840814ba158d01.pdf.

[3] WANI A L, ARA A, USMANI J A. Lead toxicity: a review[J]. Interdiscip Toxicol, 2015, 8(2): 55-64.

[4] XU M, YU Z, HU F, et al. Identification of differential plasma miRNA profiles in Chinese workers with occupational lead exposure[J]. Biosci Rep, 2017, 37(5): BSR20171111.

[5] GREIG J, THURTLE N, COONEY L, et al. Association of blood lead level with neurological features in 972 children affected by an acute severe lead poisoning outbreak in zamfara state, northern nigeria[J]. PLoS One, 2014, 9(4): e93716.

[6] FLORA G, GUPTA D, TIWARI A. Toxicity of lead: a review with recent updates[J]. Interdiscip Toxicol, 2012, 5(2): 47-58.

[7] CHEN C, LI Q, NIE X, et al. Association of lead exposure with cardiovascular risk factors and diseases in chinese adults [J]. Environ Sci Pollut Res, 2017, 24(28): 22275-22283.

[8] HARARI F, SALLSTEN G, CHRISTENSSON A, et al. Blood lead levels and decreased kidney function in a population-based cohort[J]. Am J Kidney Dis, 2018, 72(3): 381-389.

[9] WANG H, LI J, HAO J H, et al. High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants[J]. Toxicol Appl Pharmacol, 2017, 332: 75-80.

[10] JI Y L, HONG X M, WANG G Y, et al. A prospective birth cohort study on early childhood lead levels and attention deficit hyperactivity disorder: new insight on sex differences[J]. J Pediatr, 2018, 199: 124-131.e8.

[11] SOBOLEWSKI M, VARMA G, ADAMS B, et al. Developmental lead exposure and prenatal stress result in sex-specific reprograming of adult stress physiology and epigenetic profiles in brain[J]. Toxicol Sci, 2018, 163(2): 478-489.

[12] CONTERATO G M, QUATRIN A, SOMACAL S, et al. Acute exposure to low lead levels and its implications on the activity and expression of cytosolic thioredoxin reductase in the kidney [J]. Basic Clin Pharmacol Toxicol, 2014, 114(6): 476-484.

[13] FAZLI-TABAEI S, FAHIM M, ZARRINDAST M R. Effect of acute and chronic lead exposure on apomorpine-induced sniffing in rats[J]. Pharmacol Toxicol, 2003, 92(2): 88-93.

[14] LI M M, CAO J, XU J, et al. The national trend of blood lead levels among chinese children aged 0-18 years old, 1990-2012 [J]. Environ Int, 2014, 71: 109-117.

[15] TABRIZIAN K, YAZDANI A, BAHERI B, et al. Zinc chloride and lead acetate-induced passive avoidance memory retention deficits reversed by nicotine and bucladesine in mice

[J]. Biol Trace Elem Res, 2016, 169(1): 106-113.

[16]YUAN G, DAI S, YIN Z, et al. Toxicological assessment of combined lead and cadmium: Acute and sub-chronic toxicity study in rats[J]. Food Chem Toxicol, 2014, 65: 260-268.

[17]JALALI SM, NAJAFZADEH H, BAHMEI S. Protective role of silymarin and d-penicillamine against lead-induced liver toxicity and oxidative stress[J]. Toxicol Ind Health, 2017, 33(6): 512-518.

[18]GRAÇA A, RAMALHO-SANTOS J, DE LOURDES PEREIRA M. Effect of lead chloride on spermatogenesis and sperm parameters in mice[J]. Asian J Androl, 2004, 6(3): 237-241.

[19]MAHMOUD YI, SAYED SS. Effects of l-cysteine on lead acetate induced neurotoxicity in albino mice[J]. Biotech Histochem, 2016, 91(5): 327-332.

[20]WRONSKA-NOFER T, PISARSKA A, TRZCINKA-OCHOCKA M, et al. Scintigraphic assessment of renal function in steel plant workers occupationally exposed to lead [J]. J Occup Health, 2015, 57(2): 91-99.

[21]FANG F, PETERS TL, BEARD JD, et al. Blood lead, bone turnover, and survival in amyotrophic lateral sclerosis[J]. Am J Epidemiol, 2017, 186(9): 1057-1064.

[22]ZENG X, XU X, BOEZEN HM, et al. Decreased lung function with mediation of blood parameters linked to e-waste lead and cadmium exposure in preschool children[J]. Environ Pollut, 2017, 230: 838-848.

[23]TAKANO T, OKUTOMI Y, MOCHIZUKI M, et al. Biological index of environmental lead pollution: accumulation of lead in liver and kidney in mice[J]. Environ Monit Assess, 2015, 187(12): 744.

[24]OLMO R, TEIJÓN C, MUÑIZ E, et al. Modulation of lysozyme activity by lead administered by different routes. *In vitro* study and analysis in blood, kidney, and lung[J]. Biol Trace Elem Res, 2012, 149(3): 405-411.

[25]HERNÁNDEZ-PLATA E, QUIROZ-COMPEÁN F, RAMÍREZ-GARCIA G, et al. Melatonin reduces lead levels in blood, brain and bone and increases lead excretion in rats subjected to subacute lead treatment[J]. Toxicol Lett, 2015, 233(2): 78-83.

[26]WINIARSKA-MIECZAN A. Cumulative rate and distribution of Cd and Pb in the organs of adult male wistar rats during oral exposure[J]. Environ Toxicol Pharmacol, 2014, 38(3): 751-760.

[27]CELBIS O, KARAKOC Y, OZDEMIR B, et al. Investigation of lead mobilization from the buckshot residues to the critical organs[J]. Biol Trace Elem Res, 2011, 143(2): 688-694.

[28]KEIL DE, BERGER-RITCHIE J, MCMILLIN GA. Testing for toxic elements: a focus on arsenic, cadmium, lead, and mercury[J]. Lab Med, 2011, 42(12): 735-742.

[29]REDDY MS, PRASANNA L, MARMEISSE R, et al. Differential expression of metallothioneins in response to heavy metals and their involvement in metal tolerance in the symbiotic basidiomycete *Laccaria bicolor*[J]. Microbiology, 2014, 160(10): 2235-2242.

[30]DAI S, YIN Z, YUAN G, et al. Quantification of metallothionein on the liver and kidney of rats by subchronic lead and cadmium in combination[J]. Environ Toxicol Pharmacol, 2013, 36(3): 1207-1216.

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