Supplementary Online Content

Su F-C, Goutman SA, Chernyak S, et al. Association of environmental toxins with amyotrophic lateral sclerosis. *JAMA Neurol*. Published online May 9, 2016. doi:10.1001/jamaneurol.2016.0594.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Data Types and Statistical Analyses

Data Types

Occupational exposure history. Job history information was obtained using 24 questions for each of up to four previous jobs, including the two most recent and the two jobs held for the longest periods of time. Prior military experience was queried as well as job title, industry type, and employment dates. Job titles were coded using Dictionary of Occupational Titles (DOT),[1] and the workplace was described using the North American Industry Classification System (NAICS).[2] The number of occupational and industry categories was reduced using the occupation and industry coding system in the National Health and Nutrition Examination Survey (NHANES) 2007-2008[3], resulting in 20 occupation and industry categories (eTable 2). For each job, participants were asked to identify potential occupational exposures and specific hazards (lists of metals, solvents, particles, radiation, and other potential workplace hazards were provided). Inquiries included the presence, type, and use of personal protective equipment and hygiene habits (e.g., washing hands).

Persistent environmental pollutant exposure biomarkers. In brief, after collection, 1 mL blood samples were spiked with surrogate standard $^{13}C_{12}$-CB-208 (10 pg μL^{-1}), $^{13}C_{12}$-BDE-139 (10 pg μL^{-1}), and hydrochloric acid (1mL, 6M), extracted with sequential 6 mL methanol-isopropanol (1:1), 6 mL of hexane/methyl t-butyl ether (1:1), and 3 mL of hexane/MTBE, followed by cleanup involving elution of the 4 mL extract through a column containing 0.1 g of silica (top) and 1 g of silica/sulfuric acid. Extracts were eluted with hexane/DCM (8 mL, 1:1 v/v) and concentrated to 0.5 mL under nitrogen flow, dissolved with 0.5 mL of n-nonane, evaporated to 250 µL, and transferred to a 300 µL insert in a 2 mL GC-vial. Samples were spiked with 15 µL of an internal standard containing organochlorine pesticides (11 labeled $^{13}C_{12}$ OCPs), polybrominated diphenyl ethers (7.5 pg μL^{-1} of 10 different $^{13}C_{12}$ labeled PBDEs), polychlorinated biphenyls (7.5 pg μL^{-1} of 21 different $^{13}C_{12}$ PCBs), then sealed and placed into a gas chromatography/mass spectrometry (GC/MS) autosampler. Surrogate and internal standards were purchased from Cambridge Isotope Labs (Andover, MA, USA).

Analytes were identified and quantified by GC/MS (5973, Agilent Industries, Palo Alto, CA, USA) using 2 µL splitless injections, a capillary DB-5MS column (30 m length, 0.25 mm ID, 0.25 µm film thickness, J&W Scientific, Folsom, CA, USA), negative chemical ionization, and the two most abundant ions. Calibrations used authentic standards that spanned the full concentration range of the target analytes. Quality controls measures included the use of ^{13}C-labeled internal and surrogate standards, drift checks, recovery checks, and performance checks using SRM 1957 "organic contaminants in non-fortified human serum" (NIST, Gaithersburg, MD, USA). Based on 7 blank measurements, method detection limits (MDLs) for pesticides, PCBs, and BFRs ranged from 5.0 - 90, 0.002 - 0.1, and 0.06 - 0.15 ng L^{-1}, respectively (eTable 1). Measurements below MDLs were replaced by ½ MDL. Of the 32 target compounds, 4 had detection frequencies <30% and were excluded from further analyses.

Due to a protocol change, some subjects had whole blood samples and others had plasma samples. To combine the concentrations measured in these two samples, partition coefficients between plasma and whole blood for all measured compounds (eTable 1) were determined in a small study using blood and plasma samples obtained from 21 volunteers (data not shown), and used to covert whole blood concentrations to plasma concentrations. Most partition coefficients ranged from 1.59 to 2.24 (i.e., 1 ng L^{-1} in whole blood = 1.59 - 2.24 ng L^{-1} in plasma, depending on the compound), with very high R^2 (most exceeding 0.9). For further details, see: Batterman S; Chernyak S; Su F-C.[4]

Statistical Analyses

Missing data imputation. Missing values for variables with missing rate <30% were multiply imputed using the Markov chain Monte Carlo method.[4] The imputed values were rounded to 0 or 1 for binary categorical variables. Comparisons between observed and imputed datasets were performed using direct difference for survey data (percentage for imputed variable - percentage for observed variable), and relative change for biomarker data [((mean or median concentration for imputed variable - mean or median concentration for observed variable)/(mean or median concentration for observed variable))*100%]. The observed and imputed datasets for all subjects showed very small differences (mostly < 1%) and relative changes (mostly < 10%) for survey and biomarker variables (eTables 4, 5). Several higher relative changes for median chemical concentrations were due to small values of observed concentrations.

To further evaluate the performance of multiple imputation, we compared the results between observed and imputed datasets using a subset of subjects with complete survey and biomarker information (n = 181). Among these 181 subjects, we removed survey and biomarker data for 20 randomly selected subjects (missing rate = 11%). Then, we multiply imputed the datasets 10 times using 161 subjects with complete data and 20 subjects with missing data, and compared the results between observed (181 subjects with complete data) and imputed data. Imputation process and comparison methods were described in the previous paragraph. Again, the imputed data were not much different from observed data (e.g., direct difference <3% for most of the variables; relative change < 10% for most of the chemicals) (eTables 6, 7). The high relative change for median PCB 170/190 was due to very low median concentration. In general, the small differences between observed and imputed datasets indicated that the multiple imputation method was reliable in this study.

To aid in the understanding of our statistical analyses, a flowchart is presented in eFigure 1.

eReferences

1. National Academy of Sciences Committee on Occupational and Classification Analysis. Dictionary of Occupational Titles (DOT): Part I - Current Population Survey, April 1971, Augmented With DOT Characteristics and Dictionary of Occupational Titles (DOT): Part II - Fourth Edition Dictionary of DOT Scores for 1970 Census Categories. In: Washington DUSDoC, Bureau of the Census, ed. Ann Arbor, MI: Inter-university Consortium for Political and Social Research; 1981.
2. U.S. Census Bureau. North American Industry Classification System. *Office of Management and Budget, U.S. Census Bureau.* 1997.
3. CDC and NCHS. National Health and Nutrition Examination Survey Questionnaire. *Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.* 2014.

4. Schafer JL. *Analysis of incomplete multivariate data.* CRC press; 1997.

eTable 1. Method of detection limits, detection frequencies, and distributions of measured compound concentrations (ng L^{-1}) in plasma using observed data.

Compound	MDL	DF (%)	PC_{pb}	Cases								Controls							
				n	Mean	SD	Min	50th	75th	95th	Max	n	Mean	SD	Min	50th	75th	95th	Max
Pesticides																			
Pentachlorobenzene	60	90.1	2.04	127	698.61	928.66	61.19	536.37	751.21	1471.62	9500	116	313.18	332.66	61.19	208.56	340.34	1139.49	1672
Hexachlorobenzene	30	59.7	1.74	127	118.29	249.02	15.07	26.35	130.13	461.56	2445	116	64.26	49.61	16.37	51.28	84.85	172.61	265.7
β-HCH	60	95.9	1.83	127	4333.01	7741.89	54.89	2122.63	5206.51	13141.13	69486	116	1626.07	1725.63	54.89	1288.36	2068.25	3406.53	15248
Dacthal	5	57.2	1.77	127	16.41	28.56	3.09	5.37	14.29	64.57	206.8	116	17.90	23.81	4.32	7.76	20.44	67.86	133.0
trans-Chlordane	5	70.0	2.24	127	29.47	41.20	3.10	25.74	37.15	51.67	406.0	116	26.51	32.38	2.96	12.30	38.23	87.86	190.6
cis-Chlordane	5	67.1	2.14	127	110.55	164.78	5.34	19.39	176.38	424.14	813.7	116	23.66	44.04	3.45	15.84	27.97	56.40	462.8
trans-Nonachlor	10	42.8	2.14	127	20.61	20.74	10.69	10.69	25.21	61.82	150.9	116	17.13	19.91	5.81	10.69	12.93	48.64	170.5
p,p'-DDE	90	68.3	1.79	127	2484.23	5446.29	80.68	511.43	1354.79	14565.80	28920	116	948.60	1536.06	80.68	469.20	1286.21	3416.51	10386
PCBs																			
PCB 110	0.1	55.3	1.63	127	3.54	2.21	0.24	3.15	5.13	7.80	8.61	119	2.01	2.33	0.08	0.47	2.99	6.84	8.63
PCB 151	0.004	79.7	1.75	127	12.90	8.45	0.18	12.42	17.30	26.44	41.99	119	8.79	7.31	0.10	6.41	14.32	21.48	31.36
PCB 135/144	0.006	95.1	1.70	127	31.86	49.22	0.26	20.04	33.82	109.61	467.62	119	24.52	26.46	0.15	13.92	26.53	81.30	130.23
PCB 118	0.06	90.2	1.76	127	100.67	113.43	2.64	76.78	116.69	176.04	779.40	119	171.59	267.92	1.50	94.27	153.42	609.29	1950.1
PCB 132/153	0.004	97.2	1.72	127	427.59	259.64	56.26	363.28	482.93	860.91	1530.7	119	344.19	238.08	0.10	269.68	453.72	788.90	1574.0
PCB 138/163	0.008	83.3	1.66	127	266.13	194.95	57.42	209.42	341.19	644.39	1216.0	119	205.78	204.41	0.20	122.11	284.62	561.09	1325.8
PCB 175	0.02	93.5	1.69	127	2.88	2.64	0.20	2.29	3.47	8.69	18.87	119	2.28	2.70	0.11	1.56	2.51	7.21	15.47
PCB 174	0.018	66.7	1.59	127	1.46	1.54	0.15	1.09	1.80	3.77	9.80	119	1.25	1.48	0.10	1.04	1.55	4.40	9.08
PCB 202	0.04	89.4	1.84	127	3.59	3.28	0.35	3.06	4.58	7.71	29.76	119	4.77	5.77	0.26	2.62	5.53	18.30	31.47
PCB 180	0.014	72.4	1.67	127	173.06	56.23	45.16	166.77	192.13	298.99	443.45	119	158.10	58.70	11.79	148.74	174.84	275.24	486.31
PCB 170/190	0.002	52.0	1.74	127	15.13	13.39	0.05	11.77	21.62	42.33	64.57	119	8.49	14.18	0.00	0.09	16.06	30.78	98.92
PCB 198	0.02	67.1	1.59	127	1.93	2.18	0.08	1.45	2.52	6.91	11.75	119	2.05	2.46	0.05	1.57	2.88	8.11	11.49
BFRs																			
TBBPA	0.06	54.6	1.75	126	3.66	2.26	1.50	2.97	4.32	8.05	16.29	116	5.16	5.58	1.50	3.15	6.12	14.93	37.13
PBDE 28	0.15	55.0	1.60	126	11.18	14.56	3.75	8.22	12.20	25.71	150.54	116	6.40	5.45	0.12	6.00	6.00	14.78	47.18
PBDE 47	0.15	83.5	1.68	126	265.34	135.98	3.75	233.89	339.63	519.27	904.28	116	249.17	131.90	6.31	207.06	334.30	520.74	694.78
PBDE 66	0.15	65.3	1.67	126	8.83	7.20	3.75	6.27	9.22	22.19	45.95	116	10.90	7.56	0.13	9.15	16.20	25.14	45.79
PBDE 100	0.15	92.2	1.66	126	24.02	12.40	3.75	24.21	33.31	42.76	63.32	116	21.43	10.74	3.75	18.37	29.36	39.85	51.93
PBDE 99	0.15	91.3	1.67	126	19.68	14.07	3.75	16.73	29.14	48.56	67.26	116	18.07	11.93	0.13	14.10	28.17	40.39	49.07
PBDE 85	0.1	64.9	1.66	126	8.65	7.07	2.50	5.88	10.73	26.25	35.69	116	9.31	10.24	0.08	5.21	10.16	29.44	71.60
PBDE 154	0.07	59.9	1.66	126	7.05	8.51	1.75	3.60	8.64	18.89	77.35	116	7.73	6.08	0.06	5.81	10.73	20.44	27.25

MDL, method of detection limits; DF, detection frequencies; PC_{pb}, partition coefficients between plasma and whole blood samples; SD, standard deviation; β-HCH, beta-hexachlorocyclohexane; PCB, polychlorinated biphenyl; BFR, brominated flame retardant; TBBPA, tetrabromobisphenol A; PBDE, polybromodiphenyl ether.

eTable 2. Industry and occupation groups in this study with the assigned probability and intensity of exposure to pesticides.

Industry						Occupation					
	Group	Probability[1]	Intensity[1]	P*I	Score[2]		Group	Probability[1]	Intensity[1]	P*I	Score[2]
1	Agriculture, forestry, fishing and hunting	4	4	16	3	1	Management occupations	0	0	0	0
2	Mining, quarrying, and oil and gas extraction	1	1	1	1	2	Business, financial operations occupations	0	0	0	0
3	Utilities	0	0	0	0	3	Engineers, architects and scientists	1	1	1	1
4	Construction	2	2	4	2	4	Occupations in medicine and health	0	0	0	0
5	Manufacturing: durable goods	2	2	4	2	5	Education, training, library occupations	0	0	0	0
6	Manufacturing: non-durable goods	2	2	4	2	6	Writers, artists, entertainers, and athletes	0	0	0	0
7	Wholesale trade	1	1	1	1	7	Legal occupations	0	0	0	0
8	Retail trade	1	1	1	1	8	Office, administrative support occupations	0	0	0	0
9	Transportation, warehousing	3	1	3	2	9	Sales & related occupations	0	0	0	0
10	Information services	0	0	0	0	10	Community, social services occupations	0	0	0	0
11	Finance, insurance	0	0	0	0	11	Protective Service and military occupations	0	0	0	0
12	Real estate, rental, leasing	2	1	2	1	12	Food preparation, serving occupations	3	1	3	2
13	Professional, scientific, technical services	1	1	1	1	13	Building & grounds cleaning, maintenance occupations	1	1	1	1
14	Management, administrative, waste services	0	0	0	0	14	Personal care, service occupations	1	1	1	1
15	Education service	0	0	0	0	15	Private household occupations	1	1	1	1
16	Health care, social assistance	0	0	0	0	16	Farming, fishing, forestry occupations	4	4	16	3
17	Arts, entertainment, recreation	0	0	0	0	17	Construction, extraction occupations	2	2	4	2
18	Accommodation, food services	2	1	2	1	18	Installation, maintenance, repair occupations	1	1	1	1
19	Other services	1	1	1	1	19	Production occupations	2	2	4	2
20	Public administration	0	0	0	0	20	Transportation, material moving occupations	3	1	3	2

1, probability and intensity were scaled from 0 (lowest) to 4 (highest).

2, if P*I = 0, then score =0; if P*I = 1-2, then score = 1; if P*I = 3-6, then score = 2; if P*I = 7-16, then score = 3.

eTable 3. The associations between plasma concentrations of single chemicals and ALS.

Compound	Imputed			Observed			Observed Subgroup		
	OR	95% CI		OR	95% CI		OR	95% CI	
Pesticides									
Pentachlorobenzene	3.78*#	1.96	7.31	9.73*#	3.96	23.91	6.27*#	2.31	17.02
Hexachlorobenzene	1.90#	1.16	3.12	2.22#	1.11	4.45	3.09#	1.30	7.36
β-HCH	4.71*#	1.98	11.19	8.62*#	3.16	23.47	6.50*#	2.24	18.83
Dacthal	0.97	0.75	1.26	0.98	0.72	1.34	1.21	0.84	1.73
trans-Chlordane	1.19	0.89	1.61	1.17	0.81	1.67	1.08	0.71	1.63
cis-Chlordane	3.98*#	2.01	7.86	3.78*#	1.94	7.36	3.14*#	1.62	6.09
trans-Nonachlor	1.25	0.95	1.65	1.23	0.91	1.67	0.99	0.62	1.59
p,p'-DDE	2.02#	1.15	3.54	1.81#	1.08	3.02	3.06#	1.38	6.79
PCBs									
PCB 110	2.06*#	1.52	2.81	2.01*#	1.44	2.80	2.66*#	1.69	4.20
PCB 151	1.70*#	1.26	2.30	1.76*#	1.28	2.41	2.59*#	1.63	4.12
PCB 135/144	1.24	0.88	1.74	1.29	0.90	1.85	1.44	0.92	2.27
PCB 118	0.69	0.48	1.01	0.51#	0.30	0.88	0.62	0.33	1.16
PCB 132/153	1.39#	1.06	1.83	1.32	0.98	1.77	1.49#	1.04	2.14
PCB 138/163	1.40#	1.05	1.88	1.35#	1.00	1.83	1.38	0.97	1.96
PCB 175	1.23	0.94	1.61	1.27	0.96	1.69	1.29	0.92	1.80
PCB 174	1.20	0.90	1.60	1.08	0.80	1.45	1.09	0.75	1.58
PCB 202	0.80	0.61	1.06	0.82	0.61	1.10	0.74	0.47	1.16
PCB 180	1.33#	1.01	1.75	1.27	0.96	1.67	1.30	0.93	1.86
PCB 170/190	1.71*#	1.24	2.36	1.58#	1.15	2.15	2.58*#	1.59	4.18
PCB 198	0.99	0.76	1.31	0.96	0.72	1.28	1.16	0.81	1.66
BFRs									
TBBPa	0.67#	0.48	0.95	0.61#	0.41	0.91	0.63	0.35	1.14
PBDE 28	2.76*#	1.59	4.78	3.68*#	1.89	7.18	3.03#	1.39	6.62
PBDE 47	1.16	0.87	1.55	1.27	0.95	1.69	1.22	0.83	1.78
PBDE 66	0.75#	1.59	4.78	3.68*#	1.89	7.18	3.03#	1.39	6.62
PBDE 100	1.29	0.98	1.71	1.44#	1.07	1.92	1.39	0.93	2.08
PBDE 99	1.21	0.92	1.61	1.34#	1.00	1.80	1.30	0.87	1.93
PBDE 85	0.97	0.73	1.29	0.99	0.75	1.30	1.06	0.76	1.49
PBDE 154	0.92	0.71	1.19	0.97	0.74	1.27	0.89	0.53	1.49

The logistic regression models were adjusted with age, gender and educational levels, and used standardized concentrations; for imputed data, n = 284 (156 cases and 128 controls) for 10 imputations; for observed data, n = 210 (100 cases and 110 controls); for observed subgroup, n = 143 (53 cases and 90 controls).
*p-value < 0.0018 because the Bonferroni correction (α/n = 0.05/28) was made to p-values; #, p-value < 0.05 without the Bonferroni correction.
β-HCH, beta-hexachlorocyclohexane; PCB, polychlorinated biphenyl; BFR, brominated flame retardant; TBBPA, tetrabromobisphenol A; PBDE, polybromodiphenyl ether; OR, hazard ratio; CI, confidence interval.

eTable 4. Distributions of survey variables for observed and imputed (10 imputations) datasets.

Variable	Observed		Imputed		Difference (%)
	Frequency	%	Frequency	%	
Educational level					
< Bachelor's degree	128	51.8	149	52.3	0.5
≥ Bachelor's degree	119	48.2	135	47.7	-0.5
Missing	37	13.0			
Smoker					
Never	113	45.4	126	44.2	-1.2
Former	107	43.0	117	41.1	-1.8
Current	29	11.6	42	14.6	3.0
Missing	35	12.3			
C9ORF72					
Negative	169	92.9	-	-	-
Positive	13	7.1	-	-	-
Missing	102	35.9			
Ever work in the US armed forces					
No	196	79.0	221	78.0	-1.1
Yes	52	21.0	63	22.0	1.1
Missing	36	12.7			
Occupational exposure to lead					
No	212	85.8	243	85.5	-0.4
Yes	35	14.2	41	14.5	0.4
Missing	37	13.0			
Occupational exposure to pesticides					
No	211	85.4	241	84.9	-0.5
Yes	36	14.6	43	15.1	0.5
Missing	37	13.0			
Industry: health care/social assistance					
No	192	77.1	219	77.1	0.0
Yes	57	22.9	65	22.9	0.0
Missing	35	12.3			
Industry: accommodation, food services					
No	228	91.5	260	91.5	0.0
Yes	21	8.5	24	8.5	0.0
Missing	35	12.3			
Industry: public administration					
No	221	88.8	251	88.5	-0.3
Yes	28	11.2	33	11.5	0.3
Missing	35	12.3			

eTable 5. Distributions of biological variables for observed and imputed datasets.

Compound	Observed						Imputed (n = 284 x 10 imputations)					Relative change (%)	
	n	Mean	SD	50th	75th	95th	Mean	SD	50th	75th	95th	Mean	Median
Pesticides													
Pentachlorobenzene	243	514.62	734.05	373.66	669.66	1307.03	538.37	723.40	391.12	686.38	1427.06	4.61	4.67
Hexachlorobenzene	243	92.50	184.90	41.45	93.15	266.92	94.89	182.31	45.06	103.72	335.72	2.59	8.70
β-HCH	243	3040.81	5870.06	1764.10	2844.68	8729.76	3222.96	5729.52	1776.90	3287.93	10786.97	5.99	0.73
Dacthal	243	17.12	26.36	5.81	16.55	64.57	17.27	26.28	6.79	20.47	64.13	0.91	16.93
trans-Chlordane	243	28.06	37.21	21.76	37.20	69.89	29.11	36.61	22.19	38.90	80.47	3.76	1.97
cis-Chlordane	243	69.07	130.19	16.22	44.50	371.79	75.54	128.06	18.90	63.52	368.51	9.37	16.47
trans-Nonachlor	243	18.94	20.38	10.69	19.39	53.26	19.41	20.12	10.69	22.50	53.31	2.44	0.00
p,p'-DDE	243	1751.17	4141.97	511.43	1300.72	8515.29	1930.46	4052.80	547.43	1588.40	8639.41	10.24	7.04
PCBs													
PCB 110	246	2.80	2.39	2.36	4.49	7.75	2.87	2.37	2.43	4.57	7.63	2.44	2.59
PCB 151	246	10.91	8.17	10.60	16.72	22.82	11.09	8.18	10.72	16.87	23.64	1.61	1.14
PCB 135/144	246	28.31	39.96	18.12	30.39	94.97	29.28	39.21	18.61	35.38	93.72	3.44	2.68
PCB 118	246	134.97	206.03	84.30	131.04	529.72	139.00	201.56	85.24	143.27	510.83	2.98	1.12
PCB 132/153	246	387.24	252.42	336.16	469.57	855.05	388.58	253.16	340.82	492.55	851.03	0.35	1.39
PCB 138/163	246	236.93	201.45	184.59	309.87	623.28	239.47	200.88	190.50	329.54	600.14	1.07	3.20
PCB 175	246	2.59	2.68	1.92	2.96	8.06	2.62	2.66	1.96	3.14	7.66	1.37	1.71
PCB 174	246	1.36	1.51	1.04	1.71	3.77	1.38	1.48	1.06	1.78	3.78	1.84	1.70
PCB 202	246	4.16	4.68	2.83	4.70	13.83	4.19	4.59	2.90	5.00	12.81	0.80	2.73
PCB 180	246	165.82	57.81	157.72	181.14	275.24	165.84	57.79	158.34	186.14	269.74	0.01	0.39
PCB 170/190	246	11.91	14.15	7.48	19.01	33.36	12.38	14.00	8.99	19.85	35.04	3.92	20.23
PCB 198	246	1.99	2.32	1.50	2.74	6.91	2.01	2.29	1.51	2.81	6.82	1.04	0.71
BFRs													
TBBPa	242	4.38	4.25	3.07	5.35	11.07	4.41	4.18	3.17	5.45	11.10	0.64	3.38
PBDE 28	242	8.89	11.40	6.00	9.20	21.55	9.23	11.22	6.00	10.18	23.72	3.82	0.00
PBDE 47	242	257.59	134.01	221.28	338.29	519.27	257.88	135.01	224.82	340.24	510.13	0.11	1.60
PBDE 66	242	9.83	7.43	6.27	12.68	24.34	9.81	7.35	6.45	13.52	23.96	-0.18	2.90
PBDE 100	242	22.78	11.68	21.39	31.67	41.61	22.88	11.82	21.68	31.76	42.18	0.44	1.35
PBDE 99	242	18.91	13.09	14.98	28.37	41.73	19.00	13.04	15.31	28.44	41.65	0.47	2.22
PBDE 85	242	8.97	8.72	5.56	10.62	28.25	9.04	8.57	5.93	11.68	26.08	0.76	6.67
PBDE 154	242	7.38	7.44	4.94	10.42	19.73	7.41	7.31	5.13	10.64	19.51	0.45	3.91

SD, standard deviation; β-HCH, beta-hexachlorocyclohexane; PCB, polychlorinated biphenyl; BFR, brominated flame retardant; TBBPA, tetrabromobisphenol A; PBDE, polybromodiphenyl ether.

eTable 6. Distributions of survey variables for observed and imputed (10 imputations) datasets only for subjects with complete data*.

Variable	Observed		Imputed		Difference (%)
	Frequency	%	Frequency	%	
Educational level					
< Bachelor's degree	90	49.7	90	49.9	0.2
≥ Bachelor's degree	91	50.3	91	50.1	-0.2
Smoker					
Never	77	42.5	70	38.6	-4.0
Former	82	45.3	81	44.9	-0.4
Current	22	12.2	30	16.6	4.4
Ever work in the US armed forces					
No	141	77.9	138	76.2	-1.7
Yes	40	22.1	43	23.8	1.7
Occupational exposure to lead					
No	153	85.8	153	84.3	-1.5
Yes	28	14.2	28	15.7	1.5
Occupational exposure to pesticides					
No	152	85.4	150	82.7	-2.7
Yes	29	14.6	31	17.3	2.7
Industry: health care/social assistance					
No	141	77.1	141	77.8	0.7
Yes	40	22.9	40	22.2	-0.7
Industry: accommodation, food services					
No	162	91.5	162	89.5	-2.0
Yes	19	8.5	19	10.5	2.0
Industry: public administration					
No	157	88.8	155	85.4	-3.3
Yes	24	11.2	26	14.6	3.3

*There were 181 subjects with complete information on survey and biomarker data. To evaluate the performance of multiple imputation, we removed data for 20 randomly selected subjects (missing rate = 11%), and multiply imputed dataset using 161 subjects with compete data and 20 subjects with missing data.

eTable 7. Distributions of biological variables for observed and imputed datasets only for subjects with complete data*.

Compound	Observed (n = 181)					Imputed (n = 181 x 10 imputations)					Relative change (%)	
	Mean	SD	50th	75th	95th	Mean	SD	50th	75th	95th	Mean	Median
Pesticides												
Pentachlorobenzene	499.85	790.24	355.51	628.58	1246.94	524.35	818.40	355.04	658.45	1412.35	4.90	-0.13
Hexachlorobenzene	86.70	198.55	38.16	84.00	216.82	91.81	207.41	39.92	90.67	320.34	5.90	4.61
β-HCH	2730.43	3740.83	1749.59	2867.49	8729.76	2793.71	3784.60	1768.28	3045.75	8593.86	2.32	1.07
Dacthal	14.52	20.80	4.42	15.04	55.05	13.81	19.65	5.58	16.31	50.65	-4.90	26.06
trans-Chlordane	26.43	28.34	21.26	37.55	68.81	26.47	29.19	19.90	37.70	75.09	0.14	-6.39
cis-Chlordane	68.40	128.71	17.34	43.77	380.21	68.64	123.72	17.34	48.87	366.70	0.35	0.03
trans-Nonachlor	19.23	20.65	10.69	19.56	53.26	19.58	21.30	10.69	20.43	55.33	1.84	0.00
p,p'-DDE	1760.32	4348.33	414.83	1200.52	8515.29	1651.10	3805.55	433.41	1284.46	7603.77	-6.20	4.48
PCBs												
PCB 110	2.57	2.39	2.15	4.20	7.58	2.53	3.00	1.77	4.00	7.62	-1.34	-17.69
PCB 151	10.31	8.59	8.91	16.01	23.37	9.86	9.92	7.85	14.93	25.69	-4.40	-11.84
PCB 135/144	27.70	30.75	17.25	34.70	99.26	25.54	29.31	16.72	36.31	86.83	-7.79	-3.08
PCB 118	166.97	258.83	93.99	146.84	630.62	144.90	229.40	83.70	153.46	575.86	-13.22	-10.95
PCB 132/153	389.28	264.29	320.65	469.57	860.91	353.53	293.42	297.02	476.99	858.17	-9.18	-7.37
PCB 138/163	252.15	223.42	194.65	345.79	642.27	233.54	237.35	178.52	343.92	631.55	-7.38	-8.29
PCB 175	2.52	2.67	1.84	2.96	6.84	2.44	2.83	1.72	3.13	7.75	-2.88	-6.30
PCB 174	1.49	1.82	1.06	1.82	4.87	1.35	1.67	1.01	1.83	4.50	-9.62	-4.94
PCB 202	4.41	5.27	2.71	4.79	17.61	4.17	5.27	2.57	5.09	15.90	-5.44	-5.24
PCB 180	168.43	59.78	156.34	187.51	294.23	149.61	79.91	151.17	185.88	278.28	-11.17	-3.31
PCB 170/190	11.39	15.25	4.19	19.34	33.29	11.49	15.86	4.01	19.06	39.07	0.89	-4.26
PCB 198	2.09	2.51	1.41	2.82	8.11	1.94	2.35	1.29	2.79	6.56	-7.35	-8.82
BFRs												
TBBPa	4.66	4.73	3.17	5.46	11.55	4.11	4.58	2.78	5.49	10.83	-11.69	-12.45
PBDE 28	9.08	13.36	6.00	9.19	21.21	7.56	7.11	6.00	9.39	21.10	-16.76	0.00
PBDE 47	266.77	139.58	224.96	351.63	519.27	233.85	156.38	215.47	338.19	491.52	-12.34	-4.22
PBDE 66	10.15	7.21	6.57	14.03	24.37	9.20	8.02	6.27	13.38	24.69	-9.41	-4.62
PBDE 100	22.94	11.70	21.88	31.24	40.73	20.36	13.77	19.87	29.60	41.54	-11.24	-9.18
PBDE 99	19.72	13.48	15.11	28.82	41.73	17.82	14.89	14.36	27.42	44.70	-9.66	-5.01
PBDE 85	9.37	9.66	5.34	10.94	29.30	7.93	8.47	4.55	10.11	24.45	-15.42	-14.78
PBDE 154	7.52	8.31	4.60	9.48	20.58	6.81	8.98	3.46	9.04	21.34	-9.42	-24.87

*There were 181 subjects with complete information on survey and biomarker data. To evaluate the performance of multiple imputation, we removed data for 20 randomly selected subjects (missing rate = 11%), and multiply imputed dataset using 161 subjects with compete data and 20 subjects with missing data.
SD, standard deviation; β-HCH, beta-hexachlorocyclohexane; PCB, polychlorinated biphenyl; BFR, brominated flame retardant; TBBPA, tetrabromobisphenol A; PBDE, polybromodiphenyl ether.

eTable 8. Results of unmatched and matched logistic regression models for occupational risk factors and ALS.

Variable		Unmatched (126 cases, 118 controls)				Matched* (120 cases, 114 controls)			
		OR	95% CI		p-value	OR	95% CI		p-value
Win 1: Exposure ever happened in the entire occupational history									
Age	Year	1.00	0.97	1.04	0.902				
Gender	Male	0.80	0.37	1.72	0.569				
Educational level	>= Bachelor's degree	0.28	0.15	0.51	<.0001				
Smoker	Current	0.72	0.25	2.07	0.636	0.76	0.26	2.21	0.617
	Former	0.85	0.46	1.57	0.987	0.88	0.46	1.67	0.693
Ever work in the US armed forces	Yes	2.20	0.95	5.10	0.066	1.95	0.82	4.65	0.134
Occupational exposure to lead	Yes	0.32	0.13	0.81	0.015	0.30	0.11	0.78	0.013
Occupational exposure to pesticides	Yes	5.46	2.00	14.88	0.001	5.39	1.95	14.90	0.001
Industry: health care/social assistance	Yes	0.38	0.18	0.81	0.012	0.37	0.17	0.81	0.013
Industry: accommodation, food services	Yes	0.19	0.06	0.60	0.005	0.15	0.04	0.52	0.003
Industry: public administration	Yes	0.33	0.12	0.88	0.027	0.34	0.12	0.92	0.035
Win 2: Exposure ever happened in the latest 10 years									
Age	Year	1.00	0.97	1.04	0.818				
Gender	Male	1.13	0.55	2.32	0.747				
Educational level	>= Bachelor's degree	0.31	0.17	0.56	0.000				
Smoker	Current	0.65	0.23	1.79	0.485	0.67	0.24	1.88	0.446
	Former	0.83	0.45	1.53	0.919	0.79	0.43	1.46	0.454
Ever work in the US armed forces	Yes	1.76	0.79	3.89	0.166	1.66	0.73	3.74	0.224
Occupational exposure to lead	Yes	1.31	0.41	4.14	0.651	1.40	0.41	4.74	0.590
Occupational exposure to pesticides	Yes	6.18	1.64	23.35	0.007	5.72	1.48	22.09	0.012
Industry: health care/social assistance	Yes	0.58	0.26	1.28	0.176	0.52	0.23	1.21	0.129
Industry: accommodation, food services	Yes	0.30	0.06	1.45	0.134	0.19	0.03	1.16	0.072
Industry: public administration	Yes	1.74	0.26	11.79	0.570	1.51	0.20	11.40	0.692
Win 3: Exposure ever happened in 10-30 years									
Age	Year	1.00	0.97	1.03	0.942				
Gender	Male	0.99	0.48	2.05	0.984				
Educational level	>= Bachelor's degree	0.33	0.19	0.60	0.000				
Smoker	Current	0.60	0.22	1.67	0.365	0.57	0.20	1.64	0.298
	Former	0.88	0.48	1.61	0.696	0.87	0.47	1.60	0.650
Ever work in the US armed forces	Yes	2.34	1.04	5.28	0.040	2.18	0.95	5.02	0.067
Occupational exposure to lead	Yes	0.59	0.22	1.59	0.295	0.53	0.19	1.49	0.230
Occupational exposure to pesticides	Yes	4.53	1.44	14.23	0.010	4.39	1.36	14.17	0.013
Industry: health care/social assistance	Yes	0.64	0.29	1.41	0.266	0.68	0.31	1.49	0.334
Industry: accommodation, food services	Yes	0.24	0.06	1.01	0.052	0.27	0.06	1.10	0.068
Industry: public administration	Yes	0.27	0.08	0.95	0.041	0.28	0.08	0.97	0.045
Win 4: Exposure ever happened more than 30 years ago									
Age	Year	1.01	0.98	1.05	0.502				
Gender	Male	1.20	0.57	2.54	0.626				
Educational level	>= Bachelor's degree	0.28	0.15	0.53	<.0001				
Smoker	Current	0.33	0.11	1.02	0.085	0.35	0.11	1.13	0.079
	Former	0.71	0.38	1.32	0.543	0.75	0.40	1.41	0.370
Ever work in the US armed forces	Yes	2.08	0.89	4.83	0.089	1.96	0.82	4.68	0.131
Occupational exposure to lead	Yes	0.46	0.16	1.36	0.160	0.39	0.12	1.25	0.113
Occupational exposure to pesticides	Yes	2.91	0.91	9.31	0.071	2.71	0.85	8.65	0.093
Industry: health care/social assistance	Yes	0.85	0.33	2.21	0.738	0.85	0.32	2.26	0.747
Industry: accommodation, food services	Yes	0.11	0.01	0.92	0.042	0.13	0.01	1.12	0.064
Industry: public administration	Yes	0.43	0.14	1.34	0.144	0.45	0.14	1.40	0.166

*Cases and controls were frequency matched by 6 age group (<40, 40-50, 50-60, 60-70, 70-80, >80), gender, and 2 education levels (< bachelor's degree, ≥ bachelor's degree); 17 of 24 strata had matched cases and controls.

eTable 9. Results of unmatched and matched logistic regression models for single compound exposure and ALS.

Compound	Unmatched (100 cases, 110 controls)				Matched* (92 cases, 104 controls)			
	OR	95% CI		p-value	OR	95% CI		p-value
Pesticides								
Pentachlorobenzene	9.73	3.96	23.91	<.0001	7.93	3.29	19.11	<.0001
Hexachlorobenzene	2.22	1.11	4.45	0.024	2.25	1.10	4.60	0.027
β-HCH	8.62	3.16	23.47	<.0001	7.64	2.68	21.80	0.000
Dacthal	0.98	0.72	1.34	0.918	0.91	0.63	1.31	0.613
trans-Chlordane	1.17	0.81	1.67	0.404	1.09	0.77	1.56	0.621
cis-Chlordane	3.78	1.94	7.36	<.0001	3.46	1.77	6.78	0.000
trans-Nonachlor	1.23	0.91	1.67	0.180	1.24	0.92	1.66	0.158
p,p'-DDE	1.81	1.08	3.02	0.023	1.66	1.00	2.75	0.050
PCBs								
PCB 110	2.01	1.44	2.80	<.0001	2.08	1.46	2.97	<.0001
PCB 151	1.76	1.28	2.41	0.000	1.81	1.30	2.52	0.000
PCB 135/144	1.29	0.90	1.85	0.165	1.33	0.91	1.94	0.139
PCB 118	0.51	0.30	0.88	0.015	0.58	0.34	0.98	0.042
PCB 132/153	1.32	0.98	1.77	0.064	1.35	0.99	1.83	0.055
PCB 138/163	1.35	1.00	1.83	0.049	1.40	1.04	1.88	0.028
PCB 175	1.27	0.96	1.69	0.094	1.42	1.01	1.98	0.044
PCB 174	1.08	0.80	1.45	0.626	1.13	0.84	1.52	0.437
PCB 202	0.82	0.61	1.10	0.178	0.87	0.64	1.16	0.339
PCB 180	1.27	0.96	1.67	0.092	1.30	0.98	1.72	0.067
PCB 170/190	1.58	1.15	2.15	0.004	1.61	1.17	2.20	0.003
PCB 198	0.96	0.72	1.28	0.786	0.98	0.72	1.32	0.884
BFRs								
TBBPa	0.61	0.41	0.91	0.015	0.62	0.41	0.94	0.025
PBDE 28	3.68	1.89	7.18	0.000	4.07	1.98	8.34	0.000
PBDE 47	1.27	0.95	1.69	0.104	1.28	0.96	1.70	0.096
PBDE 66	0.84	0.63	1.13	0.251	0.84	0.63	1.12	0.230
PBDE 100	1.44	1.07	1.92	0.015	1.45	1.07	7.96	0.016
PBDE 99	1.34	1.00	1.80	0.048	1.30	0.97	1.74	0.082
PBDE 85	0.99	0.75	1.30	0.945	0.98	0.74	1.30	0.900
PBDE 154	0.97	0.74	1.27	0.831	0.96	0.74	1.25	0.754

Standardized concentrations for single compounds were used.

*Cases and controls were frequency matched by 6 age group (<40, 40-50, 50-60, 60-70, 70-80, >80), gender, and 2 education levels (< bachelor's degree, ≥ bachelor's degree); 16 of 24 strata had matched cases and controls.

eTable 10. Results of unmatched and matched logistic regression models for multiple compound exposure and ALS.

Compound	Unmatched (97 cases, 107 controls)				Matched* (92 cases, 104 controls)			
	OR	95% CI		p-value	OR	95% CI		p-value
Pesticides								
Pentachlorobenzene	3.87	1.54	9.75	0.004	3.67	1.46	9.28	0.006
Hexachlorobenzene								
β-HCH	3.00	0.87	10.39	0.083	6.45	1.34	31.02	0.020
Dacthal	0.25	0.10	0.62	0.003	0.19	0.06	0.60	0.005
trans-Chlordane								
cis-Chlordane	9.10	2.18	37.96	0.002	5.23	1.52	17.95	0.009
trans-Nonachlor								
p,p'-DDE								
PCBs								
PCB 110								
PCB 151	1.63	0.99	2.67	0.054	1.66	0.96	2.86	0.070
PCB 135/144								
PCB 118								
PCB 132/153								
PCB 138/163								
PCB 175	1.16	0.67	2.02	0.588	1.29	0.69	2.40	0.424
PCB 174								
PCB 202	0.40	0.21	0.78	0.007	0.41	0.20	0.84	0.015
PCB 180								
PCB 170/190								
PCB 198								
BFRs								
TBBPa	0.66	0.36	1.23	0.191	0.65	0.34	1.24	0.191
PBDE 28								
PBDE 47	1.46	0.90	2.38	0.126	1.47	0.90	2.41	0.121
PBDE 66	0.58	0.33	1.03	0.063	0.63	0.34	1.14	0.125
PBDE 100								
PBDE 99								
PBDE 85								
PBDE 154								

Standardized concentrations for multiple compounds were used.
*Cases and controls were frequency matched by 6 age group (<40, 40-50, 50-60, 60-70, 70-80, >80), gender, and 2 education levels (< bachelor's degree, ≥ bachelor's degree); 16 of 24 strata had matched cases and controls.

eFigure. Flow chart for statistical analyses in Michigan ALS study.