APPENDICES AVAILABLE ON REQUEST

Research Report 115

Validation and Evaluation of Biomarkers in Workers Exposed to Benzene in China

Appendix B. Additional Statistical Analyses

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Table B.1. Benzene Exposure-Response Regression Analyses of Blood Counts by Benzene Exposure Level (4-week Average), With and Without Adjustment for Sex, Age, Toluene and Cotinine Levels [D, E]

Variable	Benzene Regress. Coeff. ± S.E., Unadjusted, All Subjects	Benzene Regress. Coeff. ± S.E., Adjusted, All Subjects
Red blood cells ($x10^{10}$/L)	-1.01 ± .37 [B]	-.60 ± .31 [A]
Hematocrit	-.061 ± .055	-.062 ± .054
Platelets ($x10^{9}$/L)	-.164 ± .80	-.47 ± .92
White blood cells ($x10^{6}$/L)	-33.4 ± 8.5 [C]	-32.6 ± 8.8 [C]
Lymphocytes ($x10^{6}$/L)	-7.8 ± 4.5	-9.0 ± 4.6 [A]
Neutrophils ($x10^{6}$/L)	-23.6 ± 6.5 [C]	-21.6 ± 6.6 [C]
Monocytes, log($x10^{6}$/L)	-.005 ± .003	-.006 ± .003 [A]
Eosinophils, log($x10^{6}$/L)	-.005 ± .007	-.002 ± .007
Basophils, log($x10^{6}$/L)	-.003 ± .009	-.006 ± .009
Bands (√)	-.025 ±.021	-.023 ± .022
Atypical lymphocytes (√)	-.004 ± .002 [A]	-.004 ± .002 [A]

[A] $p \leq 0.05$, test for exposure-response trend
[B] $p \leq 0.01$, test for exposure-response trend
[C] $p \leq 0.001$, test for exposure-response trend
[D] the logarithms of cotinine and toluene were used in the analysis.
[E] the controls were included in the analysis and were randomly assigned values between 0 and 0.01 ppm which was the approximate the lowest detection limit

Table B.2. Regression Analyses of Blood Counts by "Lifetime" Cumulative Benzene Exposure Level, With or Without Adjusting for Sex, Age, Cotinine and Toluene Levels [D]

Variable	Benzene Regress. Coeff. ± S.E., Unadjusted	Benzene Regress. Coeff. ± S.E., Adjusted
Red blood cells ($x10^{10}$/L)	-.191 ± .053 [C]	-.123 ± .045 [B]
Hematocrit	.0009 ± .009	.017 ± .009
Platelets ($x10^{9}$/L)	.255 ± .126 [A]	.342 ± .148 [A]
White blood cells ($x10^{6}$/L)	-4.70 ± 1.26 [C]	-4.49 ± 1.30 [C]
Lymphocytes ($x10^{6}$/L)	-1.19 ± .67 [A]	-1.16 ± .67 [A]
Neutrophils ($x10^{6}$/L)	-3.02 ± .96 [C]	-2.83 ± .98 [B]
Monocytes, log($x10^{6}$/L)	-.002 ± .0005 [C]	-.002 ± .0005 [C]
Eosinophils, log($x10^{6}$/L)	-.003 ± .001 [B]	-.003 ± .001 [A]
Basophils, log($x10^{6}$/L)	-.0006 ± .001	-.0008 ± .001
Bands (√)	.003 ± .003	.004 ± .003
Atypical lymphocytes (√)	-.0005 ± .0003	-.0005 ± .0003

[A] $p \leq 0.05$, test for exposure-response trend
[B] $p \leq 0.01$, test for exposure-response trend
[C] $p \leq 0.001$, test for exposure-response trend
[D] the controls were included in the analysis and were randomly assigned value of 0

Table B.3. Regression Analyses of Blood Cell Counts by Benzene Exposure Duration and Intensity when Both were Included in the Model, Adjusting for Sex, Age, Cotinine and Toluene Levels [B]

Variable	Exposure Duration, Regress. Coeff. ± S.E. (p-value) [A]	Exposure intensity, Regress. Coeff. ± S.E. (p-value) [A]
Red blood cells ($x10^{10}$/L)	-5.4 ± 3.8	-10.1 ± 3.4 (.001)
White blood cells ($x10^{6}$/L)	-165 ± 111	-365 ± 98 (.0001)
Lymphocytes ($x10^{6}$/L)	32 ± 58	-120 ± 51 (.01)
Neutrophils ($x10^{6}$/L)	-182 ± 84 (.02)	-209 ± 74 (.002)
Monocytes, log($x10^{6}$/L)	-.04 ± .04	-.10 ± .04 (.006)
Eosinophils, log($x10^{6}$/L)	-.10 ± .09	-.17 ± .08 (.02)

A P-values ≤ 0.1 were shown

B Controls were included in the analyses and were assigned zero values for exposure duration and intensity

Table B.4 Coefficients of variation (%) for measurements in exposed workers over time, and in unexposed subjects

	Exposed group[a]	Unexposed group
S-PMA	53	115
t,t-MA	23	80
HQ	18	42
CAT	25	37
BT	24	26
Phenol	28	37

a: Geometric mean of within-subject coefficients of variation after adjust (by ANCOVA) for variations in benzene levels across three weeks

Table B.5 Intraclass correlations (R_I) for measures of benzene metabolites

	R_I (after work)	R_I (After – Before)
HQ	**0.24**	**0.48** $^{0.06}$
CAT	**0.24**	**0.54** $^{0.04}$
BT	**0.23**	**0.31**
S-PMA	**0.43** $^{0.08}$	**0.85** $^{0.003}$
t,t-MA	**0.22**	**0.67** $^{0.01}$

Table B.6. Linear-Quadratic Model: Shape of the Exposure-Response Curve

Variable	Linear Term: Coeff. ± Std. Error (p-value)	Quadratic Term: Coeff. ± Std. Error (p-value) [A]
t,t-MA (log mg/g cr.), pre-work	.053 ± .008 (<.0001)	-.052 ± .015 (.0006)
t,t-MA (log mg/g cr.), post-work	.103 ± .011 (<.0001)	-.119 ± .020 (<.0001)
t,t-MA (log mg/g cr.), post – pre	.051 ± .010 (<.0001)	-.067 ± .018 (.0002)
S-PMA (log µg/g cr.), pre-work	.128 ± .024 (<.0001)	-.156 ± .043 (.0004)
S-PMA (log µg/g cr.), post-work	.206 ± .022 (<.0001)	-.242 ± .040 (<.0001)
S-PMA (log µg/g cr.), post – pre	.078 ± .016 (<.0001)	-.086 ± .029 (.004)
Phenol (log mg/g cr.), pre-work	.118 ± .022 (<.0001)	-.183 ± .040 (<.0001)
Phenol (log mg/g cr.), post-work	.130 ± .022 (<.0001)	-.124 ± .038 (.002)
Phenol (mg/g cr.), post – pre	.299 ± .714 (.68)	3.95 ± 1.29 (.003)

[A] Quadratic coefficient was based on $[(\text{benzene exposure in ppm})/10]^2$. All analyses controlled for age, sex, cotinine and toluene.

Table B.7. Mean Scores and Standard Deviations on FISH Assays and Number of Chromosome Breaks According to 5-Week Benzene Exposure Groups

Variable	Unexposed, Mean ± S.D. (N=25)	Total exposed, Mean ± S.D. (N=25)	>0 to <30 ppm, Mean ± S.D. (N=11)	≥ 30 ppm, Mean ± S.D. (N=14)
Granulocytes, Chrom. 7, # with 0 hybridizatns	.10 ± .29	.08 ± .28	.18 ± .40	0
Granulocytes, Chrom. 7, # with 1 hybridizatn	27.2 ± 5.9	24.9 ± 5.6	25.5 ± 5.0	24.5 ± 6.2
Granulocytes, Chrom. 7, # with 3 hybridizatns	.30 ± .46	.18 ± .38	.05 ± .15	.29 ± .47
Granulocytes, Chrom. 7, # with 4 hybridizatns	.04 ± .20	.12 ± .44	0	.21 ± .58
Granulocytes, Chrom. 7, # hypodiploids	27.3 ± 5.9	25.0 ± 5.6	25.7 ± 4.8	24.5 ± 6.2
Granulocytes, Chrom. 7, # hyperdiploids	.34 ± .47	.30 ± .54	.05 ± .15	.50 ± .65
Granulocytes, Chrom. 1 (Interphase Tandem), # with 0 hybridizations	10.3 ± 4.6	13.0 ± 8.4	13.3 ± 7.1	12.8 ± 9.6
Granulocytes, Chrom. 1 (Interphase Tandem), # with 1 hybridization	33.8 ± 5.3	29.6 ± 9.1	28.5 ± 10.2	30.5 : 8.5
Granulocytes, Chrom. 1 (Interphase Tandem), # with 3 hybridizations	.67 ± .63	.52 ± .66	.55 ± .69	.50 ± .66
Granulocytes, Chrom. 1 (Interphase Tandem), # with 4 hybridizations	.08 ± .28	0	0	0
Granulocytes, Chrom. 1 (Interphase Tandem), # hypodiploids	44.1 ± 8.7	42.6 ± 10.4	41.7 ± 12.4	43.3 ± 9.1
Granulocytes, Chrom. 1 (Interphase Tandem), # hyperdiploids	.75 ± .60	.52 ± .66	.55 ± .69	.50 ± .66
G0 Lymphocytes, Chrom. 7, # with 0 hybridizations	.08 ± .28	.16 ± .47	.36 ± .67	0
G0 Lymphocytes, Chrom. 7, # with 1 hybridization	56.9 ± 9.9	57.6 ± 11.0	58.8 ± 9.9	56.8 ± 12.1
G0 Lymphocytes, Chrom. 7, # with 3 hybridizations	.10 ± .41	.32 ± .79	.32 ± .90	.32 ± .72
G0 Lymphocytes, Chrom. 7, # with 4 hybridizations	.10 ± .29	.20 ± .48	.05 ± .15	.32 ± .61
G0 Lymphocytes, Chrom. 7, # hypodiploids	57.0 ± 9.9	57.8 ± 11.0	59.1 ± 10.0	56.8 ± 12.1
G0 Lymphocytes, Chrom. 7, #	.20 ± .48	.52 ± .87	.36 ± .92	.64 ± .84

hyperdiploids				
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 0 hybridizations	16.3 ± 6.8	17.9 ± 9.5	15.3 ± 6.2	20.0 ± 11.3
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 1 hybridization	43.1 ± 7.0	38.0 ± 8.4	37.8 ± 6.9	38.1 ± 9.7
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 3 hybridizations	.28 ± .55	.75 ± .84	.64 ± .81	.83 ± .87
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 4 hybridizations	.06 ± .22	.04 ± .20	0	.07 ± .27
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # hypodiploids (√)	59.4 ± 10.4	55.9 ± 11.8	53.1 ± 11.8	58.1 ± 11.7
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # hyperdiploids (√)	.34 ± .59	.78 ± .91	.63 ± .81	.89 ± 1.00
48h Cultured Lymphocytes, Chrom. 1, # with 0 hybridizations	14.0 ± 8.7	13.8 ± 8.2	14.5 ± 8.2	13.3 ± 8.4
48h Cultured Lymphocytes, Chrom. 1, # with 1 hybridization	29.4 ± 7.0	29.8 ± 7.9	29.0 ± 8.0	30.4 ± 8.0
48h Cultured Lymphocytes, Chrom. 1, # with 3 hybridizations	.24 ± .44	.04 ± .20	.09 ± .30	0
48h Cultured Lymphocytes, Chrom. 1, # with 4 hybridizations	.04 ± .20	.08 ± .28	.09 ± .30	.07 ± .27
48h Cultured Lymphocytes, Chrom. 1, # hypodiploids	43.4 ± 12.4	43.6 ± 11.2	43.5 ± 12.3	43.7 ± 10.8
48h Cultured Lymphocytes, Chrom. 1, # hyperdiploids	.28 ± .54	.12 ± .33	.18 ± .40	.07 ± .27
72h Cultured Lymphocytes, Chrom. 7, # with 0 hybridizations	.76 ± .78	.62 ± .73	.91 ± .83	.39 ± .56
72h Cultured Lymphocytes, Chrom. 7, # with 1 hybridization	39.7 ± 9.4	37.6 ± 8.4	36.1 ± 5.1	38.8 ± 10.3
72h Cultured Lymphocytes, Chrom. 7, # with 3 hybridizations	1.6 ± 1.3	1.4 ± 1.2	1.4 ± 1.4	1.4 ± 1.0
72h Cultured Lymphocytes, Chrom. 7, # with 4 hybridizations	.30 ± .48	.46 ± .87	.09 ± .30	.75 ± 1.05
72h Cultured Lymphocytes, Chrom. 7, # hypodiploids	40.4 ± 9.7	38.3 ± 8.4	37.0 ± 5.3	39.2 ± 10.3
72h Cultured Lymphocytes, Chrom. 7, # hyperdiploids	1.9 ± 1.5	1.9 ± 1.6	1.5 ± 1.4	2.2 ± 1.7
Granulocytes, Chrom. 1 (Interphase Tandem), Total # breaks	9.1 ± 2.5	8.5 ± 2.7	8.2 ± 3.1	8.7 ± 2.5

G0 Lymphocytes, Chrom. 1 (Interphase Tandem), Total # breaks	7.2 ± 1.9	6.3 ± 2.9	6.2 ± 2.9	6.4 ± 3.0
48h Cultured Lymphocytes, Chrom. 1, Total # breaks	6.2 ± 2.8	4.8 ± 2.4	4.4 ± 1.3	5.1 ± 3.0

Table B.8 Means and Standard Deviations of Cytogenetic FISH Variables (raw values, untransformed) According to Lifetime Cumulative Exposure Groups (ppm-years)

Variable (transformation)	Unexposed (N=25)	>0 to <150 ppm-yrs (N=14)	≥ 150 ppm-yrs (N=11) [B]
Granulocytes, Chrom. 7, # with 0 hybridizatns	.10 ± .29	.07 ± .27	.09 ± .30
Granulocytes, Chrom. 7, # with 1 hybridizatn	27.2 ± 5.9	24.9 ± 6.5	25.0 ± 4.5
Granulocytes, Chrom. 7, # with 3 hybridizatns	.30 ± .46	.18 ± .37	.18 ± .40
Granulocytes, Chrom. 7, # with 4 hybridizatns	.04 ± .20	0	.27 ± .65
Granulocytes, Chrom. 7, # hypodiploids	27.3 ± 5.9	25.0 ± 6.5	25.1 ± 4.4
Granulocytes, Chrom. 7, # hyperdiploids	.34 ± .47	.18 ± .37	.45 ± .69
Granulocytes, Chrom. 1 (Interphase Tandem), # with 0 hybridizations	10.3 ± 4.6	12.9 ± 6.0	13.2 ± 11.1
Granulocytes, Chrom. 1 (Interphase Tandem), # with 1 hybridization	33.8 ± 5.3	30.6 ± 8.2	28.3 ± 10.4
Granulocytes, Chrom. 1 (Interphase Tandem), # with 3 hybridizations	.67 ± .63	.58 ± .76	.46 ± .53
Granulocytes, Chrom. 1 (Interphase Tandem), # with 4 hybridizations	.08 ± .28	0	0
Granulocytes, Chrom. 1 (Interphase Tandem), # hypodiploids	44.1 ± 8.7	43.5 ± 8.6	41.5 ± 12.8
Granulocytes, Chrom. 1 (Interphase Tandem), # hyperdiploids	.75 ± .60	.58 ± .76	.46 ± .53
G0 Lymphocytes, Chrom. 7, # with 0 hybridizations	.08 ± .28	.29 ± .61	0
G0 Lymphocytes, Chrom. 7, # with 1 hybridization	56.9 ± 9.9	58.9 ± 11.2	56.1 ± 11.0
G0 Lymphocytes, Chrom. 7, # with 3 hybridizations	.10 ± .41	.21 ± .54	.45 ± 1.04
G0 Lymphocytes, Chrom. 7, # with 4 hybridizations	.10 ± .29	.14 ± .31	.27 ± .65
G0 Lymphocytes, Chrom. 7, # hypodiploids	57.0 ± 9.9	59.1 ± 11.3	56.1 ± 11.0
G0 Lymphocytes, Chrom. 7, # hyperdiploids	.20 ± .48	.36 ± .63	.73 ± 1.10
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 0 hybridizations	16.3 ± 6.8	16.5 ± 4.6	19.7 ± 13.5
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 1 hybridization	43.1 ± 7.0	38.7 ± 5.9	37.0 ± 11.1

G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 3 hybridizations	.28 ± .55	.68 ± .83	.82 ± .88
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # with 4 hybridizations	.06 ± .22	.07 ± .27	0
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # hypodiploids (√)	59.4 ± 10.4	55.2 ± 8.8	56.8 ± 15.2
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), # hyperdiploids (√)	.34 ± .59	.75 ± .98	.82 ± .87
48h Cultured Lymphocytes, Chrom. 1, # with 0 hybridizations	14.0 ± 8.7	13.5 ± 7.8	14.2 ± 8.9
48h Cultured Lymphocytes, Chrom. 1, # with 1 hybridization	29.4 ± 7.0	32.3 ± 8.4	26.7 ± 6.2
48h Cultured Lymphocytes, Chrom. 1, # with 3 hybridizations	.24 ± .44	.07 ± .27	0
48h Cultured Lymphocytes, Chrom. 1, # with 4 hybridizations	.04 ± .20	.07 ± .27	.09 ± .30
48h Cultured Lymphocytes, Chrom. 1, # hypodiploids	43.4 ± 12.4	45.8 ± 9.9	40.9 ± 12.6
48h Cultured Lymphocytes, Chrom. 1, # hyperdiploids	.28 ± .54	.14 ± .36	.09 ± .30
72h Cultured Lymphocytes, Chrom. 7, # with 0 hybridizations	.76 ± .78	.82 ± .82	.36 ± .50
72h Cultured Lymphocytes, Chrom. 7, # with 1 hybridization	39.7 ± 9.4	39.0 ± 10.3	35.9 ± 4.9
72h Cultured Lymphocytes, Chrom. 7, # with 3 hybridizations	1.6 ± 1.3	1.2 ± 1.0	1.6 ± 1.4
72h Cultured Lymphocytes, Chrom. 7, # with 4 hybridizations	.30 ± .48	.18 ± .54	.82 ± 1.08
72h Cultured Lymphocytes, Chrom. 7, # hypodiploids	40.4 ± 9.7	39.8 ± 10.2	36.3 ± 5.2
72h Cultured Lymphocytes, Chrom. 7, # hyperdiploids	1.9 ± 1.5	1.4 ± 1.2	2.5 ± 1.9
Granulocytes, Chrom. 1 (Interphase Tandem), Total # breaks	9.1 ± 2.5	8.2 ± 2.7	8.8 ± 2.9
G0 Lymphocytes, Chrom. 1 (Interphase Tandem), Total # breaks	7.2 ± 1.9	6.8 ± 2.9	5.7 ± 2.9
48h Cultured Lymphocytes, Chrom. 1, Total # breaks	6.2 ± 2.8	5.0 ± 1.7	4.6± 3.1

[D] Values are per 1,000 cells.

Note: the hyperdiploidy values for chromosomes 1 and 7 were statistically significant when transformed and analyzed.

Table B.9 Fluorescence *in situ* hybridization studies on interphase cells: Summary results of positive and negative control slides.

Unstimulated Go lymphocyte studies: Tandem probes chromosome 1[a]

Treatment	N	Hypodiploidy 1	Hyperdiploidy 1	1q12 Breakage
0 Gy	7	42 (16.3)	0.9 (1.2)	5.3 (1.1)
2 Gy	7	59 (12.4)	1.3 (1.0)	13.4 (2.0)

Granulocyte studies: Tandem probes chromosome 1[a]

Treatment	N	Hypodiploidy 1	Hyperdiploidy 1	1q12 Breakage
0 Gy	5	48 (12.0)	0.2 (0.5)	6.2 (1.6)
2 Gy	7	56 (7.5)	1.3 (1.0)	12.4 (1.3)

48 hr cultured lymphocyte studies: Tandem probes chromosome 1[a]

Treatment	N	Hypodiploidy 1	Hyperdiploidy 1	1q12 Breakage
0 Control	7	39.6 (11.9)	0.6 (0.8)	3.1 (1.1)
2 Gy	6	39.0 (8.2)	3.0 (2.3)	13.2 (2.3)
10 µM DES	5	41.8 (13.8)	58.4 (3.3)	5.8 (3.3)

72 hr cultured lymphocyte studies: Chromosome 7 probe[a]

Treatment	N	Hypodiploidy 7	Hyperdiploidy 7
0 µM DES	6	36.8 (8.2)	1.5 (1.1)
10 µM DES	6	66.3 (7.0)	62.0 (9.7)

[a]Frequency per 1000 interphase cells

Table B.10 **Cytogenetic analyses of Giemsa-stained metaphase lymphocytes: Summary results of positive and negative control slides.**

Phase 1/year 1 analyses: 51 hr cultured metaphase lymphocyte studies[b]

Treatment	N	Hypodiploidy[c]	Hyperdiploidy[d]	SCA[e]
0 Control	6	3.4 (1.5)	0 (0)	1.7 (1.6)
2 Gy	6	5.8 (2.7)	1.5 (1.5)	11.7 (6.9)

Phase 2/year 2 analyses: 51 hr cultured metaphase lymphocyte studies[b]

Treatment	N	Hypodiploidy[c]	Hyperdiploidy[d]	SCA[e]
0 Control	13	3.0 (1.5)	0 (0)	1.6 (0.9)
2 Gy	13	6.1 (2.1)	1.2 (1.1)	11.5 (3.4)

[b]Frequency per 100 metaphase cells

[c]Hypodiploidy for all chromosomes

[d]Hyperdiploidy for all chromosomes

[e]Total structural chromosome aberrations excluding gaps

Table B.11.Aneuploidy of Chromosome 1 and Breakage Affecting the 1cen-1q12 Region Detected Using the Tandem FISH Assay in Cultured Lymphocytes from a Subset of the Benzene-Exposed Workers Participating in Phase 2 of the Study

Benzene (ppm)		Hypoploidy[a] Mean	Hypoploidy[a] SD	Hyperploidy[b] Mean	Hyperploidy[b] SD	Breaks Mean	Breaks SD
Unexposed	(n = 10)	28.6	16.0	0.3	0.5	3.3	1.5
Exposed ≤ 1	(n = 10)	34.0	10.2	0.7	0.5	5.4	2.1
Exposed ≤ 5	(n = 11)	25.0	13.8	1.2	1.5	5.9 [c]	2.4
Exposed > 5.1	(n = 9)	21.1	8.1	1.9 [d]	1.3	7.3 [d]	2.7

[a] All values are reported as aberrant cells per 1000 cells scored.
[b] Includes polyploid cells.
[c] Significantly different from unexposed group (P<0.05).
[d] Significantly different from unexposed group (P<0.01).

Table B.12 Benzene Regression Coefficients in the Low-Toluene and High-Toluene Groups (Benzene-Exposed Group only)

Variable	Toluene Interaction (Low/ High with greater effect); Interaction p-value [A]	Low Toluene Group, Benzene Regression Coeff. ± S.E. [A,B]	High Toluene Grp, Benzene Regress. Coeff. ± S.E. [A,B]
Phenol (mg/g cr.), post - pre	(Low); 0.03	2.60 ± .42	.677 ± .405
Red blood cells ($x10^{10}$/L)	(Low); 0.03	.256 ± .356	-1.67 ± .85
Monocytes, log($x10^{6}$/L)	(High); 0.008	-.010 ± .004	.014 ± .007
Chromatid gaps (√)	(Low); 0.01	.013 ± .004	-.007 ± .006
Benzene oxide adducts, log(nmol/g)	(High); 0.01	.011 ± .001	.020 ± .003