NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

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APPENDIX B:
HUMAN STUDIES OF IMMUNE EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Low Exposure (mean blood Pb levels < 15µg/dL)							
Cross-sectional Annesi-Maesano (2003) Paris	374 mother-newborn pairs from 2 hospitals in Paris; Years= study A=1985 n=137; Study B=1991-1992 n=237 male=50%	Newborn	***Blood:*** Combined: Infant cord=6.7 (4.8) Maternal=9.6 (5.8) Study A – 1985: Infant cord=10.6 (4.8) Maternal =13.3 (6.0) Study B-1991-1992: Infant cord=3.88 (1.9) Maternal=6.16 (2.5) ***Hair (ppm):*** Infant= 1.4(1.3) Maternal= 5.2(6.1) Measured when outcome assessed Note: dose in publication contains error and should be µg/L not µg/dL.	Cord blood IgE, maternal IgE	Spearman correlation coefficient (r), linear regression analysis, ANOVA Adjustments not described.	Relationship between mean Pb measures and log cord IgE for combined cohort: Infant cord Pb =6.737 (4.8); r=-0.05; p>0.05 Maternal blood Pb =9.644(5.8); r=-0.09; p>0.05 **Infant hair =1.38(1.26); r=0.21; p<0.01** Maternal hair =5.16(6.08); r=-0.04; p>0.05 Infant hair Pb was also correlated to log cord IgE when each cohort was analyzed separately. Relationship between Pb measures and log cord IgE for combined cohort by allergic status of mother: Allergic mothers - infant hair Pb r = 0.12; p>0.05 **Non-allergic mothers –infant hair Pb r=0.21; p<0.01** Fraction of variation in log cord IgE in regression: Combined Infant cord blood Pb r^2=0.01; p>0.05 Maternal blood Pb r^2=0.01; p>0.05 **Infant hair Pb r^2=0.09; p<0.0001** Maternal hair Pb r^2=0.01; p>0.05 Study A (1985) Infant cord blood Pb r^2=0.05; p=0.08 Maternal blood Pb r^2=0.02; p>0.05 Infant hair Pb r^2=0.16; p=0.06 Maternal hair Pb r^2=0.00; p>0.05 Study B (1991-1992) Infant cord blood Pb r^2=0.01; p>0.05 **Maternal blood Pb r^2=0.06; p<0.005** **Infant hair Pb r^2=0.05; p<0.02** Maternal hair Pb r^2=0.01; p>0.05 *No functional immune tests and no other immune endpoints tested*.	Increased IgE in cord blood was associated with hair levels of Pb in infants. Cord blood IgE was not related to infant blood Pb. Cord blood IgE was related to maternal blood Pb in study B where maternal blood Pb was 6µg/dL and not study A where maternal blood Pb was 13µg/dL.
Cross-sectional Belles-Isles (2002) Quebec, Canada	Newborns from subsistence fishing families (n=48 fishing) and referents (n=60) in Quebec; Years= 1995-1997; Male=53-58%	Newborns	Cord geometric mean Fishing=1.64 Referent =1.33 SD not reported Measured when outcome assessed	WBC diff.: T-cells (CD3), helper T-cells (CD4), cytotoxic T-cells (CD8), B-cells (CD19) NK cells (CD56), IgG, IgM, mitogenic (conA) response, NK function, plasma PCBs, chlorin-ated pesticides, metals	Student's t test, chi-square test, multiple linear regression, Pearson correlation coefficient Adjustments not described.	Correlation for serum IgG and cord blood: **Pb level - IgG r=0.31; p=0.002** **Sum PCBs – IgG r=0.35; p<0.001** **DDE r=0.27; p=0.007.** No correlation between blood Pb and: -NK cell lytic function (lysis of K562 / P815 targets) -serum immunoglobulins (IgM) -lymphoproliferative (mitogen) responses to ConA -WBC differentials *No other immune endpoints tested.*	Elevated serum IgG was correlated with elevated blood Pb in newborns. NK lytic function, IgM, WBC differential, conA response did not differ.

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Cross-sectional and Case-control Boscolo (1999) Pescara, Italy	17 atopic men (case) and 17 non-allergic men (control) without occupational Pb; Years not stated; Male=100%	Mean Atopic=34 Range=19-52	11 (SD not reported) Measured when outcome assessed	WBC differential: T-cells (CD3), helper T-cells (CD4), cytotoxic T-cells (CD8), B-cells (CD19), NK cells(CD16 and CD56), non/activated (HLA-DR), IL-2 activated (CD25), naive (CD45RO-), memory (CD45RO+), serum IgG, IgM, IgA, IgE, plasma cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ), blood Zn, urinary Cr, Ni	Pearson correlation, Spearman correlation Adjustments not described.	Correlation between blood Pb for total population: **CD4 r=0.525; p<0.001** **HLA-DR r=0.507; p<0.002** Correlation between blood Pb for atopic men: **CD4 r=0.493; p<0.05** **CD5(-)CD19 r=0.679; p<0.01** **HLA-DR r=0.508; p<0.05** **CD3(-)HLA-DR r=0.528; p<0.05** Correlation between blood Pb for nonallergic men: **lymphocytes r=0.565; p<0.05** **CD4 r=0.503; p<0.05** **CD4CD45RO(-) r=0.638; p<0.01** **HLA-DR r=0.511; p<0.05** **CD25 r=0.579; p<0.05** IgE in atopic men correlated with **CD19 r=0.531; p<0.05** **CD5(-)CD19 r=0.713, p<0.01** **CD4CD45RO r=0.590; p<0.05** **CD25 r=0.662, p<0.01** No correlation of Pb with serum IgA, IgE, IgM, IgG, cytokines, CD8, CD16/CD56 *No functional immune tests and no other immune endpoints tested*	Blood Pb was positively correlated with CD4 and HLA-DR in all men, CD19 in atopics, CD25, CD4CD45RO in nonallergics. Serum IgE, IgG, IgM, IgA, cytokines, CD8, CD16/CD56 were not correlated to blood Pb.
Cross-sectional & Case-control Boscolo (2000) Pescara and Chieti Italy	30 atopic women (case) and 30 non-allergic (control) women white collar staff and doctors of University of Chieti ; Years not stated; Male=100%	Atopic=34 Range=19-49	Mean not reported Median Control = 5.5 Atopic = 6.4 Measured when outcome assessed	WBC differential: T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cells (CD19), NK cells(CD16 and CD56), non/activated (HLA-DR) IL-2 activated (CD25), naive (CD45RO-), memory (CD45RO+), serum IgE, in vitro IL-4, IFN-γ), blood Zn, Cu, urinary Cr, Ni	Pearson correlation, Spearman correlation Adjustments not described.	Correlation between blood Pb for nonallergic women: **CD4CD45RO(-) r=0.464; p<0.05** **CD3CD8 r=0.430; p<0.05** **CD3(-)HLA-DR r=0.435; p<0.05** Note CD4CD45RO(-), CD3CD8, CD3(-)HLA-DR did not correlate with blood Pb in atopics or the combined population. Although serum IgE was elevated in atopic women; authors do not specifically state if potential correlation between blood Pb and IgE was examined in atopics or nonallergic women.	Blood Pb was positively correlated with memory CD4, CD8, and HLADR lymphocytes in normal women, not atopics. CD19, CD16/CD56, in vitro IL-4 and IFN-γ were not correlated to blood Pb.
In vitro Guo (1996a) Not Applicable	Blood from health volunteers	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at	TNFα secretion after LPS stimulation of peripheral blood	Friedman analysis of variance Adjustments not described.	Authors state that in vitro incubation of peripheral blood mononuclear cells with Pb: • **Increased LPS pre-treated TNF-α secretion at 10µM or 50µM Pb; p=0.025**	In vitro exposure to Pb increased TNF-α secretion as

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			10µM or 50µM $PbCl_2$	mononuclear cells		• No effect on steady-state levels of TNF-α mRNA • **Increased TNF α (TNF-R p55) surface expression** but had no effect on TNF-Rp75 surface expression Authors state $PbCl_2$ increases TNF-α expression by posttranscriptional mechanisms and enhances reactivity and uptake of TNF-α by the receptor p55 *No functional immune tests and no other immune endpoints tested*	well as increased TNFα receptor levels in monocytes.
In vitro Guo (1996b) Not Applicable	Blood from health volunteers	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 10µM or 50µM $PbCl_2$	MHC class II antigen DR (HLA-DR) surface expression of peripheral blood mononuclear cells by ELISA, RT-PCR and Western Blot after exposure to Pb or IFNγ or IL-4	Friedman analysis of variance Adjustments not described.	Authors state that in vitro incubation of peripheral blood mononuclear cells with Pb: • **increased MHC class II antigen DR (HLA-DR) surface expression by monocytes and B cells expression at 10µM and 50µM; p<0.01** • Ii surface expression was not affected by Pb, but was enhanced by IL-4 • IFNγ increased HLA-DR and Ii on monocytes but decreased in B cells *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased MHC class II antigen surface expression.
In vitro Hemdan (2005) Not applicable	Blood from 12 healthy donors	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 14 serial doses per ml: Pb acetate:5.0mg-1.5ng Pb chloride:0.5mg-0.15ng	In vitro cytokines from peripheral blood mono-nuclear cells (IFNγ, TNF-α, IL-1β, IL-4, IL-6, IL-10) after mAb (anti-CD3, andti-CD28, anti-CD40) or *Salmonella enteritidis* (hk-SE) stimulation	Wilcoxon test for paired samples Adjustments not described.	In vitro cytokine release by mAb and Pb acetate: **TNF-α release reduced at Pb above 1.5ng/ml; p<0.05** **IL-1β release reduced at Pb above 5.0ng/ml; p<0.05** **IL-6 release reduced -Pb -150ng to 14mg/ml; p<0.05** **IFN-γ release reduced at 1.5ng to 5mg/ml; p<0.05** **IL-10 increased at all doses below 150µg/ml** **IL-4 increased at all doses below 15µg/ml** **All cytokines inhibited at does above 150µg/ml** Pb polarized response toward Th2 response In vitro cytokine release by hk-SE and Pb chloride: **TNF-α release reduced at Pb above 150pg/ml; Stimulated at 0.5µg/ml to 150µg/mlp<0.05** **IL-1β release reduced at Pb above 150pg/ml; stimulated at 50 and 150 pg/ml; p<0.05** **IL-6 release reduced -Pb -1.5ng to 0.5µg/ml; p<0.05** **IFN-γ release reduced at 150 pg to 150 ng/ml;p<0.05** IL-10 increased at lower doses and reduced at higher Doses Pb polarized response toward IL-10 from IFN-γ *No functional immune tests and no other immune endpoints tested*.	In vitro exposure to Pb increased IL-6, IL-10, IL-4, and decreased IFNγ, TNF-α, IL-1β in peripheral mononuclear cells.
Cross-sectional Hegazy (2011) Qualyobia Governate,	318 children aged 6 months to 7 years; Year=2006-2008;	Range 6 months to 7 years	Mean =9.23 Stratified by class (blood Pb in µg/dL): IA (<5µg/dL); 15.8%	Serum IgE, WBC diff.: lymphocytes, granulocytes,	Student's t test, Spearman correlation, Kruskal-Wallis test	Median (min,max) IgE (IU/ml) by Pb class (IIB, III and IV combined for analyses; age and parental tobacco smoke co-variants) IgE mean, SE or SD not reported IA (<5µg/dL); 13.0 (0.8, 892)	Serum IgE was significantly different by blood Pb level

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Egypt	Male=56.3%	% of study by age in years <2; 51.9% 2-<4.5; 38.4% 4.5-7; 8.2% >7;1.6%	IB (5-9); 47.5% IIA (10-14); 24.9% IIB (15-19); 5.5% III (20-44); 5.8% IV (45-69); <0.5%	monocytes, T-cells, B-cells (CD19)	Age, parental tobacco smoke	IB (5-9µg/dL); 12.0 (0.0, 2008) IIA (10-14µg/dL); 20.8 (0.4, 611.6) IIB (15-19µg/dL); 14.9 (4.1, 1756) III (20-44µg/dL); 20.4 (3.6, 235) **IV (45-69µg/dL); 10.2; p=0.001** Authors state IgE increased in children with Pb and parental tobacco smoke exposure. Correlation between IgE and blood Pb: With parental smoking r=0.12; p=0.24 Without parental smoking; r=-0.08; p=0.5 Children with Pb and parental smoking p=0.12; although authors only present this data in the abstract and the correlation is not presented, nor is the definition provided for "exposed to both Pb and PTS". **Correlation between blood Pb and parental tobacco smoking r=0.113; p<0.05** Percent of lymphocytes, granulocytes, monocytes, T-cells, and B-cells did not differ by Pb exposure class for total population; however authors state % lymphocytes was decreased (p=0.05) and % granulocytes was increased (p=0.06) in children of non-smokers. *No other immune endpoints tested.*	in children aged 6 months to 7 years of age; however the correlation between blood Pb and IgE was not significant. No relationship between blood Pb and lymphocytes, granulocytes, monocytes, T-cells, or B-cells was evident.
Cross-sectional Hon (2009) Hong Kong *Population may overlap with Hon (2010)*	58 new patients with eczema, aged >1 month and existing patients requiring 8-month period; Year=2008-2009; Male % not stated	Not reported Pers. Com. Author report mean age "around 10 years"	Blood Pb of eczema patients by use of traditional medicine: Ever used traditional medicine=2.07 (0.83) Never used traditional medicine=1.65 (0.62) *Combined = 1.9µg/dL-calculated by CERHR* Measured when outcome assessed	Serum IgE, eosinophils, atopic dermatitis severity (SCORAD), Nottingham eczema severity score (NESS), children's dermatology life quality index (CDLQI)	Pearson correlation Adjustments not described.	Correlation between clinical parameters: **Pb and SCORAD r=0.46; p<0.001** **Pb and NESS r=0.35; p<0.05** **Pb and CDLQI r=0.41; p=0.003** **Pb and log (IgE) r=0.34; p<0.05** *No other immune endpoints tested.*	Blood Pb in children examined for eczema were correlated with serum IgE, eczema severity score, and atopic dermatitis severity.
Cross-sectional Hon (2010, 2011) Hong Kong *Population may overlap with Hon (2009)*	110 patients with eczema and 41 with other skin conditions >1 month age sampled during 8-month period from a pediatric dermatology	Eczema=9.9 (5) Other=11.5(5)	Blood Pb Eczema=1.86 (0.83) Other=1.66 (0.62) *calculated by CERHR* Measured when outcome assessed *Note: 2011 paper corrects original table; Pb*	Serum IgE, eosinophils, atopic dermatitis severity (SCORAD), Nottingham eczema severity score (NESS), children's	Pearson or Spearman correlation, Student's t test Adjustments not described.	Correlation between clinical parameters in Eczema patients: **Pb and SCORAD r=0.329; p<0.005** **Pb and NESS r=0.203; p<0.05** **Pb and CDLQI r=0.217; p<0.05** **Log Pb and sq. root Eosinophil count r=0.29; p=0.001** **Pb and log (IgE) r=0.285; p<0.005** **Serum Cd was also correlated to IgE; r=0.216 (p<0.05**) and Cu/Zn ratio was correlated to NESS, and CDLQI; all	Blood Pb in children examined for eczema were correlated with serum IgE, eczema severity score, and atopic

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	clinic; Year=2008-2009; Male=57% eczema and 27% other		*levels reflect whole blood levels not serum as originally stated*	dermatology life quality index (CDLQI), serum Cu, Zn, Hg, Cd, Se		other metal comparisons were not significant for IgE, or eczema scores. *No other immune endpoints tested.*	dermatitis severity.
Prospective Jedrychowski (2011) Krakow, Poland	Children of 224 women recruited in 2nd trimester; years = 2001-2004	Maternal age=27.8 (3.37)	Geometric mean Maternal Pb: =1.6 (1.52, 1.67) Cord blood: =1.16 (0.12, 1.22) Blood in 5-year olds: =2.04 (1.95, 2.12)	Atopic status (at least one positive skin prick test [SPT] to a common allergen) at 5 years of age, blood Hg, PAH	Logistic regression analysis Maternal age, child's age, gender, parity, maternal education, maternal atopy, and environmental tobacco smoke variables	Frequency of atopy by Pb exposure: **Maternal blood Pb p=0.006** **Cord blood Pb p=0.001** Pb in 5-year old (current) Pb = 0.425 Risk ratio for atopy by blood Pb measures: Maternal blood Pb RR=1.72 (0.98, 3) **Cord blood Pb RR=2.28 (1.12, 4.62)** Pb in 5-year old (current) RR= 1.10 (0.72, 1.64) *No other immune endpoints tested.* Authors state atopy not related to blood Hg or PAH	Frequency of sensitization to allergens (atopy) in 5 year olds was associated to maternal and cord blood. Cord blood Pb levels were associated with increased risk of atopy in 5 year olds.
Retrospective Joseph (2005) Southeastern Michigan, USA	4634 children in managed care screened for Pb at 1-3 years of age in Michigan; Years 1995-1998; Male=50.5%	1.2 (0.5)	Not reported: % ≥5µg/dL = 39% %≥10µg/dL= 8.7% Pb measured at age 1-3, asthma assessed in patient records	Prevalent asthma and incident asthma based on insurance records for medication dispensing events, or related hospitalization	Cox proportional hazard analysis, chi-square tests, Wilcoxon rank-sum test, logistic regression Income, birth weight, sex	Cox proportional HR (95% CI) of blood Pb to asthma: Asthma definition #1-less stringent Caucasian Pb<5µg/dL HR=– 1 – reference Caucasian Pb≥5µg/dL HR=1.4 (0.7,2.9); p=0.4 Caucasian Pb≥10µg/dL HR=1.1 (0.2,8.4); p=0.91 African American Pb<5µg/dL HR=1 – reference African American Pb≥5µg/dL HR=1.0 (0.8,1.3); p=0.94 African Amer. Pb≥10µg/dL HR=0.9 (0.5,1.4); p=0.58 Asthma definition #2-more stringent Caucasian Pb<5µg/dL HR=– 1 – reference Caucasian Pb≥5µg/dL HR=2.7 (0.9,8.1); p=0.09 African American Pb<5µg/dL HR=1 – reference African American Pb≥5µg/dL HR=1.1 (0.8,1.7); p=0.53 African Amer. Pb≥10µg/dL HR=1.3 (0.6,2.6); p=0.54 *No other immune endpoints tested.* Authors state that African Americans were at significantly increased risk of asthma regardless of blood Pb level.	Blood Pb was not related to incidence of asthma based on asthma-medication dispensing events, or related hospitalization in children 1-3 years of age.
Cross-sectional Karmaus (2005) Hesse, Germany	331 children aged 7-10 in Hesse; Year= 1995; Male=56.8%	Range 7-10 96% 7-8	Geometric mean=2.68 (SD not reported) Measured when outcome assessed	Serum Ig, WBC diff.: T-cells (CD3), T-helper (CD3/CD4), T cytotoxic (CD3/CD8), B-cells (CD3/CD5/CD19) NK (CD16/CD56)	Multiple linear regression; t test, F test; gender, age, number of infections in last 12 months, exposure to passive smoke, DDE, sum of PCBs, HCB, γ-HCH	Adjusted serum IgE (kU/L) by blood Pb: <2.2µg/dL; IgE=46 2.21-2.83µg/dL; IgE=30 2.84-3.41µg/dL; IgE=59 **>3.41µg/dL; IgE=59; F-test p=0.028** No effect of Pb levels on: serum immunoglobulins (IgA, IgG, IgM);WBC differentials (NK, T, B and subsets); eosinophils or IgE counts on basophils	Increased serum IgE was associated with increases in blood Pb in 7-10 year old children blood Pb range <2.2

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				and NK subset (CD16/CD56/ CD57), memory T (CD4/CD45RO), other toxicants (OC, DDE, HCB, γ-HCH, PCBs)		Authors report that higher blood Pb was associated with decreased B-cells, T-cells, and cytotoxic T-cells at blood Pb 2.2-2.83µg/dL compared to children in the first quartile (blood Pb<2.2µg/dL) not other quartiles; however the F-test was negative. DDE was also associated with increased IgE. The authors state that blood Pb above the median (2.8µg/dL) were associated with increased IgE in groups with lower blood DDE levels, not in groups with higher DDE. *No functional immune tests and no other immune endpoints tested.*	to >3.4µg/dL. Differential WBCs, IgA, IgG, IgM did not differ.
Cross-sectional Kim (2007) Incheon, Korea	300 University of Inha students; Year=2002; Male = 84-99% by blood Pb quartile	24	By quartile: 1.46 (0.34, 1.89) 2.22 (1.89, 2.5) 2.77 (2.5, 3.1) 3.93 (3.1, 10.5) Measured when outcome assessed	IL-6, TNF-α, WBC count, glutathione S transferase M1 (GSTM1) genotype, TNF-α genotype	Test for Hardy-Weinberg equilibrium, chi-square test, ANOVA, t test, linear regression analyses Age, BMI, smoking status	Regression coefficient (β) of Pb by WBC or cytokine: All-TNF-α – β= 0.32 (SE=0.20); p=0.108 No effect of genotype on TNF-α All-IL-6 – β= 0.08 (SE=0.07); p=0.292 No effect of genotype on IL-6 **All-WBC – β=0.22 (SE=0.10); p=0.035** WBC – GSTM1 present – β=0.18 (SE=0.15); p=0.244 **WBC – GSTM1 null – β=0.31 (SE=0.15); p=0.038** **WBC – TNF-α GG – β=0.26 (SE=0.11); p=0.020** WBC – TNF-α GA or AA – β=-0.12 (SE=0.29); p=0.691 Regression coefficient (β) of males with blood Pb (≥2.51µg/dL) by WBC or cytokine: **All-TNF-α – β= 0.75 (SE=0.31); p=0.015** TNF-α – GSTM1 present – β=0.12 (SE=0.28); p=0.655 **TNF-α – GSTM1 null – β=1.14 (SE=0.48); p=0.020** **TNF-α – TNF-α GG – β=0.80 (SE=0.33); p=0.017** TNF-α – TNF-α GA or AA – β=-0.21 (SE=0.28); p=0.470 All-IL-6 – β= 0.18 (SE=0.10); p=0.082 No effect of genotype on IL-6 **All-WBC – β=0.42 (SE=0.20); p=0.044** WBC – GSTM1 present – β=0.22 (SE=0.29); p=0.462 **WBC – GSTM1 null – β=0.75 (SE=0.30); p=0.017** WBC – TNF-α GG – β=0.38 (SE=0.22); p=0.095 WBC – TNF-α GA or AA – β=0.61 (SE=0.50); p=0.256 *No functional immune tests and no other immune endpoints tested.*	Blood Pb was significantly associated with increased WBC in 24 year olds. In men with blood Pb ≥2.51 µg/dL, Pb was significantly associated with increased TNF-α. Effects of Pb on WBC and TNF-α were modified by GSTM1 and TNF-α genotypes.
Cross-sectional Li (2005) China *Population may overlap with Sun*	Subsample of 70 children aged 3-6 years of 217 children in study; 63 children (high Pb) had blood	Range 3-6	Overall = 9.5 Immune samples taken from 35 individuals from each group: High Pb group=14.06(4) Low Pb group=6.43(1.3)	WBC differential (CD3, CD4, CD8, CD19, CD16/ CD56), height, weight	Student t test, Spearman correlation coefficients Adjustments not reported.	Mean % lymphocytes by Pb group (≥10µg/dL and <10): CD3% referent = 55.2 (6.8) CD3% high (≥10µg/dL) = 54.1 (7.5); p>0.05 **CD4% referent = 27.1(5.8)** **CD4% high (≥10µg/dL) = 23.9(4.8); p<0.05** **CD8% referent = 20.6(4.8)**	The percentage of CD4 cells was decreased and CD8 cells were increased in children with

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(2003)	Pb≥10 µg/dL and 154 had blood Pb <10 µg/dL (referent); city not stated; Year not stated; Male= 56%		Measured when outcome assessed			**CD8% high (≥10µg/dL) = 23.6(5.5);p<0.05** CD19% referent = 16.7(4.6) CD19 high (≥10µg/dL) = 17.0(6.4); p>0.05 CD16/CD56% referent = 16.7(6.3) CD16/CD56% high (≥10µg/dL) = 19.2(7.7); p>0.05 **Spearman correlation for CD4 r=-0.462; p<0.05 among children with blood Pb >10µg/dL**; other WBC differentials not significant. No functional immune tests and no other immune endpoints tested.	blood Pb levels ≥10µg/dL relative to children with Pb <10. CD19, CD16/CD56 did not differ.
Cross-sectional Lutz (1999) Springfield-Green County, MO	279 children aged 9 months to 6 years in WIC program in Springfield-Green county with preliminary elevated finger-stick Pb; Years not stated; Male=56%	Age stratified (in months): 9-24 mo: 52% 25-36 mo: 30% 37-48 mo: 10% 49-84 mo: 8%	Blood Pb stratified: <10µg/dL (64%)-class I 10-14µg/dL(22%)-classIIA 15-19 µg/dL (7%)-class IIB 20-44 µg/dL (7%)-class III Measured when outcome assessed	Serum IgE, IgG titer to Rubella vaccine, CD25 (soluble receptor for IL-2), CD27 (soluble receptor for TNF), WBC differentials, and IL-4	Kruskal-Wallis test; Spearman rank correlation coefficient (r); Spearman partial correlation coefficients Adjustments differed by endpoint and include age using residuals obtained from a regression model and Spearman partial correlation coefficients. Authors state gender and race considered an no differences noted.	Mean serum IgE (IU/ml) by blood Pb values: <10µg/dL (64%)-class I →IgE =51.8 (166) 10-14µg/dL (22%)-class IIA →IgE =74 (112) 15-19 µg/dL (7%)-class IIB →IgE =210 (441) **20-44 µg/dL (7%)-class III →IgE =64 (82); p<0.05** **Correlation of serum IgE and Pb r=0.22; p=0.0004** No effect of Pb levels on: anti-rubella IgG; WBC differentials; IL-4; CD25, and CD27 Authors list as differing by Pb class at 0.05<p<0.1: IL-4, % lymphocytes, % granulocytes, CD25, rubella titer *No other immune endpoints tested.*	Serum IgE was increased in association with blood Pb in children from 9 months to 6 years of age. IL4, WBC differentials, anti-rubella did not differ.
Cross-sectional Min (2008) Seoul, Korea	523 adult office workers in Seoul; Years not stated; Male=52%	40 Range 19-58	Total = 2.9 Male = 3.3 Female = 2.5 Measured when outcome assessed	Methacholine bronco-provocation test	Multiple regression analysis Age, sex, height, smoking, and asthma diagnosis	Significant factors in regression model for bronchial responsiveness – β (SE): **Blood Pb (µg/dL) β=0.018 (0.007); p=0.015** **FEV1 (L) β= -0.067 (0.021); p=0.0013** **Male to female β= -0.074 (0.029); p=0.012** **Smoking to non-smoking β = 0.053 (0.024); p=0.026** *No other immune endpoints tested.*	Blood Pb was significantly associated with increased bronchial responsiveness in adults.
Cross-sectional Myers (2002) Chicago, IL	151 patients of inner-city clinic with blood Pb ≥25µg/dL (high Pb) and 101 matched referents blood Pb <5µg/dL; Years 1996-1999; Male=54%	Not reported Age in months at Pb measurement: High Pb= 26.6 Referent=24.2	Not reported Blood Pb obtained before 8 years of age, asthma assessed in patient records	Medical diagnosis of asthma, or asthma symptoms, or clinical diagnosis of bronchiolitis, or report of wheezing	Matched-pairs analyses, odds ratios, and Wilcoxon signed rank tests Adjustments not reported.	Odds ratio (95% CI) for diagnosis of asthma by Pb: Blood Pb <5µg/dL 11% asthma diagnosis Blood Pb ≥25µg/dL 6% OR=0.5 (0.2,1.4) Odds ratio (95% CI) for history of symptoms by Pb: Blood Pb <5µg/dL 34% asthma symptoms Blood Pb ≥25µg/dL 26% OR=0.7 (0.4,1.3) *No other immune endpoints tested.*	Incidence of asthma based on medical records did not differ between children with blood Pb≥25 µg/dL and others <5µg/dL aged <8 at Pb measurement.
Cross-sectional Nriagu (2008) Nigeria	653 children in major cities of Nigeria with	3.7	Mean = 8.9 (4.8) Range = 1-52µg/dL By city:	Malaria, worms, disease symptoms	Spearman correlation (r), bivariate and multivariate regression	Significant bivariate association of blood Pb: **Blood Pb x malaria r = -0.149; p<0.01** Blood Pb x worms r = -0.030; p>0.05	Blood Pb was associated with a decreased

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	different levels of pollution; Year not stated; Male = 56.5%		Port Harcourt = 4.7 (2.2) Nnewi = 8.3 (3.5) Ibadan = 9.9 (5.2)	(headaches, restlessness, irritability, depressed mood, worms)	Age, gender, town, pets in house, car ownership, education level of caregiver, hours outdoor play	**Blood Pb x town r = -0.356; p<0.001** **Blood Pb x age r=0.116; p=0.004** **Blood Pb x hours outdoor play r=0.175; p<0.001** **Blood Pb x car ownership; r=0.127; p<0.01** **Blood Pb x caregiver education r=-0.240; p<0.01** **Blood Pb x pets in house; r=0.091; p=0.023** **Multiple regression of blood Pb and co-morbid malaria β=-0.108; p=0.020** *No other immune endpoints tested.*	risk of malaria in young children in Nigeria.
Cross-sectional Pizent (2008) Zagreb, Croatia	216 office workers without occupational metal exposure; Year not stated; Male= 23%	Median Men = 45 Women=43 Range Men =20.5-67 Women=19-67	Median Men = 2.16 Women= 3.17 Range Men = 0.99-7.23 Women= 0.56-7.35 Measured when outcome assessed	Serum IgE, SPT to common allergens, trace elements (Cadmium, Cu, Zn, Se), SOD, GPx, non-specific bronchial and nasal reactivity (histamine challenge), ventilatory function	Mann-Whitney U test, Pearson chi-square test, Spearman correlation, multiple regression	Authors state in women, excluding women on HRT and oral contraceptives, **a positive association was observed between total IgE and blood Pb :** **β = 0.173; p=0.046** **Regression of association between non-specific bronchial reactivity and Pb in men:** **Log blood Pb β=-0.368; p=0.016** Authors state regression showed association between positive SPT and decrease in Pb in men: OR=0.92 (0.86, 0.98) Spearman correlation between blood Pb and: **Age in men r=0.366; p<0.02** **Age in women r=0.345; p<0.0001** **Zn in men r=-0.179; p<0.05** **Zn in women r=-0.300; p<0.02** **SOD in men r=-0.219; p<0.02** **SOD in women r=-0.321; p<0.005** **Alcohol consumption in women r=0.154; p<0.05** *No other immune endpoints tested.*	Blood Pb was associated with increased IgE in female office workers. Blood Pb was associated with decease in SPT and non-specific bronchial reactivity in men.
Cross-sectional Cohort Pineda-Zavaleta (2004) Lagunera, Mexico	65 children at schools different distances from a Pb smelter; Gomez Palacio (8Km referent), Heroes de Nacozari (1.7Km Pb-1); Pedro Garcia (<1Km Pb-2); Year not stated; Male=54%	Mean not reported Range 6-11	Median Referent=7.02 Pb 1=20.6 Pb 2=30.38 Range Referent=3.47-25.27 Pb 1=10.8-49.19 Pb 2=10.3-47.49 Measured when outcome assessed	Macrophage nitric oxide (NO) and superoxide (O_2^-) production following indirect (PHA) or direct (IFNγ-LPS) stimulation, urinary As	Mann-Whitney U test, Chi-square test, multiple linear regression Age and sex	Multivariate analyses for NO by blood Pb all children: **Indirect β=-0.00089 (-0.0017, -0.00005); p=0.036** Direct – not significant Multivariate analyses for O_2^- by blood Pb all children: **Direct β=0.00389 (0.00031, 0.00748); p=0.034** Indirect – not significant Multivariate analyses for O_2^- by blood Pb by sex: **Direct boys β=0.00826 (0.00236, 0.01416); p=0.008** Direct girls – not significant **Indirect boys β=0.00792 (0.00135, 0.01449); p=0.021** Indirect girls – not significant NO and O_2^- were also negatively associated with As *No other immune endpoints tested.*	Blood Pb was negatively associated with macrophage NO production in children; Pb was also associated with increased macrophage O_2^- production in boys.
Retrospective Pugh Smith (2011) Michigan, USA	356 children with in STELLAR database; Years	Age-stratified: <3 – 32% 4-6 – 40%	Not reported 19% of children had blood Pb≥10µg/dL	Doctor diagnosis of asthma	Multivariate regression analysis, Adjustments differ by	Significant odds ratio (95% CI) for factors predicting asthma in children: **Blood Pb child ≥10µg/dL OR=7.5 (1.3,42.9); p=0.023**	Children with blood Pb≥10µg/dL

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	=1996-2003; Male=49%	7-9 – 18% 10-12 – 10%	Measured prior to and when outcome assessed		endpoint including: age, gender, income, number of stories in unit, cat, dog, problem cockroaches, # persons in home, smoker in home, clutter, candles/ incense, stove type, heating source, clutter, musty, air conditioning, peeling paint, wall damage, age of house, Pb work or hobby	**Ceiling/wall damage OR= 10.93 (2.3, 52.2); p=0.003** **Cat in home OR=10.3 (1.4, 75.5); p=0.022** Significant odds ratio (95% CI) for factors predicting elevated blood Pb (≥10µg/dL) in children: **Age OR=0.645 (0.496, 0.837); p=0.001** **Gender OR= 2.87 (1.0, 7.98); p=0.043** **Pb related work activities OR=6.8 (1.1, 40); p=0.035** **Asthmatic child OR=5.17 (1.3,21.4); p=0.023** *No other immune endpoints tested.*	had an increased odds ratio for asthma.
In vitro Pyatt (1996) Not Applicable	Blood from health volunteers	Not reported	Blood Pb was not measured. In vitro experiments involved Pb exposure at 100µM, 1 µM, 10nM, 100pM Pb acetate	NF-κB; binding of nuclear factors to the NF-κB binding site by electrophoretic mobility shift assay; lucerifase activity by NK-κB dependent luciferase reporter gene	Statistical methods not reported.	Authors state that in vitro incubation of CD4+ T cells with Pb: • activated NF-κB and stimulated translocation to the nucleus down to 1.0µM Pb • induced p50:p65 heterodymer • stimulation of luciferase gene activity indicating activation of functional gene expression Authors state that the Pb concentration resulting in NF-κB translocation corresponds to a blood Pb concentration of 20µg/dL *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased NFκ-B activation in CD4 T cells.
Retrospective Rabinowitz (1990) Boston, MA	1768 children born at Boston hospital for women 1979-to 1981; teeth submitted 1985-1987; % male not stated.	Age not reported	Mean not reported Children classified by cord blood or deciduous tooth Pb	Questionnaire for incidence of asthma, eczema, ear infections, respiratory conditions, and school absence in past year by cold, flu or other illness	Relative risk defined as incidence in the highest exposure group (cord blood Pb ≥10µg/dL or tooth ≥5µg/g)/ rest of population. Adjustments not considered.	Relative risk (95%CI) of condition for cord blood Pb>10µg/dL compared to cord blood Pb<10µg/dL: Asthma RR=1.3 (0.8, 2.0) Eczema RR=1.0 (0.6, 1.6) Ear infections – any RR=1.0 (0.9, 1.0) Ear infections - ≥5 RR=1.1 (0.9, 1.3) Ear infections ≥10 RR=1.1 (0.9, 1.3) **Ear infections severe RR=1.2 (1.0, 1.4)** **Other respiratory RR=1.5 (1.0, 2.3)** Other infections RR=1.0 (0.7, 1.5) Other immune RR=1.2 (0.8, 2.0) **School absence other than flu RR=1.3 (1.0, 1.5)** School absence flu or cold RR=1.0 (0.9, 1.1) Authors present similar data for tooth Pb. Authors report similar results for analysis split by sex. Note: Although 95% CI for severe ear infections, other respiratory infections, and school absence other than flu include 1.0 to 1.4, 1.0 to 1.5, and 1.0 to 2.3, authors state failure to demonstrate any increased occurrence of diseases in children with highest cord or tooth Pb.	Increased relative risk of severe ear infections, other respiratory infections, and school absence other than flu in children with cord blood Pb>10µg/dL. No difference in asthma, eczema, or other disease incidence.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Rabito (2010) USA	73 Latino migrant laborers identified in New Orleans 2005 followed monthly over a year; Year=2007: Male=100%	Mean not reported	Exposure determined by occupation/ job type and blood Pb determined at final time point Geometric mean = 2.67 Range =0.6 to 38.4µg/dL	Survey for symptoms including sino-nasal, respiratory, eye, skin, and headache	Multivariable logistic regression Adjustments differ by outcome including smoking, mask use, eye protection, glove use ** utility limited by lack of direct comparison of effects with blood Pb level*	Regression model for association between construction work and symptoms: Sino-nasal OR=2.62 (0.86, 7.98) Respiratory OR=2.91(0.94, 9.06) Headache OR=0.87 (0.31, 2.5) Throat OR=1.12 (0.31, 4.0) Eye OR=0.62 (0.2, 1.93) Skin OR=1.18 (0.26, 5.22) **Association of construction work with blood Pb; p=0.034 and p=0.037 after adjustment for mask use.**	Odds ratio of symptoms was not significantly associated with construction activities in migrant workers.
Cross-sectional Sarasua (2000) USA	1561 people in 4 sites near high Pb and Cd soil levels and 480 matched referents combined for analyses; Year =1991; %Male not stated	4 age groups: 6-35 months 36-71 months 6-15 years 16-75 years	6-35 mo= 7.0 (5.2) 36-71 mo= 6.0 (4.3) 6-15 yr=4.0 (2.8) 16-75 yr=4.3 (3.9) Measured when outcome assessed	IgA, IgM, IgG, lymphocytes, WBC differentials (# and % B-cell, T-cell, NK cells, CD4, CD8), urinary Cd	Pearson correlation coefficients, linear regression analysis, least square means Adjustments differ by endpoint including age, sex, study (KS, IL, MO, PA)	Regression coefficient for blood Pb for children < 3: **IgA (mg/dL) = 0.8; p<0.01** **IgG (mg/dL) = 4.8; p<0.01** **IgM (mg/dL) = 1.0; p=0.03** T-cell count = 7.2; p=0.59 **B-cell count = 16.9; p<0.01** **% T cells = -0.18; p=0.03** **% B cells = 0.19; p=0.02** No effect in children <3 of Pb levels on NK cells, CD4, or CD8 cell counts or percentages. Among children < 3 years of age: 1) IgA was increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb. 2) IgG was increased in children with blood Pb ≥5µg/dL relative to children <5 µg/dL Pb. 3) IgM was increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb 4) B-cell and lymphocyte count were increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb No effect of Pb levels in children >3 years of age, or in adults on serum immunoglobulins (IgA, IgG, IgM) or WBC differentials. *No functional immune tests and no other immune endpoints tested.*	Serum IgA, IgM, IgG, and B-cell count were increased in association with blood Pb in children under 3 years of age. CD4, CD8 did not differ. No effect in children over 3 years of age or adults on serum Ig or WBC differentials.
Cross-sectional Songdej (2010) USA	9,145 individuals ≥40 years of age in NHANES 1999-2004	Population >40; mean not reported.	1.89 in entire population Measured when outcome assessed	WBC count, c-reactive protein (CRP), fibrinogen	Logistic regression Age, gender, race/ethnicity, education, income, BMI, physical activity, smoking status, diabetes status, inflammatory disease status, and cardiovascular disease status	Blood Pb was not related to CRP, fibrinogen, or WBC count when the population was analyzed together or males and females were analyzed separately. *No functional immune tests and no other immune endpoints tested.*	Blood Pb was not related to CRP, WBC count or fibrinogen in people >40.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Sun (2003) China *Population may overlap with Li (2005)*	Subsample of 72 preschool children aged 3-6 of 217 children in study; 63 children (high Pb) had blood Pb≥10µg/dL and 154 had blood Pb <10µg/dL (referent); Year not stated; Male =56%	Range 3-6	Overall =9.52 (5.59) Immune samples taken from 38 individuals from the ≥10µg/dL (high) group and 35 in the <10µg/dL (low/referent): High Pb group=14.06(4) Low Pb group=6.43(1.3) Measured when outcome assessed	Serum IgG, IgM, IgE	Mann-Whitney U test; Spearman rank correlation coefficient (r) Age, sex, weight index	**Spearman correlation for IgE r=0.48; p=0.002 among children with blood Pb >10µg/dL.** Mean rank of serum Immunoglobulin by Pb group/sex: IgG referent males (<10µg/dL) = 20.71 IgG high Pb males (>10µg/dL) = 34.76; p=0.913 IgM referent males (<10µg/dL) = 20.32 IgM high Pb males (>10µg/dL) = 19.61; p=0.596 IgE referent males (<10µg/dL) = 20.22 IgE high Pb males (>10µg/dL) = 21.61; p=0.713 **IgG referent females (<10µg/dL) = 18.41** **IgG high Pb females (>10µg/dL) = 13.60; p=0.047** **IgM referent females (<10µg/dL) = 20.44** **IgM high Pb females (>10µg/dL) = 12.03; p=0.013** **IgE referent females (<10µg/dL) = 13.06** **IgE high Pb females (>10µg/dL) = 20.40; p=0.027** Authors state multiple variable analyses of blood Pb, age, sex, and weight index showed high blood Pb level could increase serum IgE. *No functional immune tests and no other immune endpoints tested.*	Serum IgE was correlated with blood Pb in boys and girls with blood Pb>10µg/dL. Increased serum IgE and deceased IgM and IgG were associated with increased blood Pb levels in girls aged 3-6; not observed in boys.
In vitro Villanueva (2000) Not applicable	Blood from a single healthy female	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 10, 50, and 100µM using $(CH_3OO)Pb$	In vitro cytokines from peripheral blood mono-nuclear cells (IFNγ, TNF-α, IL-1β, IL-6, IL-8, IL-10); exposure to Cadmium, Cr, and Hg also examined	ANOVA; Multiple Comparison Tukey test Adjustments not described.	Production of TNF-α and IL-6: 10µM Pb – not different relative to control; p>0.05 **50µM Pb– increased relative to control; p<0.05** **100µM Pb – increased relative to control; p<0.05** The authors did not report an effect of in vitro Pb exposure on IFNγ, IL-1β, IL-8, and IL-10. *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased TNF-α and IL-6 in peripheral mononuclear cells.
Cross-sectional Zhao (2004) Zhejiang Province, China	Subsample of 72 children aged 3-6 years of 217 children in study; 63 children with blood Pb≥10 µg/dL (high Pb); and 154 had blood Pb <10 µg/dL (referent); city not stated; Year not stated; Male=44%	Not reported Range = 3-6	Children with blood Pb ≥10µg/dL: Boys=10.1(6) Girls=10.1 (5) Overall range: Authors report two different ranges: 2.32 to 43.7µg/dL 10.0 to 19.0 µg/dL and it is unclear whether data apply to entire population or subset used for immune	WBC differentials: T-cells (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cell (CD19), CD35, RBC-C3b and RBC-IC rosette forming rate	t test Adjustments not described.	Mean Lymphocyte % by Pb group: CD3 – referent = 55.2 (6.77) CD3 – high Pb = 54.61 (4.81); p>0.05 **CD3CD4 – referent = 27.1 (5.83)** **CD3CD4 – high Pb = 23.68 (4.81); p<0.01** **CD3CD8-referent =20.57 (4.84)** **CD3CD8 – high Pb =23.21 (5.77); p<0.05** **CD4CD8-referent = 1.41 (0.50)** **CD4CD8- high Pb = 1.09 (0.37); p<0.01** CD19-referent = 16.58 (4.6) CD19- high Pb = 16.82 (6.64); p>0.05 **Authors report that RFIR and CD35 average fluorescence intensity was decreased p<0.05.** Authors report CD35 average fluorescence intensity	Children with blood Pb ≥10µg/dL had a decreased CD4% and CD4CD8% T-cells, and increased CD8% relative to children blood Pb<10µg/dL. CD19, CD3, CD35, RBC-C3b, RBC-IC dud bit

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			analyses (n=35 referent; n=38-40 high Pb)			that RBC-C3b, RBC-IC, RFER, and rate of CD35 positive findings did not differ between Pb groups. *No functional immune tests and no other immune endpoints tested.*	differ.
High Exposure (mean blood Pb levels > 15µg/dL and referent group often above 10µg/dL)							
Cross-sectional Anetor (1998) Nigeria	80 workers in the Pb industry (high Pb) and 50 referents without occupational Pb exposure; Male=% not stated; Years not stated N=80 workers N=50 referents	36 (SEM 0.03) 36.6(SEM 1.2)	Pb-workers =56.3(0.95) Referent =30.4(1.4) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Total lymphocyte count, serum immunoglobulin, IgA, IgG, IgM, CRP	Pearson correlation, Student's t test, multiple regression analysis Adjustments not described	Immunological indices in Pb-workers and referents: Total lymphocyte count/mm^3 referent = 2515 (115) **Total lymphocyte count/mm^3 Pb= 2157 (63); p<0.01** Total globulin (g/dL) referent = 3.2 (0.07) **Total globulin (g/dL) Pb = 3.73 (0.05); p<0.001** IgA (mg/dL) referent = 187.51 (14.2) **IgA (mg/dL) Pb = 143.79 (6.76); p<0.01** IgG (mg/dL) referent = 1997.33(108.33) **IgG (mg/dL) Pb = 1187.73 (65.33); p<0.0001** IgM (mg/dL) referent = 215.43 (12.66) IgM (mg/dL) Pb = 190.87 (11.76); p>0.05 CRP (mg/dL) referent = 0.50 (0.03) **CRP (mg/dL) Pb = 0.60 (0.03); p<0.01** Multiple regression for globulin and IgA in combined Pb-workers and referents: **Total globulin p<0.01** **IgA p<0.01** Correlation between blood Pb and IgA in Pb workers: **r=-0.28; p<0.009** *No functional immune tests and no other immune endpoints tested.*	Serum levels of IgA, IgG, and total lymphocytes were decreased in Pb-workers relative to referents; and IgA was negatively associated with Pb in workers and in the referents. IgM did not differ.
Cross-sectional Ayatollahi (2002) Yazad, Iran	66 Pb-workers (n=12 car battery workers, n=12 car painters, n=12 car radiator workers, n=21 printing office workers) in Yazd; Year not stated; Male= 100%	32.02 (1.77) Range=15-70	45.52 all workers >25µg/dL – 61/66 Mean =46.77 (SE 2.14) <25µg/dL – 5/61 Measured when outcome assessed *Note: unknown source of "standard" values used; no referent group*	Serum IgG, IgM, IgA	Z test, t test, and Pearson correlation Adjustments not described. ** Statistical difference relative to "standard" decreases utility	Serum IgG (mg/dL) = 706.52 Relative to standard 1350 (mg/dL) =-643.5 p **listed as P=#0 or P~0 "significant"** Serum IgA (mg/dL) = 173.43 (SE=12.15) Relative to standard 350 (mg/dL) =-176.54 **p listed as P=#0** Serum IgM (mg/dL) = 165.6 (SE=10.48) Relative to standard 150 (mg/dL) =15.6; p=0.14 Correlations between blood Pb and: **Serum IgA r=0.31; p listed as P~0** Serum IgM r=0.14; p =0.25 Serum IgG r=-0.08; p =0.47 Authors report blood Pb by intestinal helminthes: With intestinal helminthes Pb = 54.78 **No helminthes Pb=40.89; p listed as P=0** *No functional immune tests and no other immune endpoints tested*	Serum IgA was positively related to blood Pb in Pb workers. Serum IgG was decreased and IgA was increased in Pb workers relative to "standard". IgM did not differ.
Cross-sectional	25 male Pb-	Referent =	Referent = 17 (5)	Serum IgG, IgA,	Student's t test, Mann-	Significant differences in immune values by Pb group:	Neutrophil

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Basaran (2000) Ankara, Turkey *Population may overlap with Undeger (1996)*	battery workers (high Pb) and 25 referent from university staff; Year not stated; Male=100%	33(9) High Pb=33(8.5)	High Pb = 75(18) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	IgM, complement C3, C4, WBC differentials, neutrophil chemotaxis and neutrophil intracellular killing	Whitney U test, linear regression Adjustments not described	T-helper(CD4) # – referent=1140.3(681.2) **T-helper(CD4) # – Pb worker=858.8 (341.2); p<0.05** Serum IgG (mg/dl) – referent = 1212.1(393.6) **Serum IgG (mg/dl) – Pb = 854.6 (415.6); p<0.05** Serum IgM (mg/dl) – referent = 140.4(66.1) **Serum IgM (mg/dl) – Pb = 93.3 (39.6); p<0.05** Serum C3 (mg/dl) – referent = 61 (17.4) **Serum C3(mg/dl) – Pb = 45.1 (18.5); p<0.05** Serum C4 (mg/dl) – referent = 22.1 (7.8) **Serum C4(mg/dl) – Pb = 17.8 (8.5); p<0.05** Neutrophil chemotactic ind.–referent = 1.85(0.42) **Neutrophil chemotactic ind. Pb=1.24(0.28); p<0.001** Neutrophil random migration – referent = 19 (4.6) **Neutrophil random mig. Pb = 10 (3.2); p<0.001** No difference between workers and referents on: -serum immunoglobulins (IgA) -WBC differentials (CD3, CD8, CD20, CD56) -Neutrophil phagocytosis (NBT reduction) Complement was negatively correlated with blood Pb level; No other immune parameter was correlated with blood Pb levels. *No other immune endpoints tested*	chemotaxis was reduced in male Pb workers relative to referents and serum levels of IgG, IgM, C3, C4, and CD4 T-cells were decreased in Pb workers relative to referents. No difference in neutrophil phagocytosis, CD3, CD8, CD20, CD56, or IgA.
Cross-sectional Bener (2001) Al-Ain, United Arab Emirates	100 male industrial workers (high Pb taxi drivers, gas filling, garage, chemical, printing, building metal industry) and 100 matched referent professional workers; Year= 1999; Male= 100%	High Pb=34.6(8) Referent=8.3(6)	Geometric mean High Pb = 77.5 (42.8) Referent = 19.8 (12.3) *Note: Referent/Low Pb group over 10µg/dL*	Survey for self-reported symptoms classified by the authors as gastrointestinal, neuromuscular psychiatric, or allergic	Mantel-Haenszel test odds ratio Adjustments not described.	Relative risk of symptoms by Pb group: **Nausea/vomiting RR=1.68 (1.27, 2.22); p=0.014** Abdominal pain RR=1.08 (0.74, 1.58); p>0.05 Headache RR=1.09 (0.74, 1.48); p>0.05 Myalgia RR=1.12 (0.61, 2.04); p>0.05 **Muscular symptoms RR=1.61 (1.24, 2.08); p=0.004** Dizziness RR=1.33 (0.96, 1.86); p>0.05 **Fatigue RR=1.61 (1.22, 2.13); p=0.016** **Irritability RR=1.51 (1.13, 2.00); p=0.029** **Memory disturbances RR=1.91 (1.51, 2.43); p=0.013** Insomnia RR=1.39 (0.99, 1.95); ; p>0.05 Allergic conjunctivitis RR=1.24 (0.89, 1.73); p>0.05 **Rhinitis RR=1.78 (1.39, 2.28); p=0.0001** Dermatitis RR=1.47 (1.07, 2.0); p>0.05 Relative risk of respiratory symptoms by Pb group: Throat discomfort RR= 1.06 (0.67, 1.66); p>0.05 Cough RR= 1.11 (0.82, 1.51); p>0.05 **Phlegm RR=1.50 (1.12, 2.01)p=0.0385** Shortness of breath RR=1.33 (0.96, 1.86); p>0.05 Wheeze RR=1.08 (0.79, 1.48); p>0.05 **Diagnosed asthma RR=1.75, 2.26); p=0.002** *No other immune endpoints tested.*	Relative risk of self-reported symptoms of nausea, memory, muscular, dizziness, irritability, rhinitis, phlegm, and diagnosed asthma were elevated in industrial workers (Pb 77µg/dL) than in professional workers (Pb 20µg/dL).

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Bergeret (1990) Location not stated; authors work in France	38 male Pb-battery workers (high Pb) and 34 matched referents	Referent = 38 High Pb= 40	Referents = 9.0 (4.3) High Pb=70.6 (18)	Neutrophil phagocytosis and chemotaxis	Student's t test and Chi-square test Adjustments not described.	Neutrophil Phagocytosis: Peak time – referent= 303.5(104) **Peak time – Pb worker=414.5(187); <0.01** Peak height – referent= 20.5(14.5) Peak height Pb worker= 17.7(11.1); not sig. Integral – referent =22509(16767) Integral Pb worker =19054(12015); not sig. Chemotaxis: Spontaneous –referent =42.5 (15.9) no statistics Spontaneous –Pb worker =35.5(15.8) no statistics Activated –referent =100.8(40.1) **Activated –Pb worker= 81.2(28.5); p<0.05** Differential – referent= 58.2(25.1) **Differential – Pb worker = 47.1(18.3); p<0.05** *No other immune endpoints tested*	Neutrophil phagocytosis and chemotaxis were decreased or delayed in Pb workers relative to referents.
Cross-sectional Coscia (1987) Location not stated, authors work in Italy	38 Pb-workers (13 battery workers, 9 plastics, 5 car industry, 2 ceramics, 2 Pb salts, 6 other) and 25 referents; Years not stated; % male not stated	High Pb =42.8 (11.5) Referent = 38.6 (13.3)	High Pb = 62.3 (21.6) Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility*	Leukocytes, T-cells, B-cells, CD4, CD8, IgG, IgM, IgA, complement C3 and C4,	Student's t test, Pearson correlation Adjustments not described.	Significantly different mean measures by Pb group: % lymphocytes - referents=31.2(6.6) **% lymphocytes – Pb exposed=37(8.6)** IgM – referents=182 (50.1) **IgM – Pb-exposed=144.5 (63)** C4 – referent=27.8 (8.5) **C4 – Pb workers=37.1 (15.9)** No difference by Pb-group in leukocytes, CD4, IgG, IgA, or C3 *No functional immune tests and no other immune endpoints tested*	Percentage of lymphocyte and complement C4 were increased and IgM decreased in Pb-workers relative to referents. CD4, IgG, IgA, C3 did not differ.
Cross-sectional Cohen (1989) Location not stated, authors work in Israel	10 men chronically exposed to Pb (high Pb; 7 battery workers and 3 scribes using Pb ink) and 10 hospital personal referents; Years not stated; Male=100%	High Pb=40(7) Range=22-70 Referent =not stated	Referent =≤19µg/dL High Pb=40-51µg/dL; mean not reported *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Mitogenic response to conA, PHA, WBC differentials T-helper (OKT4), T-cytotoxic (OKT8), E-rosette-forming cells	Student's t test Adjustments not described.	Percent suppression of responder cell thymidine incorporation in presence of conA-induced suppressor cells was increased in Pb workers relative to referents; **p<0.02.** No difference by Pb-group in mitogenic response to conA or PHA, or T-cell subsets (T-helper, T-cytotoxic), or E-rosette-forming cells *No functional immune tests and no other immune endpoints tested*	There was no difference between T-helper and T-cytotoxic cells # or mitogenic response to conA or PHA between 10 Pb workers and referents.
Cross-sectional Ewers (1982) West Germany	72 Pb-battery workers (high Pb) and 53 referents from various occupations;	Pb=36.4(10) Referents=35 (9)	Referent=11.6 Pb-worker =51.4 *Note: Referent/Low Pb group over 10µg/dL*	Serum IgM, IgG, IgA, complement C3, frequency colds and influenza	Student's t test, Pearson correlation, Mann Whitney U test, Kullback's 2I test Adjustments not described.	Correlation between Pb and Ig or C3 in Pb workers **Pb x log C3 r=-0.312; p=0.008** Pb x log IgM r=0.179; p>0.05 **Pb x log IgG r=-0.320; p=0.006** **Pb x log IgA r=0.256; p=0.03**	Serum IgG was negatively correlated to blood Pb in male Pb-

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	Years not stated; Male=100%				Note: Authors state Pb workers had lower salivary IgA but this contradicts a table in the publication.	Correlation between Pb and Ig or C3 in referents Pb x log C3 r=0.045; p>0.05 Pb x log IgM r=0.050; p>0.05 Pb x log IgG r=0.126; p>0.05 Pb x log IgA r=0.191; p>0.05 Correlation between Pb and Ig or C3 all subjects **Pb x log C3 r=0.231; p=0.01** Pb x log IgM r=-0.125; p>0.05 **Pb x log IgG r=-0.227; p=0.01** Pb x log IgA r=0.044; p>0.05 Authors state Pb workers had a slight tendency toward an increased frequency of colds and influenza infections, but did not demonstrate statistical relationship. *No functional immune tests and no other immune endpoints tested*	workers and combined Pb/referents. Serum IgA and complement C3 were also associated with blood Pb in Pb-workers. IgM was not affected by Pb.
Cross-sectional Fischbein (1993) USA	51 firearms instructors (Pb-1<25µg/dL, Pb-2≥25) and 36 referent industrial workers ; Years not state; Male= 100%	Referent = 47.1 (10.8) Pb-1= 48.8 (7) Pb-2=47.9 (9.4)	Referents = "tested negative" limit of detection not reported. Pb-1=14.6 (4.6) Pb-2=31.4 (4.3)	CD3, CD4, CD8, CD16, CD20, HLA-DR, spontaneous secretion of IgG (sIgG), mixed lymphocyte response (MLR), Hb, mitogenic response to PHA, PWM, and SAC	ANOVA, Pearson correlation, multiple regression Age, sex	Correlation in immune measure and Pb in Pb workers: **CD4% r=-0.45; p=0.001** **MLR r=-0.56; p=0.0001** Multiple regression of immune measures to Pb: **MLR B=-0.66 (0.21); p=0.004** CD4% B=-0.24 (0.19); p=0.2 CD8% B=0.09 (0.19); p=0.6 PHA B=-3.88(5.85); p=0.51 **Hb B=0.09 (0.03); p=0.002** **Percent and number of CD4 cells were decreased in both Pb-groups relative to referents; p<0.01 to <0.002.** **Percent of CD3 and HLA-DR were also decreased in both Pb-groups relative to referent; p<0.05 to p<0.002.** **Percent of CD20 were increased in both Pb-groups relative to referent; p<0.05 to p<0.002**. MLR and mitogenic response to PHA were decreased in Pb workers≥25µg/dL and mitogenic response PWM were decreased in both Pb-worker groups relative to referents. CD16, sIgG, and mitogenic response to SAC not related to Pb level or Pb-worker group. *No other immune endpoints tested*	Mixed lymphocyte response and % CD4 T-cells were negatively correlated to blood Pb. Mitogenic response to PHA and PWM, and % CD3 and HLA-DR were lower and CD20 was higher in firearms workers than referents. CD16 and SAC response did not differ.
Cross-sectional Garcia-Leston (2011) Portugal	70 male Pb workers (high Pb; n=34 plant 1 Pb chemical and	Referent=34.6(8) Pb=45.2(9.3)	Graphically displayed Referent ≈ 4 Pb-exposed ≈ 32 Plant 1≈ 28	WBC differential: T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8),	ANOVA, Student's t test, Fisher's exact test, Bonferroni's test, Pearson correlation	Significant difference in % lymphocytes by Pb group: **CD8% - referent ≈36** **CD8% - Pb-exposed ≈ 32; p<0.05** **CD8% - plant 1 ≈ 31; p<0.05**	Percent of CD8 T-cells was decreased in Pb workers

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	n=36 plant 2 Pb battery workers) and 38 referents; Years not stated; Male=100%		Plant 2≈37	B-cells (CD19), NK cells(CD16 and CD56)	Adjustments not described.	CD8% - plant 2 ≈ 33 No difference by Pb-group in CD3, CD4, CD19, CD16/CD56 *No functional immune tests and no other immune endpoints tested*	relative to referents. CD3, CD4, CD19, CD16/CD56 did not differ.
Cross-sectional Governa (1988) Location not stated; authors work in Italy	9 Pb battery workers (high Pb) and 18 referents with no occupational Pb; years not stated; Male= 100%	High Pb= 38(13) Referent "age-matched"	Referent = 19.2 (6.4) High Pb=63.2 (8.2) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Polymorphonuclear leukocytes (PMNs) chemotaxis	Student's t test Adjustments not described.	Chemotactic index: Referent =75.6 (13.4) **Pb worker = 56.4 (8.7); p<0.05** Authors state PMN chemotaxis was not correlated to blood Pb levels. *No other immune endpoints tested*	PMN chemotaxis was decreased in Pb workers relative to referents.
In vitro Governa (1987) Location not stated; authors work in Italy	In vitro Pb exposure of blood from 24 health subjects years not stated; % Male not stated	Range 26 to 54	Prior to in vitro Pb exposure blood Pb ranged from 10.35 to 14.49µg/dL .5µM to 0.7 µM	Polymorphonuclear leukocyte (PMNs) phagocytosis, chemotaxis, and superoxide formation	Student's t test and linear regression analysis Adjustments not described.	Significant difference by in vitro Pb concentration: **Chemotaxis p<0.01 at Pb>2.4µM** **Phagocytosis p<0.01 at Pb>28.8µM** **Fluorescence polarization p<0.01 at Pb>57.6µM** Regression analysis: **Chemotaxis r=0.70; p<0.01** **Phagocytosis r=0.68; p<0.01** *No other immune endpoints tested*	In vitro exposure to Pb decreased PMN chemotaxis and phagocytosis.
Cross-sectional In vitro Guillard (1989) Location not stated; authors work in Belgium	25 Pb battery workers (high Pb) and 21 not occupationally exposed referents; in vitro exposure of referent PMNs also performed; years not stated; Male= 100%	Range 22 to 52	Mean Pb-workers = 60.3 Referent not reported Range Pb-workers=34.8-76.5 Referent not reported Measured when outcome assessed	Polymorphonuclear leukocytes (PMN) and monocyte respiratory burst by phorbolmyristate acetate (PMA)	Kruskal Wallis test, regression Adjustments not described.	Mean PMNs and monocytes/µl Referent = 3987 **Pb workers = 5546; p<0.05** Peak PMA respiratory burst chemiluminescence Referent = 11.57 Pb workers = 11.24; p>0.05 In vitro $PbCl_2$ exposure tested for inhibition of PMA-induced respiratory burst (referent PMN/monocytes) and Pb inhibited chemiluminescence at concentrations from 2 x 10^{-4}, 2 x 10^{-4}, and 10^{-3} mole/L and 2.8x10^{-4}M produced 50% inhibition of peak. *No other immune endpoints tested*	Respiratory burst of PMNs and monocytes was not different between Pb workers and referents.
Ecological Heinrich (1999) East Germany	2470 children aged 5-14 living in 2 industrial areas (Pb1, Pb2) or a referent area: Year=1992-1993; Male=50-51%	Range 5-14	No blood Pb data Pb emissions and Pb dustfall differ by 3 3 counties. Referent – Zebst -no emissions -dust=16-18µg/m^2/day Pb-1-Bitterfeld -no emissions -dust=18-41µg/m^2/day Pb-2-Hettstedt -0.22-.34 tons/km^2/year	Dermatological exam, test of pulmonary function, skin prick testing (SPT) for aller-gens, serum IgE, self-reported symptoms or doctor diagnosis of asthma, bronchitis,	Logistic regression analysis Adjusted for potential predictors	Odds ratio OR (95% CI) for self-reported doctor-diagnosis for lifetime prevalence rates: **Asthma Bitterfeld vs Zebst OR=4.4 (1.84,10.5)** **Bronchitis Hettstedt vs Zebst OR=1.52 (1.20,1.92)** **Allergy Hettstedt vs Zebst OR=1.69 (1.21,2.36)** Eczema Bitterfeld vs Zebst OR=1.42 (0.94,2.15) **Eczema Hettstedt vs Zebst OR=1.52 (1.03,2.24)** Bitterfeld not significant for bronchitis, allergy Hettstedt not significant for asthma Odds ratio OR (95% CI) for parent-reported symptoms lifetime prevalence rates **Wheezing Hettstedt vs Zebst OR=1.79 (1.37,2.34)**	Respiratory disease and allergy were elevated in children from a polluted area in Germany that also has higher Pb emissions and dustfall. Data include increased odds

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			-dust=47-367µg/m^2/day * lack of blood Pb data limits utility	allergy, eczema, wheezing, cough, shortness of breath		**Short Breath Hettstedt vs Zebst OR=2.36 (1.65,3.38)** **Cough Hettstedt vs Zebst OR=1.72 (1.05,2.81)** Bitterfeld not significant Odds ratio OR (95% CI) for physical exam data Bron. React. Bitterfeld vs Zebst OR=1.69 (0.93,3.07) **SPT (sens.) Hettstedt vs Zebst OR=1.38(1.02,1.86)** **Specific IgE Hettstedt vs Zebst OR=1.75(1.31,2.33)** Bitterfeld not significant one or more positive SPT, one or more specific IgE, atopic dermatitis Hettstedt not significant for bronchial reactivity, atopic dermatitis	ratio for sensitization based on positive SPT and elevated specific IgE to common allergens, bronchitis, allergy, eczema, wheezing, shortness of breath, cough. No blood Pb data.
Cross-sectional Heo (2004) Korea	606 Pb battery factory workers; no referent population; Year not stated; Male=91%	Age-stratified: <30 (n=184) 30-39 (n=299) >40 (n=123)	Age-stratified µg/dL: <30 years = 22 (10) 30-39 years =23(11) >40 years= 24(9) Measured when outcome assessed	Serum IgE, IL-4, IFNγ,	ANOVA, Dunnett's t test, Kruskal-Wallis test, Dunn's test, Student's t test, Mann-Whitney U test Adjustments not reported.	**Correlation of serum IgE by blood Pb:** **r=0.0872; p=0.0318** Mean serum IgE level by blood Pb in factory workers: <10µg/dL blood Pb – IgE=270 (46) ng/mL 10-29µg/dL blood Pb – IgE= 536 (91) ng/mL **≥30µg/dL blood Pb – IgE= 1286 (457) ng/ml; p<0.05** The authors also reported analyses of IgE stratified by blood Pb and age groups (<30, 30-39, and ≥40 years of age) that was significant for the ≥30µg/dL blood Pb for all age groups except the 30 year-olds. Mean IL-4 level by blood Pb in <30 year-old workers: <10µg/dL blood Pb – IL-4= 22 (3) pg/mL 10-29µg/dL blood Pb – IL-4= 24 (5) pg/mL **≥30µg/dL blood Pb – IL-4= 11 (2) pg/ml; p<0.05** No effect of Pb levels on IL-4 in other age groups or on IFNγ in any age group. *No functional immune tests and no other immune endpoints tested.*	Serum IgE was correlated with blood Pb and elevated in Pb-factory workers with blood Pb levels ≥30µg/dL relative to other workers. Serum IL4 was lower in Pb-workers <30 years of age with blood Pb≥30g/dL, but IL4 and IFNγ were not associated with blood Pb in any other group.
Cross-sectional Horiguchi (1992a) Osaka, Japan	56 Pb refinery workers in Osaka; Year not stated; Male=82%	49.5 Range 18-73	Pb-workers Blood =47.4 (28.1) Urine (µg/L)=57.7 (45.7) Reference values Blood = 11 (0.28) Urine (µg/L)=35.5 (0.45) Measured when outcome assessed *Note: source of*	Frequency of colds during previous year	Chi-square test Adjustments not described.	Mean frequency of colds by Pb level in Pb workers: <20µg/dL mean=1.5 20-40µg/dL mean=1.07 40-60µg/dL mean=1.62 >60µg/dL mean=2.18 Frequency of colds by blood Pb level: Less than 1.5 cold/year – Pb<60µg/dL = 31 Less than 1.5 cold/year – Pb>60µg/dL = 7 More than 2 colds/year – Pb<60µg/dL = 8	Significantly increased frequency of colds in workers with blood Pb>60 µg/dL than other Pb workers.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			"reference values" not stated; reference >10µg/dL; no referent group			More than 2 colds/year – Pb>60µg/dL = 10 Chi-square=7.967>6.630 (1%)	
Cross-sectional Horiguchi (1992b) Osaka, Japan	106 Pb refinery workers in Osaka (n=47 in 1988; n=56 in 1989); Years=1988-1989; Male=100%	Mean 1988=49.9 1989=48.6 Range 1988=18-73 1989=19-74	Pb-workers Blood 1988=50.4(28) Blood 1989=43.2 (24.8) Urine 1988=60.0 (47.1) Urine 1989=53.7(40.3) Reference values Blood = 11 (0.28) Urine (µg/L)=35.5 (0.45) Measured when outcome assessed *Note: source of "reference values" not stated; reference >10 µg/dL; no referent group*	Serum IgA, IgG, IgM, IgE, complement C3	Chi-square test, correlation statistical methods not reported	Authors state in 1988 significant correlation blood Pb: Serum IgA r=0.296 Serum IgE r=0.314 Authors state significantly higher number of: Workers with IgE (400 IU/ml) had blood Pb >60µg/dL No significant correlations between blood Pb and: -serum complement C3 -serum immunoglobulins (IgG, IgM) in 1988 -serum immunoglobulins (IgG, IgA) 1989 (IgM not tested) *No functional immune tests and no other immune endpoints tested*	Significant correlation between serum IgE and blood Pb; and increased serum IgE in workers with blood Pb >60µg/dL relative to other Pb workers. IgA, IgG, IgM, C3 did not differ.
Cross-sectional Jaremin (1983a) Location not stated *Same population as Jaremin (1983b)*	80 male manufacturers (group A, n=20 Pb workers with 7-24 years of exposure and chronic Pb poisoning; B, n=30 Pb workers with 1-10 years of exposure; C, referents, no occupational Pb exposure); Year not stated; Male =100%	Range 22-62	Pb: mean (SD) µg/dL Referents = 24.06 (5.93) Pb workers-A=51.8 (16) Pb workers-B=26.6(6) Pb: range Referents = 14.3-40.6 Pb workers-A=36.4-92.1 Pb workers-B=18.2-42.1 Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Lymphocyte count, albumen, serum immunoglobulin (IgG, IgM, IgA)	Student's t test Adjustments not described.	Mean serum Immunoglobulin mg/100ml by Pb group: IgG referent (24µg/dL) = 1075.90 (141) **IgG Pb worker A (51.8µg/dL) = 946.5 (135), p<0.01** IgG Pb worker B (26.6µg/dL) = 1047.66 (136) IgA referent (24µg/dL) = 225 (48) IgA Pb worker A (51.8µg/dL) = 230.25 (53) IgA Pb worker B (26.6µg/dL) = 238.36 (43) IgM referent (24µg/dL) = 66.4 (17) **IgM Pb worker A (51.8µg/dL) = 51.41 (13), p<0.001** IgM Pb worker B (26.6µg/dL) = 64.93 (16) Mitogenic response, rosette test, and migration inhibition test performed in Jaremin (1983b). *No other immune endpoints tested*	Serum IgG and IgM were decreased in Pb workers with a mean blood Pb of 52µg/dL relative to referents with mean blood Pb of 24µg/dL. IgA did not differ.
Cross-sectional Jaremin (1983b) Location not stated *Same population as Jaremin (1983a)*	80 male manufacturers (group A, n=20 Pb workers with 7-24 years of exposure and chronic Pb poisoning; B, n=30 Pb workers	Range 22-62	Pb: mean (SD) µg/dL Referents = 24.06 (5.93) Pb workers-A=51.8 (16) Pb workers-B=26.6(6) Pb: range Referents = 14.3-40.6 Pb workers-A=36.4-92.1 Pb workers-B=18.2-42.1 Measured when	Mitogenic transformation to PHA, rosette test, leukocyte migration inhibition test	Student's t test, linear correlation factor (r) Adjustments not described.	Mean lymphoproliferative (mitogen) responses to PHA Referents = 61.05 (7.31) **Pb workers-A = 45.94 (5.99), p<0.001** Pb workers-B = 58.86 (7.68) **Mitogenic response of Pb workers was increased relative to referents for spontaneous response, and response to Pb ions at 1-2x10^{-5}mg/ml, p<0.001** Correlation between blood Pb and mitogenic response Spontaneous r=0.917	PHA mitogenic response was decreased and spontaneous or Pb-stimulated lympho-proliferative responses were increased in Pb

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	with 1-10 years of exposure; C, referents, no occupational Pb exposure); Year not stated; Male =100%		outcome assessed *Note: Referent/Low Pb group over 10µg/dL*			PHA-stimulated r=-0.720 No difference between Pb workers and referents on: -rosette test or migration inhibition test Serum Ig's tested in Jaremin (1983a). *No other immune endpoints tested*	workers (blood Pb of 52µg/dL) relative to referents with mean blood Pb of 24µg/dL. Rosette and migration inhibition test did not differ.
Cross-sectional Jaremin (1990) Location not stated	127 male manufacturers (Pb workers with 0.5-24 years of exposure [A1-n=41 no Pb poisoning; A2-n=32 Pb poisoning traits; A3 n=4 clinical Pb poisoning]; n=50 referents, no occupational Pb exposure); Year not stated; Male =100%	Pb worker=38 Referent=39 Range 19-59	Pb: mean (SD) µg/dL Referents = 16.4 (7.1) A1 not Pb poisoning A2 - Pb poisoning traits A3 - clinical Pb-poison Pb-A1 = 40.1 (7) Pb-A2 = 72.2 (10) Pb-A3 = 106.7 (18) Pb: range Referents = 5-35 Pb-A1 = 18-58 Pb-A2 = 60-100 Pb-A3 = 87-129 Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Serum immunoglobulin (IgG, IgM, IgA), C_3 complement rosette test, antibody response to typhoid immunization	Student's t test Adjustments not described.	Mean absolute rosette count (SD) Referents (n=30) = 1321 (553) Pb workers-A1 (n=40) = 1218 (203) **Pb workers-A2 (n=30) = 1025 (439), p<0.02** **Pb workers-A3 (n=4) = 1080 (348), p<0.02** Mean serum Immunoglobulin mg/100ml by Pb group: IgG referent = 1213 (296) IgG Pb worker A1 = 1157 (238) **IgG Pb worker A2 = 1010 (275), p<0.02** **IgG Pb worker A3 = 906 (195), p<0.02** IgM referent = 157 (37) **IgM Pb worker A1 = 91 (34), p<0.02** **IgM Pb worker A2 = 56 (15), p<0.02** **IgM Pb worker A3 = 54 (14), p<0.02** IgA did not differ between Pb workers and referents Increase in IgG after anti-typhoid immunization: Referent (n=20) = 270 Pb worker-A1 (n=20) = 181 **Pb worker-A2 (n=20) = 42, p<0.02** Complement was significantly lower in workers with clinical Pb poisoning traits, however "n" reported as 20 when only 4 individuals were in the study. *No functional immune tests and no other immune endpoints tested*	Antibody response to typhoid immunization, rosette count, and serum IgG were decreased in workers with mean blood Pb of 70µg/dL or greater relative to referents with mean blood Pb of 16µg/dL. Serum IgM was also decreased in Pb workers with a mean blood Pb of 40µg/dL or greater. IgA and complement did not differ.
Cross-sectional Kimber (1986) Location not specified; authors located in UK	39 tetraethyl Pb plant workers (high Pb) and 21 age and sex-matched referents; Year not stated; Male=100%	Mean Referent = 38 High Pb=45 Range Referent=20-60 HighPb= 25-61	Referent=11.8(2.2) High Pb =38.4(5.6) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	NK cell function (K562 lysis), serum IgA, IgG, IgM, mitogenic response to PHA	Correlation (r), statistical methods not reported Adjustments not described. ** lack of study and statistical information limits utility	No difference between Pb workers and referents on: -NK cell lytic function (lysis of K562 target cells) -serum immunoglobulins (IgA, IgG, IgM) -lymphoproliferative (mitogen) responses to PHA *No functional immune tests and no other immune endpoints tested*	NK cell function, serum IgG, IgM, IgA, and mitogenic response to PHA did not differ between Pb workers and referents.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Kuo (2001) Taiwan	20 Pb battery workers and 34 high school teacher referents; Years not stated; %Male=50 referent and 76% Pb workers	Mean not reported	Mean not reported for blood or urine. Authors state average blood Pb had decreased from 60µg/dL to 30µg/dL Measured when outcome assessed	WBC differential: lymphocytes, monocytes, granulocytes, T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cells (CD19), NK cells(CD16 and CD56)	Chi-square test, Pearson correlation, multiple linear regression analysis Age, sex, disease status	Significant Pearson correlation for log blood Pb and: **Monocytes (% or #) r=0.4547; p<0.001** **CD8 (%) r=-0.3269; p<0.01** **B-cells (%) r=-0.3000; p<0.05** Significant difference by Pb group: **Monocytes (% or #) – referent = 4.17(0.45)** **Monocytes (% or #) – Pb = 6.00 (0.41); p=0.0013** **B-cells (%) – referent = 15.4 (1.51)** **B cells (%) – Pb = 11.17 (1.37); p=0.0246** **Lymphocytes (#/ml) – referent =1849(193)** **Lymphocytes (#/ml) – Pb =967 (140); p=0.0001** **Granulocytes (#/ml) – referent =5096(426)** **Granulocytes (#/ml) – Pb =2422 (310); p=0.0001** Authors report similar correlation to urinary Pb. *No functional immune tests and no other immune endpoints tested*	Blood Pb was correlated with % monocytes and negatively correlated to %B-cells and %CD8 T cells. Lymphocytes, granulocytes, and % B-cells were reduced in Pb workers relative to referents; # and % monocytes were increased. CD4 and NK cells did not differ.
Cross-sectional Mishra (2003) Lucknow, India *Population may overlap with Mishra (2006, 2010)*	84 male Pb-workers in Lucknow (n=34 Pb-battery workers, 30 three-wheel drivers, 20 silver jewelry makers, and 30 referents); Years not stated	29-32 by group: Range 17-65	Referent = 4.5 (2) 3-wheel drivers=6.5(4.7) Pb-battery = 128.1(105) Jewelry = 17.8 (18.5) Measured when outcome assessed	NK cell function (K562 lysis), IFN-γ production and mitogenic response to PHA of peripheral blood mononuclear cells (PBMCs)	ANOVA, Student Neuman Keuls test, Pearson correlation Adjustments not reported.	IFN-γ (pg/ml) (SD) by group: Referent-unstimulated = 63 (112) Pb-battery workers-unstimulated = 56 (95) Referent-PHA stimulated = 173 (227) **Pb-workers-PHA stimulated = 812 (778); p<0.001** Pearson correlation between blood Pb and IFN-γ in PHA stimulated lymphocytes of referent and Pb-workers combined: r=0.384; p=0.005 Stimulation Index for PHA lymphoproliferative (mitogen) response by group: Referent = 70 (55) **3-wheel drivers = 42 (28); p<0.001** **Pb-battery = 32 (22); p<0.001** **Jewelry = 36 (22); p<0.001** Authors state that PHA stimulation was not correlated to blood Pb levels despite group-related difference. Percent NK cell cytotoxicity (SD) by group at 50:1 E:T: Referent = 47 (14) 3-wheel drivers = 49 (15) Pb-battery = 42 (16) Jewelry = 41 (18) Similar results reported for 25:1 E:T ratio. *No other immune endpoints tested.*	Blood Pb was significantly associated with increased IFN-γ production in response to PHA in male adults. NK cell function and mitogenic response to PHA did not differ by blood Pb.
Cross-sectional Mishra (2006)	30 male Pb-battery workers	Median Pb =27	Pb-workers =106 (107) Referents = 4.5 (2.2)	Serum IgA, IgG, and IgM,	Mann-Whitney U test; student Neuman Keuls test,	Mean serum IgA by Pb group: Referents IgA = 138 (53) mg/dL	Serum IgA was significantly

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Location not stated, authors work in Lucknow India *Population may overlap with Mishra (2003, 2010)*	and 27 referents; Years not stated	Referent=28 Range Pb =19-45 Referent=25-45	Measured when outcome assessed	neutrophil respiratory burst and nitric oxide (NO) production	Pearson correlation coefficient Adjustments not described.	**Pb-workers IgA = 182 (53) mg/dL; p<0.05** Authors report serum IgG and IgM did not differ between Pb-workers and referents (data shown graphically). Authors report neutrophil respiratory burst and nitric oxide (NO) production did not differ between the Pb-workers and the referents (data shown graphically). *No other immune endpoints tested.*	elevated in Pb-workers relative to referents. IgM, IgG, and neutrophil NO and respiratory burst did not differ.
Cross-sectional Mishra (2010) Location not stated, authors work in Lucknow India *Population may overlap with Mishra (2003, 2006)*	59 male Pb-workers (n=26 three-wheel drivers, n=33 Pb-battery workers) and 21 referents; Years not stated	Median 27-33 by group: Range 17-65	Referent = 4.5 (2) 3-wheel drivers=6.7(4.5) Pb-battery = 132(103) Measured when outcome assessed	Lymphocyte subsets (CD4, CD45RA [naïve], CD8, CD56)	ANOVA, Pearson correlation coefficient Adjustments not described.	Percentage of lymphocytes by Pb-group: CD4 – referent = 55 (13) **CD4 – three-wheeler = 37 (11); p<0.001** **CD4 – Pb-battery workers = 31 (8); p<0.001** CD4/CD8 – referent = 2.6 (2.3) **CD4/CD8 – three-wheeler = 1.4 (0.5); p<0.001** **CD4/CD8 – Pb-battery workers = 1.3 (0.5); p<0.001** CD45 RA – referent = 61 (15) **CD45 RA – three-wheeler = 73 (10); p<0.05** **CD45 RA – Pb-battery workers = 70 (14); p<0.05** CD8, CD16, CD25, CD45 RO did not differ by group **Correlation of blood Pb and % CD4 r=-0.374; p<0.01** **Correlation exposure time % CD4 r=-0.428; p<0.001** *No functional immune tests and no other immune endpoints tested.*	Percent of CD4 T-cells was decreased and percent of CD45RA B-cells was increased in Pb-workers relative to referents. CD8, CD16, CD25, CD45RO did not differ.
Cross-sectional Pinkerton (1998) USA	145 Pb-smelter workers (high Pb) and 84 referent workers from hardware manufacturing company; Male=100%	Pb=32.9 (8.6) Referent=30.1(9)	Median: Referent = <2 High Pb = 39 Range: Referent <2-12 High Pb= 15-55 Measured when outcome assessed Cumulative exposure also estimated by integrating blood Pb concentration over time	NK function (target lysis), serum IgG, IgM, IgA, salivary IgA, complement, WBC differentials: neutrophil, lymphocytes, monocytes, eosinophils, basophils, CD14/CD45, CD8/CD3, CD8/CD56, CD2/CD19, CD45RA (naïve) mitogenic (tetanus toxoid) response	Wilcoxon rank sum tests, chi-square tests, multivariate regression Age, race, smoking status, work shift	Geometric mean of immune parameter differing by Pb-workers and unexposed workers: **Monocytes (%) r^2 = 5.1; p=0.03** **Immature T cells (CD4/CD8) r^2 = 5.3; p=0.003** **Subset of NK cells (CD8/CD56) r^2 = 11.0; p=0.04** **Among Pb-workers the # and % of B-cells (CD19+) was positively associated (p≤0.01) with blood Pb. Among Pb-workers, negative association of cumulative Pb with IgG(p=0.03), and positive association of cumulative Pb with % and # of CD4/CD45RA(p<0.01)** No difference between Pb-workers and referents or effect of blood Pb in workers on: -serum complement -serum immunoglobulins (IgA, IgG, IgM) or-salivary IgA -lymphoproliferative responses to tetanus toxoid -WBC differentials (except effect noted above) *No functional immune tests and no other immune endpoints tested*.	Decreased percent NK cells, monocytes, and immature T cells were observed in Pb workers to referents. Increased number and percent of B-cells among Pb workers and naïve T cells were correlated with cumulative Pb exposure. Serum IgG, IgA,

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
							IgM, C3 and other lymphocyte populations were not related to Pb.
Cross-sectional Queiroz (1994b) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1993, 1994a)*	33 male Pb battery workers and 20 referents from blood bank donors; Year not stated; Male= 100%	Pb=32.4 (11) Referent not stated	Referent= <10µg/dL Pb: range=12-80 <30µg/dL – 6 workers 30-40µg/dL-4 workers 40-50µg/dL-6 workers 50-60µg/dL-5 workers 60-70µg/dL-8 workers >70µg/dL-4 workers Measured when outcome assessed	Serum IgG, IgA, and IgM, mitogenic response to PHA	Student's t test Adjustments not described.	No difference between workers and referents on: -serum immunoglobulins (IgA, IgG, IgM) -lymphoproliferative (mitogen) responses to PHA *No functional immune tests and no other immune endpoints tested*	Serum IgG, IgM, IgA, and mitogenic response to PHA did not differ between Pb-workers and referents.
Cross-sectional Queiroz (1993) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1994a, 1994b)*	39 male Pb battery workers and 39 referents from blood bank donors; Year not stated; Male= 100%	Pb =33.9 (12) Referent not stated	Referent= <10µg/dL Pb: range=14.8-91.4 <30µg/dL – 7 workers 30-40µg/dL-4 workers 40-50µg/dL-4 workers 50-60µg/dL-7 workers 60-70µg/dL-12 workers >70µg/dL-5 workers Measured when outcome assessed	Neutrophil chemotaxis and nitroblue tetrazolium test (NBT) reduction activity (measure of phagocytosis and respiratory burst activity)	Mann Whitney U test, ANOVA, Duncan test Adjustments not described.	Neutrophil function by Pb group: **Chemotaxis p<0.001** **NBT reduction p<0.001** Neutrophil function by Pb group > or < 60µg/dL presented graphically by median: Chemotaxis – referent≈35µm Chemotaxis Pb<60µg/dL≈9µm **Chemotaxis Pb>60µg/dL≈27µm;p<0.001** NBT positive neutrophils– referent≈51% NBT positive neutrophils Pb<60µg/dL≈22% **NBT positive neutrophils Pb>60µg/dL≈19%;p<0.001** No other immune endpoints tested	Neutrophil chemotaxis and respiratory burst activity of Pb-workers was decreased relative to referents.
Cross-sectional Queiroz (1994a) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1993, 1994a)*	60 male Pb battery workers and 39 referents from blood bank donors; Year not stated; Male= 100%	Pb =33.9 (12) Referent not stated	Referent= <10µg/dL Pb: range=14.8-91.4 <30µg/dL – 8 workers 30-40µg/dL-4 workers 40-50µg/dL-7 workers 50-60µg/dL-14 workers 60-70µg/dL-12 workers >70µg/dL-15 workers Average of 33 workers in safe range (<60µg/dL) =43.2(14.9) Measured when outcome assessed	Polymorphonuclear (PMN) *Candida* phagocytosis and lytic activity, and splenic phagocyte function by quantitation of red blood cell "pits"	Mann Whitney U test, ANOVA, Duncan test Adjustments not described.	PMN function by Pb group: Candida phagocytosis p>0.05 **Candida killing/lytic activity p<0.001** **NMT reduction p<0.001** PMN function by Pb group > or < 60µg/dL presented graphically by mean: Candida killed – referent≈29 (15)% **Chemotaxis Pb<60µg/dL≈17(12)%; p<0.05** **Chemotaxis Pb>60µg/dL≈12(14)%; p<0.05** Lytic activity toward *C. albicans* was affected, but not *C. pseudotropicalis* *No other immune endpoints tested*	PMN lytic activity of Pb-workers was decreased relative to referents, but PMN phagocytic activity was not affected.
Cross-sectional Reigart (1976) Location not	19 preschool age children; 12 with blood (high Pb)	Mean not reported Range 4-6	High Pb= 45.3µg/dL Low /referent 22.6µg/dL	Recall response to soluble antigen (tetanus	Statistical methods not reported	No statistical difference between the high Pb group and the low Pb group in: -IgG-specific antibody titer for tetanus toxoid	No difference was observed in tetanus

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
stated; authors work in Charleston, SC	Pb≥40µg/dL; and 7 <30µg/dL (referent); Year not stated; Male%=unknown		Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	toxoid), IgG, IgM, IgA, serum complement	Adjustments not described. * lack of study and statistical information limits utility	-serum complement -serum immunoglobulins (IgA, IgG, IgM) *No other immune endpoints tested.*	toxoid-specific antibodies, complement, serum IgG, IgM, or IgA, between 12 children with blood Pb >40 and 7 below 30µg/dL.
Cross-sectional Sata (1998) Location not stated; authors work in Japan *Population may overlap with Sata (1997)*	71 male Pb stearate workers (high Pb) and 28 referents for another chemical factory; year not stated; Male=100%	Mean High Pb=48 Referents=55	High Pb=19 Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility but correlation to blood Pb also demonstrated.*	WBC differentials T-cell (CD3), memory T(CD3CD45RO), naïve T (CD3CD45RA), T-helper (CD4), CD29A, T-cytotoxic (CD8), B-cell (CD19)	Pearson correlation, multiple regression analysis Adjustments not described.	**Regression relationship of blood Pb and memory T CD3CD45RO B=-172.4; p<0.05** **Correlation between blood Pb in Pb workers and naïve T (CD3CD45RA); p<0.05** Significantly different mean measures by Pb group: **Memory T (CD3CD45RO)# – referents = 850 (450)** **Memory T CD3CD45RO # Pb- = 740 (310);p<0.05** **Cytotoxic T (CD8) % -referents = 34(7)** **Cytotoxic T (CD8)% - Pb workers = 38(9); p<0.05** No difference by Pb-group in CD19 or CD4 lymphocytes. *No functional immune tests and no other immune endpoints tested*	Memory T cells were negatively correlated to blood Pb and naïve T cells were positively correlated to blood Pb in workers. Memory T cells were reduced and CD8 T cells were increased in Pb-sterate workers relative to referents. CD4 and CD19 did not differ.
Cross-sectional Sata (1997) Location not stated; authors work in Japan *Population may overlap with Sata (1998)*	29 male Pb stearate workers (high Pb) and 19 referents without Pb history; year not stated; Male=100%	Mean High Pb=29 Referents=55 Range High Pb=23-74	Mean Pb workers=18 Low-Pb<20µg/dL; n=19 High-Pb ≥20µg/dL; n=10 Range Pb workers= 7-35 Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility but correlation to blood Pb also demonstrated*.	WBC differentials T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cell (CD19), NK (CD16 and CD57)	Students' t test, Welch's test, ANCOVA Age	Correlation between CD16 cells per mm^3 and blood Pb among Pb workers r=-0.39; p<0.05 Significantly different mean measures by Pb group: NK cell (CD16) % -referents = 32(8) NK cell (CD16) % - Pb low = 33(13) **NK cell (CD16) % - Pb high = 22 (6); p<0.05 to ref. and low Pb group; also for CD16 cell number.** Cytotoxic T (CD8) % -referents = 36(6) Cytotoxic T (CD8)% - Pb low = 35(10) **Cytotoxic T (CD8)% - Pb high = 43(6); p<0.01 to referent and p<0.05 to low Pb group** **CD3 % was increased in high Pb group relative to low Pb group at p<0.05.** No difference by Pb-group in CD3, CD4, CD19, CD57. *No functional immune tests and no other immune*	NK cell number was negatively correlated to blood Pb in Pb workers. NK cell number and percentage were reduced and CD8 T cells were increased in Pb-sterate workers relative to referents. CD3, CD4, CD19, and CD57 did not

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
						endpoints tested	differ.
Cross-sectional Undeger (1996) Ankara, Turkey *Population may overlap with Basaran (2000)*	25 male Pb-battery workers (high Pb) and 25 referents from University of Hacettepe; Years not stated; Male=100%	Referent=33(9) Pb=33 (8.5)	Referent=16.7 (5) High Pb=74.8 (17.8) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Serum IgG, IgM, IgA, complement C3 and C4, WBC differential (CD3, CD4, CD8, CD20, CD56)	Mann-Whitney U test, linear regression Adjustments not described.	Significantly different mean measures by Pb group: T-helper (CD4) – referents=1140(681)/mm^3 **T-helper (CD4) – high Pb=858.8(341)/mm^3; p=<0.05** IgG – referents=1202(393.6) **IgG – high Pb=854.6(415.6); p<0.05** IgM – referents=140.4(66.1) **IgM – high Pb=93.3 (39.6); p<0.05** C3 – referents=61(17.4) **C3 – high Pb=45.1(18.5); p<0.005** C4 – referents=22.1(7.8) **C4 – high Pb=17.8(8.5); p<0.05** No difference by Pb-group in leukocytes, lymphocytes, B-cells, T-cells, T-suppressor, CD4/CD8 ratio, NK cells and serum IgA. *No functional immune tests and no other immune endpoints tested*	Number of CD4 T-cells and serum IgG, IgM, C3, and C4 were lower in Pb-workers than referents. Leukocytes, lymphocytes, CD8, CD20, CD56, and serum IgA did not differ.
Cross-sectional Valentino (2007) Location not stated; authors work in Italy	58 male Pb workers (Pb-1; n=14 pottery, Pb-2 n=44 foundry) and 59 alimentary plant referents ;Years not stated; Male=100%	Mean Referent=47(7) Pb-1=38.8(4) Pb-2=45.8(7) Range Referent=25-61 Pb=30-61	Blood Referent=3.9(1.8)) Pb-1=9.7(4.2) Pb-2=21.7(8.8) Urine Referent=1.9(1.2) Pb-1=12.8(12.3) Pb-2=35.7(21) Measured when outcome assessed	Plasma cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ), nitrates and nitrites	ANOVA, Chi-square test, Spearman correlation, multiple regression Adjustments not described.	Plasma cytokines by Pb group (pg/ml): IL-10 – referents =4.55(3.89) IL-10 – Pb- 1 = 4.68 (1.53) **IL-10 – Pb-2 = 7.37 (8); p<0.05** TNF-α – referents = 2.30 (1.39) TNF-α – Pb-1 = 3.66(2.69) **TNF-α – Pb-2 = 3.05(1.66); p<0.05** No difference by Pb-group in IFN-γ, IL-2, IL-4, IL-6, nitrates and nitrites *No functional immune tests and no other immune endpoints tested*	Plasma IL-10 and TNF-α were increased in Pb workers relative to referents. IL-2, IL-4, IL-6, IFN-γ did not differ.
Cross-sectional Valentino (1991) Location not stated; authors work in Italy	10 Pb refinery workers (high Pb) and 10 referents; Years not stated; Male=100%	Referent Pb=41.1 (7.3)	Referent = 12.4(2.5)µg/dL High Pb=33.1(5.6) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Polymorphonuclear leukocytes (PMNs) phagocytosis, chemotaxis, and superoxide formation	Student's t test Adjustments not described.	Chemotaxis by Pb group: Toward C5a –referent =82.2 (6.0) **Toward C5a –Pb worker =65.0 (13.2); p<0.002** Toward F-MLP –referent =85.3 (12.9) **Toward F-MLP –Pb worker= 63.2 (11.8); p<0.001** LTB4 production – referent= 22.8(7.5) **LTB4 production – Pb worker = 53.8 (13.7); p<0.001** No difference by Pb-group in random migration or chemiluminescence, respiratory burst *No other immune endpoints tested*	PMN chemotaxis was decreased in Pb workers relative to referents.
Cross-sectional Wagnerova (1986) Czechoslovakia	Children living near a Pb smelter (high Pb) and referent children in a rural area followed for	11 at start of study	Presented graphically Referent boys ≈18-23 Referent girls≈12-21 Pb boys≈30-42 Pb girls≈23-41	Serum IgG, IgA, IgM, IgE	Statistical methods not reported Adjustments not described. ** lack of statistical information limits utility	Authors state IgE was significantly decreased in children during all 4 sampling times from the children living closer to the Pb smelter. Authors state IgM was significantly decreased in girls living closer to the Pb smelter during all 4 sampling times from the referents, and no difference	Decreased serum IgE in boys and girls living near a Pb smelter and decreased IgM

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	every 6 months for 2 years; n varied from 53 to 92 per group per sample; Year not stated; Male=52-58%		*Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed			in IgM in the boys. Authors state IgA was significantly increased in Pb children during the first sampling time, with no difference at the other 3 sampling times between children living closer to the Pb smelter and referents. *No functional immune tests and no other immune endpoints tested*	in girls living near a Pb smelter relative to referents. IgG did not differ and IgA was equivocal.
Cross-sectional Yucesoy (1997b) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997a, 1997c)*	20 male Pb-battery workers (Pb-1), 20 male Pb/Cd (Pb-2)workers, and 12 age-matched referents; Years not stated; Male= 100%	Pb-1=35.9 Pb-2=41.7 Referent=36.8 Range: Pb-1=19-49 Pb-2=39-48 Referent=21-39	Referent = 4.83 (0.99) Pb-1 = 59.4 (3.2) Pb-2= no Pb data Measured when outcome assessed	Serum IL-1β, IL-2, TNF-α, γ-IFN, serum cadmium	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	Mean serum cytokine (SE) by Pb group: IL-1β -referents = 33.5 (3.09) pg/ml **IL-1β - Pb-workers = 22.67 (1.35) pg/ml; p<0.05** IL-2 -referents = 4.15 (0.78) pg/ml IL-2 - Pb-workers = 4.58 (0.52) pg/ml TNF-α -referents = 3.07 (0.86) pg/ml TNF-α - Pb-workers = 2.34 (0.58) pg/ml γ-IFN – referents = 0.59 (0.01) IU/ml **γ-IFN – Pb-workers = 0.55 (0.01) IU/ml; p<0.01** IL-1β was also lower and γ-IFN was elevated in relation to combined Pb/cadmium exposure workers. *Other immune data reported in other publications*.	Plasma IL-1β and γ-IFN levels were decreased in Pb-workers (n=20) relative to referents (n=12). IL-2 and TNF-α did not differ.
Cross-sectional Yucesoy (1997a) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997b, c)*	20 male Pb-battery workers (high Pb) and 20 age-matched referents; Years not stated; Male= 100%	high Pb =35.9 Referent=36.8 Range: highPb =19-49 Referent=21-39	Referent = 4.5 (0.7) high Pb = 59.4 (3.2) Measured when outcome assessed	NK function (K562 lysis), mitogenic response to PHA	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	NK cell function – mean % cytotoxicity) by Pb group: Referents (12.5:1)= 31.0 (2.3) Referents (25:1)= 44.8 (2.4) Referents (50:1)= 51.8 (2.1) Pb-workers (12.5:1)= 33.8 (2.7) Pb-workers (25:1)= 42.1 (2.6) Pb-workers (50:1)= 51.6 (2.2) Mitogenic response to PHA (BrdU incorporation): Referents = 1548 (174) Pb-workers = 1462 (236) *Other immune data reported in other publications*.	NK cell function and mitogenic response to PHA did not differ between 20 Pb workers and referents.
Cross-sectional Yucesoy (1997c) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997a, 1997b)*	50 male Pb-battery workers (n=20 Pb-1; n=30 Pb-2), 14 Pb/Cd workers (Pb-3), and 10 age-matched referents; Years not stated; Male= 100%	Pb-1=35.9 Pb-2=34 Pb-3=37.4 Referent=35.6 Range: Pb-1 =19-49 Pb-2 =24-45 Pb-3 =27-55 Referent=25-42	Referent = 4.0 (0.4) Pb-1 = 59.4 (3.2) Pb-2 = 58.4 (2.5) Pb-3 =68.7(4.7) Measured when outcome assessed	NK function (K562 lysis), CD4, and CD20	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	% mean (SE) lymphocyte surface markers by Pb group: CD4 % -referents = 30.8 (1.0) CD4 % -Pb-workers = 30.1 (1.5) CD4 % -Pb/Cd workers = 28.5 (2.3) CD20 % -referents = 15.1 (1.5) CD20 % -Pb-workers = 13.8 (0.9) **CD20 % -Pb/Cd workers = 11.1 (1.0); p<0.05** Other immune data reported in other publications. NK data reported in Yucesoy (1997a) *Other immune data reported in other publications*.	Percent of CD4 T-cells and CD20 B-cells did not differ between 20 Pb workers and referents.

Abbreviations: CD – cluster differentiation (e.g., CD3 – T cells, CD4 – helper T cells, CD8 – cytotoxic T cells); conA – concanavalin A; Cr – chromium; Cu – copper; ELISA – enzyme-linked immunosorbent assay; glutathione S transferase M1 gene (GSTM1); Hb – hemoglobin; HCB – hexachlorobenzene; γ-HCB-hexachlorocyclobenzene; Hg – mercury; HLA-DR - human leukocyte-assisted D-related antigen; IFNγ – interferon gamma; Ig – immunoglobulin; IL – interleukin; LPS – lipopolysaccharide; MHC – major histocompatibility complex; Ni – nickel; NK – natural killer cells; NO – nitric oxide; OC – organochlorine compounds; PCB – polychlorinated biphenyls; PHA – phytohemagglutanin; PMN – polymorphonuclear leukocytes; PWM – pokeweed mitogen; RT-PCR - reverse transcriptase-polymerase chain reaction; SAC – formalin-fixed *Staphylococcus aureus* Cowan Strain I antigen; Se – selenium; SOD – superoxide dismutase; SPT – skin prick test; TNF – tumor necrosis factor; WBC – white blood cell; Zn – zinc

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