

An Updated Study of North American Synthetic Rubber Workers - Mortality from Lymphohematopoietic Cancer

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by
Nalini Sathiakumar, MD, DrPH
University of Alabama at Birmingham
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Investigators

Nalini Sathiakumar, MD, DrPH

Elizabeth Delzell, SD

Project Staff

Mark Leader, BFA

Ilene Brill, MPH

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Background

- Research on potential health effects of work in synthetic rubber industry workers has focused on exposure to:
 - 1,3-butadiene (BD) monomer
 - Styrene (STY) monomer

Butadiene (BD) - Carcinogenicity

- IARC 2008 (Vol 97): Group 1, carcinogenic to humans
 - “This conclusion is primarily based on the evidence for a significant exposure–response relationship between exposure to butadiene and mortality from leukaemia ... It is also supported by elevated relative risks for non-Hodgkin lymphoma ... particularly in the butadiene monomer production industry. The Working Group was unable to determine the strength of the evidence for particular histological subtypes of lymphatic and haematopoietic neoplasms ... However, the Working Group considered that there was compelling evidence that exposure to butadiene is associated with an increased risk for leukaemias.”
- IARC 2012 (Vol 100F)
 - Sufficient evidence for hematolymphatic organs (*not limited to leukemias*)
 - Carcinogenicity entails a genotoxic mechanism of action mediated by reactive epoxide metabolites
- NTP, known human carcinogen

Butadiene

- EPA air toxic
- Sources of environmental exposure
 - Incomplete combustion of gasoline & diesel fuels
 - Industrial emissions
 - Biomass burning
 - Environmental tobacco smoke

Styrene (STY)

- Carcinogenicity
 - IARC 2002: Group 2B, possibly carcinogenic to humans
 - IARC 2014: Recommended as high priority for re-evaluation by IARC in 2015-2019, after update of European cohort study
 - NTP, reasonably anticipated to be a human carcinogen
- Sources of environmental exposure
 - Industrial emissions
 - Motor-vehicular emissions
 - Offgassing of building materials and consumer products
 - Industrial accidents resulting in styrene spills
 - Environmental tobacco smoke
 - Food products

Experimental Research

BD, mediated by its metabolites, induces (IARC 100F, 2012):

- Tumors in lymphohematopoietic tissue (malignant lymphoma/leukemia), heart (hemangiosarcoma), lung and forestomach in male and female mice
- Mammary tumors in both female mice and female rats and ovarian tumors in female mice

Experimental Research

STY or its metabolites induce (IARC, 2002):

- Benign and malignant tumors in the lungs in male and female mice

BD Polymer Workers

- **Workers with relatively high exposure to BD & relatively low exposure to STY**
 - Studied by McMichael et al., Meinhardt et al., Matanoski et al., Delzell et al., Sathiakumar et al. & others
 - Positive relation between BD exposure & leukemia (Delzell et al.; Sathiakumar et al.; Cheng et al.)
 - Styrene also associated positively with leukemia, but research in other industrial groups suggests that relation is not causal
 - STY & BD exposure strongly correlated

BD Polymer Workers Leukemia

Group	Observed	SMR	95% CI
Polymer workers Total hourly*	63	123	94-157
Polymer workers Highest BD exposure (425+ ppm-years)*	14	246	134-412
Employment for >2 years in SBR production, Lymphatic leukemia [†]	14	3.9	2.6-8.0

*Delzell et al., 2006;Sathiakumar et al., 2005.

†McMichael et al., 1976

BD Polymer Workers – NHL and MM

- NHL associated with STY but RRs did not display a consistent response relation with BD or STY (Delzell et al., 2006)
- Other studies of occupational groups are exposed to STY in higher concentrations than synthetic rubber industry did not report consistent increase in NHL deaths or incident cases (Nicholson et al., 1978; Hodgson and Jones, 1985; Bond et al., 1982; Kogevinas et al., 1993, 1994; Coggon et al., 1994; Kolstead et al., 1994, 1995; Matanoski et al., 1997)
- No evidence to support causal relation between BD exposure and MM (Delzell et al., 2006)

BD Monomer Workers Leukemia

Group	Observed	SMR	95% CI
Monomer workers, total*	18	129	77-204
Monomer workers, hired <1950*	18	152	90-240
Monomer workers, hired <1950, highest potential BD exposure*	13	197	105-337
BD production workers†	2	112	20-442
Monomer workers ≥ 5 years worked LHC‡	3	110	30-150

*Divine et al., 2001.
†Ward et al., 1996.
‡Tsai et al., 2001. LHC, lymphohematopoietic cancer.

BD Monomer Workers – NHL and MM

- NHL
 - Ward et al., (1995, 1996) reported four cases → six-fold increase
 - Divine and Hartman(2001) reported 50% excess, no exposure-response and concentrated among workers during WWII
 - Tsai et al., (2001) Third study reported 1 cases (0.2 expected)
- MM
 - Divine and Hartman (2001) found more than expected MM deaths (7 obs/5.4 exp) but data were sparse and internally inconsistent

BD and STY Exposure and LHC Epidemiologic Studies Since 2005

Reference (location)	Population	Exposures	Outcomes	Results
Budroni et al., 2010 (Sardinia, Italy)	Male Petrochemical workers (n=5350)	BD and STY	All cancers	No excess cancer risk for BD or STY
Collins et al. 2013 (US)	Workers (n=15,826) in US reinforced plastics and composite history	STY	LHC, lung and pancreatic cancer	No association between STY exposure and LHC
Ruder et al. 2014 (US)	Workers (n=5203) in reinforced plastics - boat Building industry	STY and fiberglass	All cancers	No excess leukemia or lymphoma

Research Objectives

- To evaluate mortality patterns among men employed in the North American synthetic rubber industry, extending earlier studies
 - Men, 1944-1998 through 2009
 - Women, 1943-2002 through 2009
 - To determine if there is any increase in leukemia mortality in workers hired ≥ 1960
- To determine if cancers of strongest *a priori* interest are associated with employment factors and quantitative estimates of exposure to:
 - BD (monomer)
 - Styrene (monomer)

Methods

- Retrospective follow-up study
- Subjects
 - Worked at least 1 year (men) or 1 day (women) at any of 7 US plants or 1 Canadian plant during 1943-1991
- Data development:
 - Historical employment records - specific job assignments
 - BD and STY exposure estimates
 - Vital status data
 - Death certificates of subjects dying of LHC (1999-2009)

Exposure Estimation

- Limited to 6 of 8 study plants
- Approach
 - In-depth plant- & time period-specific analyses of sources of exposure associated with tasks comprising each job in the industry
 - Models to estimate the intensity of exposure resulting from each source
 - Job-exposure matrix (JEM) for each plant, with job- & year-specific TWA concentrations
 - JEM linked to each employee's work history to estimate BD and STY exposure (several exposure indices)
- Validation (Sathiakumar et al., 2007)
 - Used industrial hygiene data from largest plant
 - Found that BD estimates for typical SBR jobs appeared to be useful for ranking subjects by cumulative exposure (correlation between estimates and mean value of measurements of primary typical SBR jobs, $r=0.81$, $p<0.0001$)

Vital Status

- Update time period: men, 1999-2009; women, 2003-2009
- Data sources:
 - US subjects
 - Social Security Administration (decedents and IRS records)
 - Pensions Benefits Insurance (deaths)
 - National Death Index (deaths \geq 1979)
 - Canadian subjects
 - Canadian Mortality Data Base
 - Annual tax files

External Analysis

- Compares mortality rates of employees with general state or provincial population rates
 - Standardized mortality ratio (**SMR**) & 95% confidence interval (CI)
 - Adjusted for age, time period, race, state/province
 - Not yet completed

Internal Analysis

- Compares mortality rates of employees in a particular BD or STY exposure category with rates of employees with no or low exposure
- Results currently available for
 - Leukemia
 - Non-Hodgkin Lymphoma (NHL)
 - Multiple Myeloma (MM)

Internal Analysis

- BD exposure variables
 - Cumulative BD and STY ppm-years
 - Exposure deciles, categorical
 - Exposure deciles, continuous ("scored" with decile-specific mean to obtain a continuous variable)
 - BD continuous, untransformed
 - BD continuous, natural log-transformed
 - BD continuous, square root-transformed
 - BD continuous, \log_{10} -transformed

Internal Analysis

- Cox regression beta coefficient (β) & standard error (se)
 - Age was "time" variable
 - Model 1: BD or STY & age
 - Model 2: BD or STY, age, race, plant, years since hire (<20, 20-29, 30-39, 40+), year of birth (quintiles)

Results

Male Workers

Subject Characteristics, 8 Plants, Follow-up 1944-2009

Total subjects	17,924
Total person-years	661,260
Deceased as of 12/31/2009	50%
Lost to follow-up	1%
Ever-hourly	84%
Median hire year	1958
Median years worked*	11
Median years since hire*	39
Median age*	68

*At end of follow-up.

Data Added by Most Recent Update, 8 Plants

	1944-1998	1999-2009	% increase	1944-2009
Total person-years	540,537	111,842	21%	661,260
Total deaths	6,240 [£]	2,720	44%	8960
Leukemia*	86 [†]	37	43%	123
NHL*	65	32	49%	97
MM*	30 [†]	21	70%	51
Hodgkin lymphoma*	13	1	8%	14

*Includes both underlying and contributing cause of death.

£ Includes 3 additional deaths in the current update

† Includes one CML and one MM death identified in the current update.

Number of LHC Cases by Time Period, 6 Plants

Group	1944-1998	1999-2009	1944-2009
	N	N	N
All LHC	171	83	254
Leukemia	82*	32	114
CLL	25	11	36
AML	26	10	36
CML	17*	1	18
Other leukemia	14	10	24
NHL	58	31	89
MM	28†	20	48
Hodgkin lymphoma	13	1	14

* Includes 1 decedent with CML previously with an unknown cause of death.

† Includes 1 decedent with multiple myeloma previously with an unknown cause of death.

Subject Characteristics, 6 Plants Leukemia Decedents and Other Subjects

Characteristic	Leukemia	Others
Total subjects, N (%)	114 (100)	16,297 (100)
Race white or unknown, N (%)	97 (85)	14,253 (87)
Race nonwhite, N (%)	17 (15)	2,044 (13)
Year of birth, mean	1923	1931
Age at end of study, mean	66	68
Years since hire, mean	34	37
BD ppm-years, exposed, N (%)	99 (87)	12,587 (77)
mean* (sd)	379.5 (888.2)	196.8 (535.3)
median*	124	54
STY ppm-years, exposed, N (%)	104 (91)	13,756 (84)
mean* (sd)	64.3 (161.7)	40.1 (101.0)
median*	28	13

*Means & medians computed for exposed subjects.

Categorical (Decile) BD ppm-years & Leukemia

Decile range of values	Mean	N	RR [†]	RR [‡]
0	0	15	1.0	1.0
>0<12.47	8.45	10	0.98	0.97
12.47-<25.84	19.73	10	1.70	1.72
25.84-<45.51	37.56	10	1.79	1.83
45.51-<70.05	56.23	10	1.91	1.96
70.05-<124.38	90.50	10	1.43	1.46
124.38-<213.43	185.16	10	1.54	1.57
213.48-<289.91	258.20	10	3.23*	3.18*
289.91-<448.17	378.94	10	2.63*	2.62*
448.17-<908.35	675.63	10	2.68*	2.78*
908.35+	2273.85	9	3.63*	3.75*
Ln likelihood test, df, p-value			19.94, 10, 0.03	31.08, 23, 0.12

*p<0.05

†Model 1: controls only for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous BD ppm-years & Leukemia

Continuous BD exposure variable	β (S.E) [†]	β (S.E) [‡]
Untransformed	2.6×10^{-4} (0.9)*	2.9×10^{-4} (1.0)*
Decile scored with mean	4.7×10^{-4} (1.6)*	4.7×10^{-4} (1.6)*
Square root-transformed	2.6×10^{-2} (0.6)*	3.0×10^{-2} (0.7)*
Log base 10-transformed	2.0×10^{-1} (0.6)*	2.0×10^{-1} (0.6)*

*p < 0.05.

† Model 1: Adjusted for age.

‡ Model 2: Adjusted for age, race, years since hire, year of birth and plant.

Categorical (Decile) STY ppm-years & Leukemia

Decile range of values	Mean	N	RR [†]	RR [‡]
0	0	10	1.0	1.0
>0 -< 2.77	2.10	10	1.06	1.04
2.77 -< 5.02	3.91	10	1.95	1.93
5.02 -< 9.34	7.50	10	1.63	1.64
9.34 -< 16.00	12.54	10	1.69	1.67
16.00 -< 27.01	21.54	10	1.59	1.52
27.01 -< 36.15	31.75	10	2.33	2.20
36.15 -< 48.26	41.84	11	3.16*	3.08*
48.26 -< 67.30	58.08	11	2.88*	2.83*
67.30 -< 112.45	85.40	11	2.92*	2.89*
112.45 +	350.74	11	2.53*	2.55*
Ln likelihood test, df, p-value			16.81, 10, 0.08	27.42, 23, 0.24

*p<0.05

†Model 1: controls only for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous STY ppm-years & Leukemia

Continuous STY exposure variable	β (SE) [†]	β (SE) [‡]
Untransformed	1.2×10^{-3} (0.6)*	1.2×10^{-3} (0.6)
Decile scored with mean	1.7×10^{-3} (0.9)	1.6×10^{-3} (0.9)
Square root-transformed	5.0×10^{-2} (1.5)*	5.6×10^{-2} (1.8)*
Log base 10-transformed	1.1×10^{-1} (0.3)*	1.0×10^{-1} (0.3)*

*p < 0.05.

[†] Model 1: Adjusted for age.

[‡] Model 2: Adjusted for age, race, years since hire, year of birth and plant.

Subject Characteristics, 6 Plants Leukemia Decedents & Other Subjects, Men Hired ≥1960

Characteristic	Leukemia	Others
Total subjects, N (%)	21 (100)	7,691 (100)
Race white or unknown, N (%)	17 (81)	6,603 (86)
Race nonwhite, N (%)	4 (19)	1,088 (14)
Year of birth, mean	1940	1945
Age at end of study, mean	56	62
Years since hire, mean	25	34
BD ppm-years, exposed, N (%)	17 (81)	5,678 (74)
mean* (sd)	162.2 (463.8)	105.3 (322.9)
median*	32	23
STY ppm-years, exposed, N (%)	19 (90)	6,335 (82)
mean* (sd)	16.3 (16.1)	23.2 (59.3)
median*	9	7.8

*Means & medians computed for exposed subjects.

Subject Characteristics, 6 Plants Leukemia Decedents & Other Subjects, Men Hired <1960

Characteristic	Leukemia	Others
Total subjects, N (%)	93 (100)	8,606 (100)
Race white or unknown, N (%)	80 (86)	7,650 (89)
Race nonwhite, N (%)	13 (14)	956 (11)
Year of birth, mean	1919	1918
Age at end of study, mean	69	73
Years since hire, mean	36	40
BD ppm-years, exposed, N (%)	82 (88)	6,909 (80)
mean* (sd)	424.5 (948.7)	272.0 (651.0)
median*	195	97
STY ppm-years, exposed, N (%)	85 (91)	7,421 (86)
mean* (sd)	75.1 (177.1)	54.5 (124.2)
median*	36	22

*Means & medians computed for exposed subjects.

Continuous BD ppm-years & Leukemia by Period of Hire (<1960, ≥1960)

Continuous BD exposure variable	Hired <1960 β (SE) [†]	Hired ≥1960 β (SE) [†]
Untransformed	2.7 x 10 ⁻⁴ (1.1)*	3.5 x 10 ⁻⁴ (4.5)
Decile scored with mean	4.1 x 10 ⁻⁴ (1.7)*	5.3 x 10 ⁻⁴ (5.5)
Square root-transformed	0.8 x 10 ⁻² (0.8)*	2.4 x 10 ⁻² (2.5)
Log base 10-transformed	0.9 x 10 ⁻¹ (0.7)*	1.4 x 10 ⁻¹ (1.2)

*p < 0.05.

† Adjusted for age, race, years since hire, year of birth and plant.

Leukemia Cases by BD and STY ppm-years, 6 Plants, 1944-2009

BD ppm-years (quartiles)	STY ppm-years (< and ≥ Median)		
	0	>0-<28.18	28.18 +
0	10	4	1
>0-<37.21	0	22	3
37.21-<124.38	0	19	6
124.38 -<374.31	0	6	19
374.31 +	0	1	23

Correlation Coefficients Leukemia and Others

		Leukemia cases	Others
BD ppm-years, STY ppm-years	r^*	0.90	0.86
	p-value	(< 0.0001)	(<0.0001)
BD categorical deciles, STY categorical deciles	r^*	0.82	0.77
	p-value	(<0.0001)	(<0.0001)

* r , Pearson's coefficient.

Subject Characteristics, 6 Plants NHL Decedents and Other Subjects

Characteristic	NHL	Others
Total subjects, N	89 (100)	16,118 (100)
Race white or unknown, N (%)	81 (91)	14,104 (88)
Race nonwhite, N (%)	8 (9)	2,014 (12)
Year of birth, mean	1923	1930
Age at end of study, mean	69	68
Years since hire, mean	37	37
BD ppm-years, exposed, N (%)	72 (81)	12,465 (77)
mean* (sd)	236.5 (304.6)	198.9 (542.6)
median*	121	54
STY ppm-years, exposed, N (%)	79 (89)	13,604 (84)
mean* (sd)	43.0 (50.0)	40.4 (102.2)
median*	25	13

*Means & medians computed for exposed subjects.

Categorical (Decile) BD ppm-years & NHL

Decile range of values	Mean	N	RR [†]	RR [‡]
0	0	17	1.0	1.0
>0 -< 4.06	2.0003	7	1.31	1.31
4.06 -< 11.23	9.3461	7	1.37	1.29
11.23 -< 24.88	19.0927	7	1.02	1.02
24.88 -< 56.13	42.5134	7	0.74	0.74
56.13 -< 114.98	74.4256	7	0.67	0.67
114.98 -< 167.41	143.4498	7	1.30	1.33
167.41 -< 301.48	239.7469	7	0.92	0.92
301.48 -< 355.58	326.7597	7	3.45*	3.51*
355.58 -< 490.66	421.1073	8	2.85*	2.91*
490.66 +	957.4436	8	1.14	1.28
ln likelihood test, df, p-value			16.28, 10, 0.09	30.29, 23, 0.14

*p<0.05

†Model 1: controls for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous BD ppm-years & NHL

Continuous BD exposure variable	β (S.E) [†]	β (S.E) [‡]
Untransformed	2.5×10^{-5} (18.6)	9.5×10^{-5} (19.5)
Decile scored with mean	4.0×10^{-4} (3.5)	5.2×10^{-4} (3.6)
Square root-transformed	9.6×10^{-3} (9.0)	1.4×10^{-2} (1.0)
Log base 10-transformed	4.9×10^{-2} (5.4)	5.5×10^{-2} (5.6)

[†] Model 1: Adjusted for age.

[‡] Model 2: Adjusted for age, race, years since hire, year of birth and plant.

Categorical (Decile) STY ppm-years & NHL

Decile range of values	Mean	N	RR [†]	RR [‡]
0		10	1.0	1.0
>0 -< 1.80	0.71	8	1.29	1.23
1.80 -< 4.62	2.93	8	1.12	1.07
4.62 -< 8.58	6.84	8	1.42	1.41
8.58 -< 15.75	11.67	8	1.24	1.22
15.75 -< 24.66	20.99	8	1.53	1.45
24.66 -< 33.80	30.26	8	1.75	1.59
33.80 -< 50.17	42.50	8	1.58	1.53
50.17 -< 82.35	66.60	8	1.50	1.54
82.35 -< 112.78	101.04	8	3.73*	3.92*
112.78 +	161.44	7	1.51	1.80
ln likelihood test, df, p-value			8.14, 10, 0.61	22.38, 23, 0.50

*p<0.05

†Model 1: controls only for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous STY ppm-years & NHL

Continuous STY exposure variable	β (S.E) [†]	β (S.E) [‡]
Untransformed	-1.1×10^{-4} (10.7)	3.4×10^{-4} (11.4)
Decile scored with mean	3.2×10^{-3} (2.1)	4.5×10^{-3} (2.2)*
Square root-transformed	2.2×10^{-2} (2.0)	3.7×10^{-2} (2.4)
Log base 10-transformed	4.9×10^{-2} (3.2)	5.3×10^{-2} (3.3)

[†] Model 1: Adjusted for age.

[‡] Model 2: Adjusted for age, race, years since hire, year of birth and plant.

NHL Cases by BD and STY ppm-years, 6 plants, 1944-2009

		STY ppm-years ($<$ and \geq Median)	
		>0 - <24.59	24.59 +
BD ppm-years (quartiles)	0		
0	10	6	1
>0 - <20.03	0	15	3
20.03- <117.22	0	12	6
117.22 - <334.83	0	4	14
334.83 +	0	2	16

Subject Characteristics, 6 Plants MM Decedents and Other Subjects

Characteristic	MM	Others
Total subjects, N	48 (100)	15,387 (100)
Race white or unknown, N (%)	37 (77)	13,475 (88)
Race nonwhite, N (%)	11 (23)	1,912 (12)
Year of birth, mean	1921	1930
Age at end of study, mean	71	69
Years since hire, mean	37	38
BD ppm-years, exposed, N (%)	34 (71)	11,951 (78)
mean* (sd)	359.6 (559.9)	203.1 (547.3)
median*	124	57
STY ppm-years, exposed, N (%)	37 (77)	13,004 (85)
mean* (sd)	89.9 (187.7)	41.3 (102.8)
median*	20	14

*Means & medians computed for exposed subjects.

Categorical (Decile) BD ppm-years & MM

Decile range of values	Mean	N	RR [†]	RR [‡]
0		14	1.0	1.0
>0 -< 2.92	1.6121	3	0.86	0.89
2.92 -< 26.09	16.3209	3	0.28*	0.29
26.09 -< 44.65	37.3573	3	0.62	0.63
44.65 -< 67.89	59.4393	3	0.64	0.65
67.89 -< 107.78	95.0743	3	0.53	0.53
107.78 -< 124.94	120.5377	3	1.75	1.76
124.94 -< 364.52	244.4692	4	0.34	0.32*
364.52 -< 435.19	399.8754	4	2.85	2.56
435.19 -< 660.98	592.6011	4	1.55	1.36
660.98 +	1571.9474	4	0.99	0.65
ln likelihood test, df, p-value			17.40, 10, 0.07	27.96, 23, 0.22

†Model 1: controls only for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous BD ppm-years & MM

Continuous BD exposure variable	β (S.E) [†]	β (S.E) [‡]
Untransformed	1.3×10^{-4} (1.8)	-3.9×10^{-5} (21.2)
Decile scored with mean	3.3×10^{-4} (3.2)	5.6×10^{-5} (34.3)
Square root-transformed	1.2×10^{-2} (1.1)	1.1×10^{-3} (12.2)
Log base 10-transformed	-4.8×10^{-2} (6.6)	-7.2×10^{-2} (6.7)

[†] Model 1: Adjusted for age.

[‡] Model 2: Adjusted for age, race, years since hire, year of birth and plant.

Categorical (Decile) STY ppm-years & MM

Decile range of values	Mean	N	RR [†]	RR [‡]
0		11	1.0	1.0
>0 -< 1.18	0.5810	3	0.70	0.75
1.18 -< 1.69	1.5524	3	1.50	1.67
1.69 -< 2.88	2.5477	3	0.81	0.90
2.88 -< 6.51	5.2112	4	0.51	0.54
6.51 -< 14.68	12.7732	4	0.45	0.43
14.68 -< 30.14	22.3517	4	0.41	0.41
30.14 -< 41.08	38.5433	4	0.82	0.79
41.08 -< 98.05	69.2871	4	0.41	0.36
98.05 -< 212.87	154.0653	4	0.93	0.69
212.87 +	525.7459	4	2.01	1.03
ln likelihood test, df, p-value			10.39, 10, 0.41	20.21, 23, 0.63

†Model 1: controls only for age.

‡Model 2: controls for age, race, plant, year of birth & years since hire.

Continuous STY ppm-years & MM

Continuous STY exposure variable	β (S.E)*	β (S.E)†
Untransformed	1.2×10^{-3} (0.7)	3.3×10^{-4} (8.9)
Decile scored with mean	2.0×10^{-3} (1.1)	8.1×10^{-4} (12.3)
Square root-transformed	2.8×10^{-2} (2.6)	-2.1×10^{-3} (28.6)
Log base 10-transformed	-3.1×10^{-2} (3.6)	-5.0×10^{-2} (3.6)

* Adjusted for age.

† Adjusted for age, race, years since hire, year of birth and plant.

Summary

- Update increased the amount of information on men in the synthetic rubber industry:
 - 21% more person-years
 - 44% more total deaths
 - 43% more leukemias
 - 49% more NHL
 - 70% more MM

Summary – BD & Leukemia

- Positive exposure-response between BP ppm-years and leukemia among men
- Overall, results for men in the present update similar to those reported previously
- Lagging exposure had little impact on results
- **Positive exposure-response, regardless of functional form of BD ppm-years exposure variable**
- Among men hired in or after 1960, exposure-response was positive but was not statistically significant

Summary – STY & Leukemia

- STY exposure (ppm-years) also associated positively with leukemia, similar in magnitude as BD-leukemia association
- BD and STY exposure strongly correlated and thus, difficult to delineate independent effects
- Studies of glass fiber-reinforced plastic workers exposed to STY at higher levels than those in the SBR industry and not exposed to BD do not report consistent relation with leukemia

Summary - NHL

- Positive exposure-response between and BD and STY in categorical decile analysis
- Exposure-response with either BD or STY in continuous exposure analysis
 - Compared to leukemia, associations similar but not statistically significant
- Occupational groups exposed to higher STY concentrations than those found in the SBR industry have not reported any consistent associations for STY and NHL

Summary – MM and HD

MM

- No evidence of an association with BD or STY exposure in the SBR industry
- Our previous study found a slight excess based on small numbers and no exposure-response
 - One study of BD production workers reported an excess of MM, a result based on small numbers and internally inconsistent (Divine and Hartman, 2001)

HD

- Only 13 deaths, a number too small for detailed analysis

Strengths

- Long follow-up period
- Objective procedures to classify subjects according to exposure, cause of death and presence/type of LHC
- Evaluated several exposure variables

Limitations

- Exposure estimates not comprehensively validated
- Exposure misclassification inevitable
- Lack of information on lifestyle factors (e.g., cigarette smoking)
- High correlation between BD and STY

Plans for Further Analysis

- External analysis
 - Men, women, and combined
- Internal analysis
 - Cell types of leukemia, lymphoid and myeloid neoplasms
 - Other exposure measures
 - Alternate time variable (time since hire instead of age)
 - Analysis by period of hire (1960+)

Papers

- Overall results of external analysis
- Leukemia
- Women
- Cells type of leukemia?
- Non-Hodgkin lymphoma?
- Multiple myeloma?
- Other causes of death (e.g., lung cancer)?

Thank you