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Supplementary Material for Valdez-Flores and Sielken (2013)

Despite the 2007 SAB's recommendation for EPA to focus on individual data, EPA's modeling continues to focus on a few categorical rate ratios. In ACC's comments on the charge questions, we suggested the following addition to question 3a:

“Please comment on EPA’s method of implementing their linear regression of the categorical results and EPA’s rejection (discussed in EPA’s Appendix J.3.1) of the modeling recommendations in Valdez-Flores and Sielken (2013).”

EPA's method results in a poor basis for model selection and, as we show in our 2013 paper, EPA's method is based on a misinterpretation of categorical rate ratios which leads to inappropriate exposure–response model fitting and biased estimates of risk.

This document is the Supplementary Material from our 2013 paper. Whereas the body of our 2013 paper provides specific modeling results for breast cancer mortality (the NIOSH breast cancer incidence data are not publicly available), the supplementary material provides specific modeling results for lymphohematopoietic cancers and lymphoid cancers. The supplementary material also provides more than just 4 categorical RRs for each endpoint (namely, 20 categorical RRs and also one categorical RR for each exposed individual with the cancer).

In the supplementary material, for results for lymphohematopoietic cancers see pages 4 to 11 (Tables 3S through Figure 3S) especially page 8 (Table 6S), and for lymphoid cancers see pages 12 to 19 (Tables 7S through Figure 6S) especially page 16 (Table 10S).

In the supplementary material, for results for lymphoid cancers see pages 12 to 19 (Tables 7S through Figure 6S) especially pages 18 and 19 (Figures 5S and 6S).

The supplementary material is available online at <http://dx.doi.org/10.1016/j.yrtph.2013.07.011>. Herein, we have corrected a few typographical errors. These corrections do not change our results but are identified for full disclosure.

Supplementary Material

Misinterpretation of categorical rate ratios and inappropriate exposure-response model fitting can lead to biased estimates of risk: Ethylene oxide case study

Ciriaco Valdez-Flores and Robert L. Sielken, Jr.

Breast Cancer Mortality Rate Ratios for 20 and 61 Categories

Table 1S. Rate ratios estimated using 20 categories

Cumulative Exposure Interval (ppm-days)	Breast Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	41	1.000	1.000	1.000	1.000
(0.0, 61.3]	4	2.674	1.001	1.000	1.000
(61.3, 155.7]	3	1.213	1.005	1.001	1.001
(155.7, 238.0]	3	1.473	1.009	1.002	1.002
(238.0, 453.6]	3	0.791	1.016	1.004	1.003
(453.6, 703.5]	3	0.911	1.028	1.006	1.005
(703.5, 765.2]	3	3.879	1.035	1.008	1.007
(765.2, 931.1]	3	2.019	1.040	1.009	1.008
(931.1, 1309.6]	3	1.063	1.053	1.012	1.011
(1309.6, 1702.4]	3	1.358	1.072	1.016	1.014
(1702.4, 2634.6]	3	0.886	1.103	1.024	1.021
(2634.6, 3104.0]	3	2.249	1.137	1.031	1.027
(3104.0, 3814.4]	3	2.001	1.165	1.038	1.033
(3814.4, 4196.8]	3	3.660	1.191	1.044	1.038
(4196.8, 5899.8]	3	1.296	1.241	1.056	1.049
(5899.8, 10900.0]	3	0.795	1.401	1.095	1.082
(10900.0, 12853.2]	3	4.339	1.567	1.137	1.118
(12853.2, 14967.4]	3	4.586	1.664	1.162	1.140
(14967.4, 19165.2]	3	3.727	1.814	1.202	1.174
(19165.2, 47308.7]	3	1.460	2.586	1.432	1.367
>47308.7	3	2.578	3.928	1.940	1.782

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 2S. Rate ratios estimated using 61 categories

Cumulative Exposure Interval (ppm-days)	Breast Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	41	1.000	1.000	1.000	1.000
(0.0, 16.4]	1	3.054	1.001	1.000	1.000
(16.4, 34.5]	1	1.907	1.002	1.000	1.000
(34.5, 46.1]	1	3.104	1.003	1.000	1.000
(46.1, 61.3]	1	3.099	1.004	1.001	1.001
(61.3, 73.7]	1	2.920	1.005	1.001	1.001
(73.7, 88.0]	1	3.137	1.006	1.001	1.001
(88.0, 155.7]	1	0.549	1.009	1.001	1.001
(155.7, 222.0]	1	0.601	1.013	1.002	1.002
(222.0, 234.1]	1	3.518	1.016	1.002	1.002
(234.1, 238.0]	1	12.227	1.016	1.002	1.002
(238.0, 250.7]	1	4.294	1.017	1.002	1.002
(250.7, 328.3]	1	0.685	1.020	1.003	1.003
(328.3, 453.6]	1	0.473	1.027	1.004	1.004
(453.6, 559.9]	1	0.640	1.035	1.005	1.005
(559.9, 649.3]	1	0.924	1.042	1.006	1.006
(649.3, 703.5]	1	1.529	1.047	1.007	1.006
(703.5, 728.9]	1	4.080	1.050	1.007	1.007
(728.9, 751.6]	1	2.811	1.052	1.007	1.007
(751.6, 765.2]	1	5.847	1.053	1.007	1.007
(765.2, 791.0]	1	3.940	1.054	1.008	1.007
(791.0, 860.9]	1	1.606	1.058	1.008	1.008
(860.9, 931.1]	1	1.645	1.063	1.009	1.008
(931.1, 1068.7]	1	0.898	1.070	1.010	1.009
(1068.7, 1203.9]	1	0.950	1.079	1.011	1.011
(1203.9, 1309.6]	1	1.529	1.088	1.012	1.012
(1309.6, 1417.1]	1	1.472	1.095	1.013	1.013
(1417.1, 1485.0]	1	2.663	1.101	1.014	1.014
(1485.0, 1702.4]	1	0.862	1.111	1.016	1.015
(1702.4, 1879.4]	1	1.140	1.125	1.017	1.017
(1879.4, 2197.0]	1	0.877	1.142	1.020	1.019
(2197.0, 2634.6]	1	0.723	1.169	1.024	1.023
(2634.6, 2769.1]	1	2.774	1.188	1.026	1.026
(2769.1, 2875.1]	1	3.710	1.197	1.028	1.027
(2875.1, 3104.0]	1	1.405	1.209	1.029	1.029
(3104.0, 3285.7]	1	2.536	1.223	1.031	1.031
(3285.7, 3567.4]	1	1.713	1.239	1.034	1.033
(3567.4, 3814.4]	1	1.943	1.257	1.036	1.035
(3814.4, 3992.4]	1	2.707	1.272	1.039	1.037
(3992.4, 4154.9]	1	2.687	1.284	1.040	1.039
(4154.9, 4196.8]	1	11.863	1.291	1.041	1.040
(4196.8, 4347.1]	1	4.393	1.298	1.042	1.041
(4347.1, 5137.8]	1	0.904	1.331	1.047	1.046
(5137.8, 5899.8]	1	1.019	1.385	1.055	1.053

Cumulative Exposure Interval (ppm-days)	Breast Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
(5899.8, 7112.9]	1	0.730	1.454	1.065	1.063
(7112.9, 9155.7]	1	0.658	1.567	1.082	1.080
(9155.7, 10900.0]	1	1.127	1.700	1.102	1.099
(10900.0, 12017.9]	1	2.567	1.799	1.117	1.114
(12017.9, 12332.8]	1	7.251	1.849	1.125	1.121
(12332.8, 12853.2]	1	6.202	1.879	1.130	1.126
(12853.2, 13738.3]	1	4.032	1.928	1.137	1.133
(13738.3, 14409.3]	1	4.362	1.982	1.146	1.142
(14409.3, 14967.4]	1	6.499	2.025	1.153	1.148
(14967.4, 15290.8]	1	11.875	2.055	1.158	1.153
(15290.8, 16158.7]	1	5.729	2.097	1.164	1.160
(16158.7, 19165.2]	1	1.877	2.232	1.186	1.181
(19165.2, 32422.7]	1	0.732	2.800	1.284	1.275
(32422.7, 45344.7]	1	1.619	3.713	1.457	1.442
(45344.7, 47308.7]	1	13.939	4.232	1.566	1.547
(47308.7, 56496.6]	1	2.869	4.621	1.653	1.630
(56496.6, 96735.4]	1	1.465	6.345	2.099	2.057
>96735.4	1	5.829	9.152	3.099	3.005

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Results for lymphohematopoietic cancers

Table 3S. LH - Rate ratios estimated using four categories

Cumulative Exposure Interval (ppm-days)	Breast LH Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	13	1.000	1.000	1.000	1.000
(0, 1175.0]	16	1.698	1.052	1.014	1.001
(1175.0, 3489.1]	15	2.451	1.206	1.056	1.004
(3489.1, 12851.6]	15	2.243	1.720	1.211	1.016
>12851.6	15	2.114	2.545	1.507	1.034

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 4S. LH - Rate ratios estimated using 20 categories

Cumulative Exposure Interval (ppm-days)	Breast LH Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	41 13	1.000	1.000	1.000	1.000
(0.0, 175.4]	4	1.644	1.003	1.000	1.000
(175.4, 437.3]	3	1.193	1.009	1.001	1.001
(437.3, 645.8]	3	1.991	1.016	1.003	1.001
(645.8, 867.8]	3	2.180	1.022	1.004	1.001
(867.8, 1175.0]	3	1.962	1.030	1.005	1.002
(1175.0, 1532.5]	3	2.007	1.040	1.007	1.003
(1532.5, 1589.5]	3	11.908	1.046	1.008	1.003
(1589.5, 2098.3]	3	2.003	1.054	1.009	1.004
(2098.3, 2441.4]	3	3.502	1.067	1.011	1.004
(2441.4, 3489.1]	3	1.543	1.088	1.015	1.006
(3489.1, 4155.8]	3	2.916	1.113	1.019	1.007
(4155.8, 5413.1]	3	2.066	1.141	1.024	1.009
(5413.1, 7033.3]	3	2.073	1.184	1.031	1.012
(7033.3, 9012.3]	3	2.661	1.237	1.040	1.015
(9012.3, 12851.6]	3	1.927	1.323	1.055	1.021
(12851.6, 17901.9]	3	2.032	1.454	1.078	1.030
(17901.9, 27070.9]	3	1.921	1.664	1.116	1.044
(27070.9, 60348.2]	3	1.279	2.290	1.237	1.087
(60348.2, 114438.8]	3	2.957	3.580	1.531	1.181
>114438.8	3	5.316	5.177	1.992	1.308

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 5S. LH-Rate ratios estimated using 61 categories

Cumulative Exposure Interval (ppm-days)	Breast LH Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	44-13	1.000	1.000	1.000	1.000
(0.0, 63.3]	1	1.140	1.002	1.000	1.000
(63.3, 114.9]	1	1.406	1.006	1.000	1.000
(114.9, 150.7]	1	1.937	1.010	1.001	1.000
(150.7, 175.4]	1	2.899	1.012	1.001	1.000
(175.4, 230.6]	1	1.558	1.015	1.001	1.000
(230.6, 337.4]	1	0.988	1.021	1.002	1.001
(337.4, 437.3]	1	1.147	1.028	1.002	1.001
(437.3, 486.2]	1	2.307	1.033	1.003	1.001
(486.2, 511.0]	1	6.368	1.036	1.003	1.001
(511.0, 645.8]	1	1.073	1.042	1.003	1.001
(645.8, 797.1]	1	0.967	1.052	1.004	1.001
(797.1, 846.1]	1	3.905	1.059	1.004	1.002
(846.1, 867.8]	1	9.791	1.062	1.005	1.002
(867.8, 912.8]	1	4.126	1.064	1.005	1.002
(912.8, 1030.3]	1	1.656	1.070	1.005	1.002
(1030.3, 1175.0]	1	1.425	1.080	1.006	1.002
(1175.0, 1340.6]	1	1.436	1.091	1.007	1.002
(1340.6, 1472.8]	1	1.654	1.102	1.008	1.003
(1472.8, 1532.5]	1	4.559	1.109	1.008	1.003
(1532.5, 1569.2]	1	5.456	1.112	1.008	1.003
(1569.2, 1577.3]	1	32.391	1.114	1.009	1.003
(1577.3, 1589.5]	1	23.840	1.115	1.009	1.003
(1589.5, 1623.6]	1	9.762	1.116	1.009	1.003
(1623.6, 1791.6]	1	1.695	1.124	1.009	1.003
(1791.6, 2098.3]	1	1.205	1.141	1.011	1.004
(2098.3, 2278.9]	1	1.977	1.158	1.012	1.004
(2278.9, 2307.2]	1	11.453	1.166	1.013	1.004
(2307.2, 2441.4]	1	3.525	1.172	1.013	1.005
(2441.4, 2577.6]	1	2.522	1.182	1.014	1.005
(2577.6, 3025.5]	1	1.139	1.203	1.015	1.005
(3025.5, 3489.1]	1	1.427	1.236	1.018	1.006
(3489.1, 3607.3]	1	4.693	1.257	1.019	1.007
(3607.3, 3736.9]	1	4.832	1.266	1.020	1.007
(3736.9, 4155.8]	1	1.610	1.286	1.022	1.008
(4155.8, 4868.9]	1	1.314	1.327	1.025	1.009
(4868.9, 5268.0]	1	1.899	1.367	1.028	1.010

Cumulative Exposure Interval (ppm-days)	Breast LH Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
(5268.0, 5413.1]	1	5.352	1.387	1.029	1.010
(5413.1, 5955.2]	1	1.979	1.412	1.031	1.011
(5955.2, 6697.1]	1	1.397	1.458	1.035	1.012
(6697.1, 7033.3]	1	3.991	1.497	1.038	1.013
(7033.3, 7106.9]	1	22.620	1.512	1.039	1.014
(7106.9, 7336.9]	1	7.739	1.523	1.040	1.014
(7336.9, 9012.3]	1	1.031	1.592	1.045	1.016
(9012.3, 10773.7]	1	1.163	1.716	1.055	1.019
(10773.7, 11652.4]	1	3.448	1.812	1.063	1.022
(11652.4, 12851.6]	1	2.297	1.887	1.069	1.024
(12851.6, 14568.3]	1	1.794	1.993	1.077	1.026
(14568.3, 16586.9]	1	1.773	2.128	1.088	1.030
(16586.9, 17901.9]	1	2.520	2.249	1.098	1.033
(17901.9, 18491.2]	1	5.431	2.318	1.104	1.035
(18491.2, 21142.3]	1	1.654	2.435	1.113	1.038
(21142.3, 27070.9]	1	1.234	2.746	1.140	1.047
(27070.9, 33181.3]	1	1.476	3.182	1.177	1.059
(33181.3, 45568.1]	1	1.114	3.851	1.238	1.078
(45568.1, 60348.2]	1	1.232	4.835	1.332	1.106
(60348.2, 70021.4]	1	2.776	5.721	1.424	1.132
(70021.4, 88429.7]	1	2.446	6.737	1.536	1.162
(88429.7, 114438.8]	1	3.635	8.346	1.733	1.213
(114438.8, 127373.3]	1	11.897	9.756	1.926	1.258
(127373.3, 137243.4]	1	25.333	10.581	2.049	1.286
>137243.4	1	2.186	11.296	2.161	1.310

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 6S. LH - Parameter estimates for the Cox proportional hazards log-linear model fit to the ~~breast~~ LH cancer mortality in NIOSH epidemiological data and the models fit to the categorical RRs

Model	Number of cumulative exposure intervals	Intercept	Slope
Restricted Linear Model fitted to Categorical RRs using least squares (Model 2)	4	Fixed at 1.00	8.81E-05
	20	Fixed at 1.00	2.95E-05
	61	Fixed at 1.00	7.24E-05
Unrestricted Log-Linear Model fitted to Categorical RRs using least squares (Model 3)	4	1.59	2.34E-05
	20	2.06	4.87E-06
	61	2.48	5.42E-06
Cox proportional Log-Linear hazards model fitted to NIOSH individual cohort data (Model 4)		Unknown (not estimated)	1.90E-06

Figure 1S. LH - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical RRs when the data were split into four categories

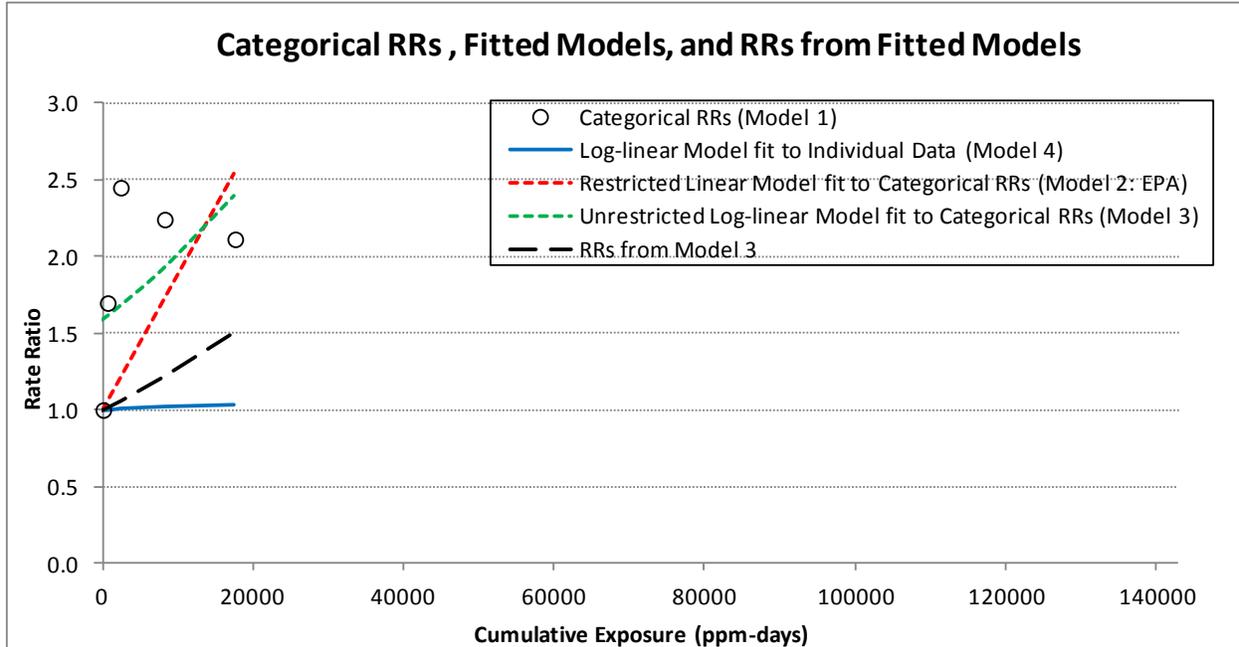


Figure 2S. LH - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical RRs when the data were split into 20 categories

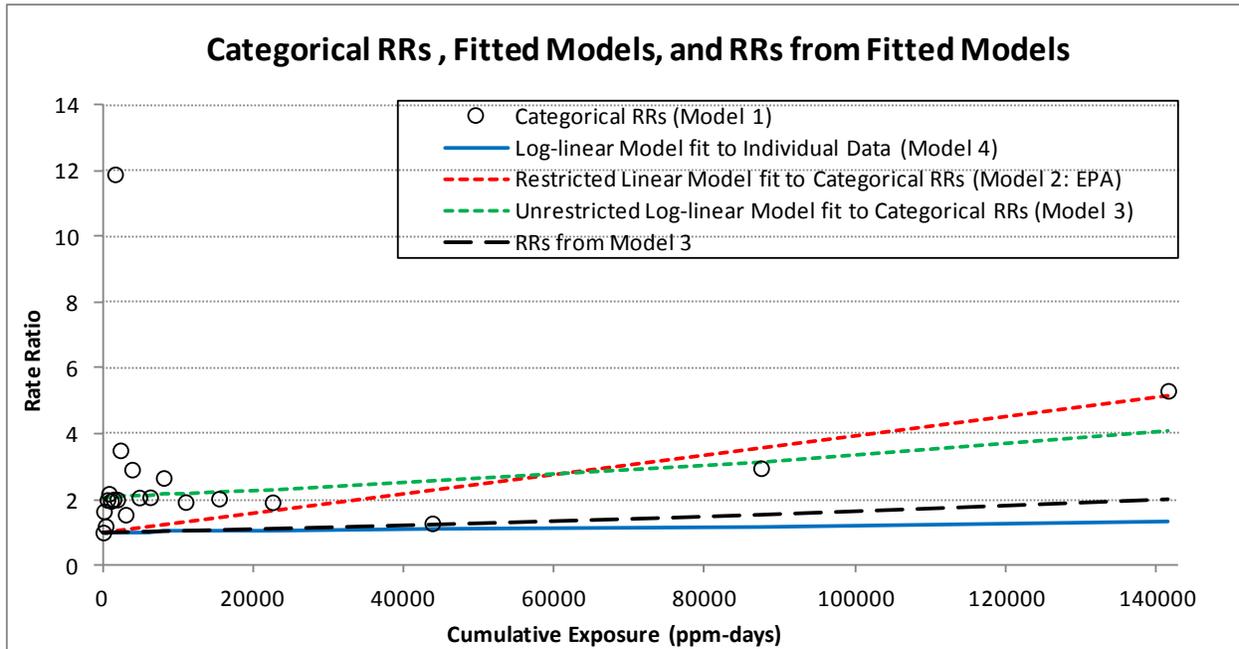
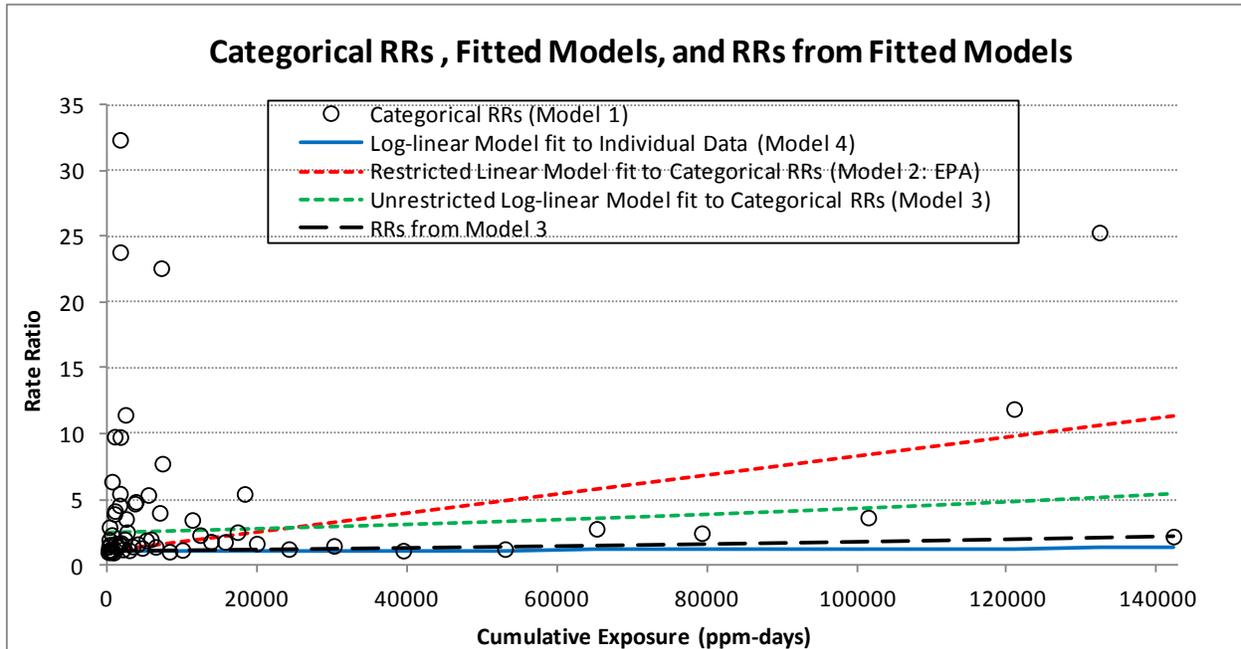


Figure 3S. LH - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical RRs when the data were split into 61 categories



Results for lymphoid neoplasms

Table 7S. Lymphoid - Rate ratios estimated using four categories

Cumulative Exposure Interval (ppm-days)	Breast Lymphoid Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	9	1.000	1.000	1.000	1.000
(0.0, 1532.5]	11	1.042	1.029	1.014	1.002
(1532.5, 4155.8]	11	1.903	1.107	1.053	1.008
(4155.8, 17901.9]	11	1.458	1.416	1.220	1.031
>17901.9	11	1.823	1.934	1.562	1.072

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 8S. Lymphoid - Rate ratios estimated using 20 categories

Cumulative Exposure Interval (ppm-days)	Breast Lymphoid Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	9	1.000	1.000	1.000	1.000
(0.0, 230.6]	3	1.034	1.003	1.001	1.000
(230.6, 486.2]	3	1.369	1.009	1.002	1.001
(486.2, 1150.9]	3	0.780	1.021	1.006	1.002
(1150.9, 1570.6]	3	1.645	1.036	1.009	1.004
(1570.6, 1623.6]	2	11.706	1.042	1.011	1.004
(1623.6, 2307.2]	2	0.990	1.052	1.013	1.006
(2307.2, 2577.6]	2	2.840	1.064	1.017	1.007
(2577.6, 3489.1]	2	1.257	1.079	1.021	1.009
(3489.1, 4155.8]	2	1.852	1.100	1.026	1.011
(4155.8, 6697.1]	2	0.719	1.142	1.037	1.015
(6697.1, 7336.9]	2	4.720	1.184	1.048	1.020
(7336.9, 10773.7]	2	1.058	1.237	1.063	1.026
(10773.7, 12851.6]	2	2.569	1.310	1.083	1.034
(12851.6, 16586.9]	2	1.674	1.386	1.104	1.042
(16586.9, 18491.2]	2	3.035	1.460	1.125	1.050
(18491.2, 29707.8]	2	1.082	1.632	1.176	1.070
(29707.8, 60348.2]	2	0.920	2.180	1.353	1.135
(60348.2, 88429.7]	2	2.444	2.949	1.649	1.232
(88429.7, 127373.3]	2	5.445	3.827	2.065	1.354
>127373.3	2	3.758	4.848	2.683	1.510

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 9S. Lymphoid - Rate ratios estimated using 64 44 categories

Cumulative Exposure Interval (ppm-days)	Breast Lymphoid Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
Controls	9	1.000	1.000	1.000	1.000
(0.0, 114.9]	1	0.683	1.005	1.000	1.000
(114.9, 154.7]	1	1.773	1.011	1.000	1.000
(154.7, 230.6]	1	1.146	1.016	1.000	1.001
(230.6, 337.4]	1	1.060	1.024	1.001	1.001
(337.4, 437.3]	1	1.215	1.033	1.001	1.001
(437.3, 486.2]	1	2.384	1.039	1.001	1.001
(486.2, 625.8]	1	1.112	1.047	1.001	1.002
(625.8, 809.5]	1	0.804	1.060	1.002	1.002
(809.5, 1150.9]	1	0.584	1.083	1.002	1.003
(1150.9, 1472.8]	1	0.706	1.110	1.003	1.004
(1472.8, 1532.5]	1	4.545	1.127	1.003	1.004
(1532.5, 1570.6]	1	5.105	1.131	1.004	1.004
(1570.6, 1589.5]	1	14.49	1.133	1.004	1.004
(1589.5, 1623.6]	1	9.821	1.135	1.004	1.005
(1623.6, 1972.2]	1	0.894	1.151	1.004	1.005
(1972.2, 2307.2]	1	1.079	1.180	1.005	1.006
(2307.2, 2441.4]	1	3.406	1.200	1.005	1.007
(2441.4, 2577.6]	1	2.378	1.211	1.006	1.007
(2577.6, 3025.5]	1	1.105	1.236	1.006	1.008
(3025.5, 3489.1]	1	1.443	1.274	1.007	1.009
(3489.1, 3646.3]	1	3.416	1.300	1.008	1.010
(3646.3, 4155.8]	1	1.276	1.329	1.009	1.011
(4155.8, 5476.9]	1	0.632	1.406	1.011	1.014
(5476.9, 6697.1]	1	0.824	1.513	1.014	1.017
(6697.1, 7049.8]	1	3.745	1.579	1.016	1.019
(7049.8, 7336.9]	1	6.339	1.606	1.017	1.020
(7336.9, 9012.3]	1	1.019	1.688	1.019	1.023
(9012.3, 10773.7]	1	1.099	1.833	1.023	1.028
(10773.7, 11652.4]	1	3.250	1.944	1.026	1.032
(11652.4, 12851.6]	1	2.097	2.032	1.028	1.035
(12851.6, 14568.3]	1	1.666	2.155	1.032	1.039
(14568.3, 16586.9]	1	1.616	2.312	1.036	1.045
(16586.9, 17901.9]	1	2.162	2.452	1.040	1.050
(17901.9, 18491.2]	1	4.927	2.533	1.043	1.052
(18491.2, 21142.3]	1	1.533	2.669	1.046	1.057
(21142.3, 29707.8]	1	0.831	3.141	1.060	1.074

Cumulative Exposure Interval (ppm-days)	Breast Lymphoid Cancer Deaths	RRs from Model 1 ¹	RRs from Model 2: EPA ²	RRs from Model 3 ³	RRs from Model 4 ⁴
(29707.8, 45568.1]	1	0.761	4.170	1.090	1.111
(45568.1, 60348.2]	1	1.143	5.460	1.129	1.160
(60348.2, 70021.4]	1	2.538	6.490	1.161	1.201
(70021.4, 88429.7]	1	2.257	7.672	1.199	1.249
(88429.7, 114438.8]	1	3.401	9.543	1.261	1.329
(114438.8, 127373.3]	1	11.499	11.183	1.319	1.404
(127373.3, 137243.4]	1	24.114	12.143	1.354	1.450
>137243.4	1	1.936	12.974	1.385	1.490

¹ Categorical model fit to individual data

² Continuous linear model used by EPA with restricted intercept fit to RRs from Model 1

³ Log-linear model with unrestricted intercept fit to RRs from Model 1

⁴ Continuous log-linear model fit to individual data

Table 10S. Lymphoid - Parameter estimates for the Cox proportional hazards log-linear model fit to the breast lymphoid cancer mortality in NIOSH epidemiological data and the models fit to the categorical RRs

Model	Number of cumulative exposure intervals	Intercept	Slope
Restricted Linear Model fitted to Categorical RRs using least squares (Model 2)	4	Fixed at 1.00	3.77E-05
	20	Fixed at 1.00	2.62E-05
	44	Fixed at 1.00	8.42E-05
Unrestricted Log-Linear Model fitted to Categorical RRs using least squares (Model 3)	4	1.21	1.80E-05
	20	1.57	6.72E-06
	44	1.60	9.26E-06
Cox proportional Log-Linear hazards model fitted to NIOSH individual cohort data (Model 4)		Unknown (not estimated)	2.81E-06

Figure 4S. Lymphoid - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical RRs when the data were split into four categories

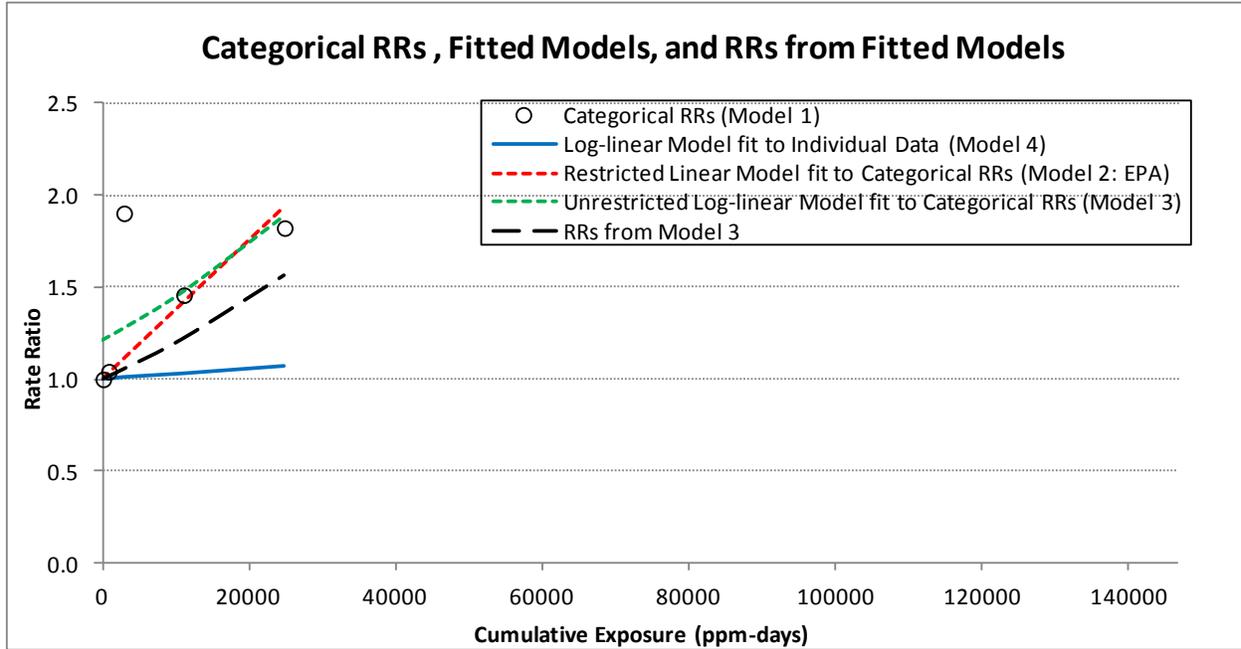


Figure 5S. Lymphoid - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical

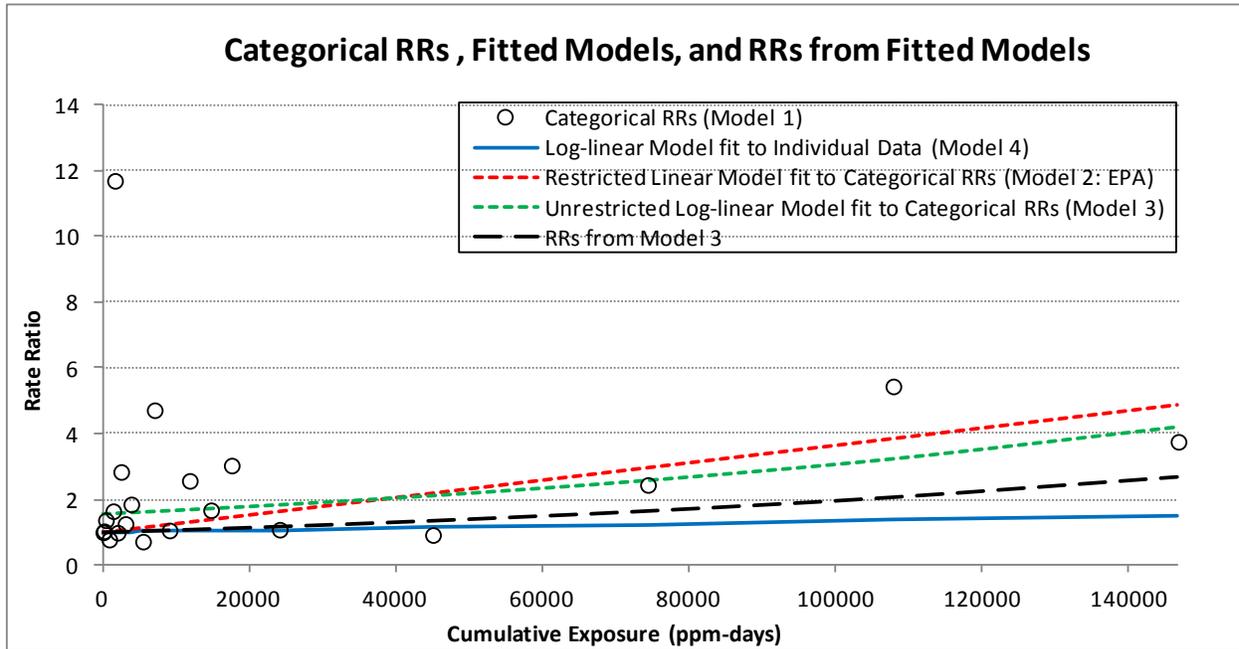
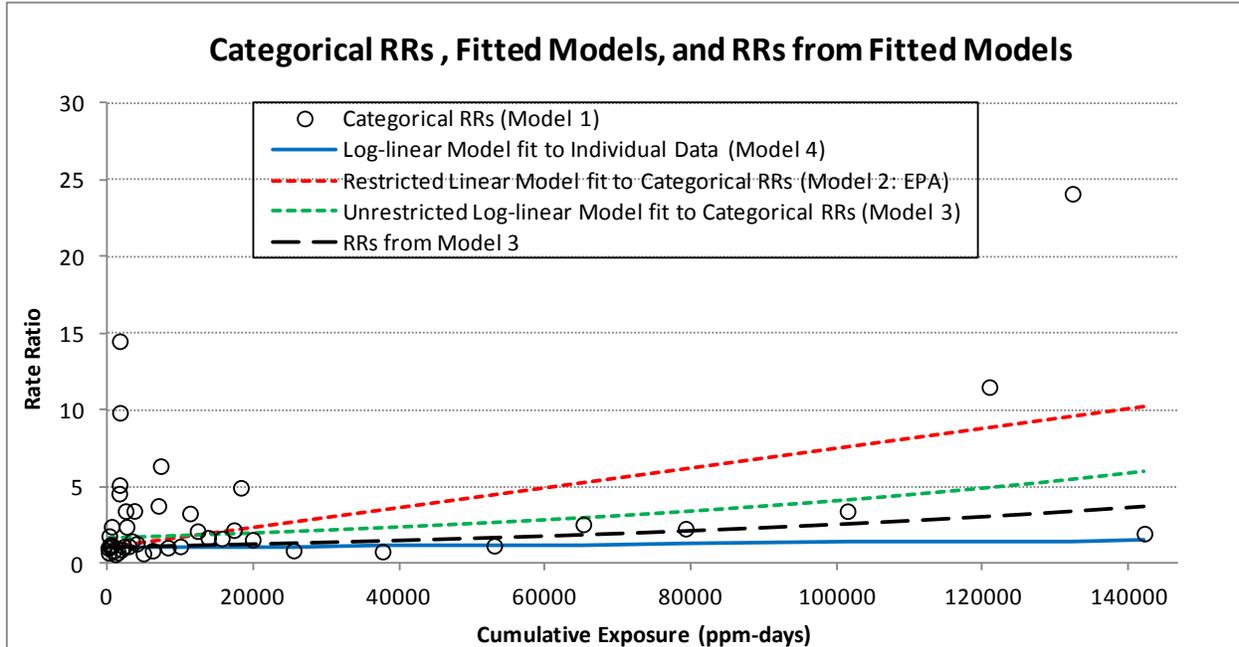


Figure 6S. Lymphoid - Categorical RRs (Model 1) and continuous log-linear RRs (Model 4) estimated from the individual NIOSH epidemiological data versus the restricted linear model (Model 2) and the unrestricted log-linear model (Model 3) fitted to the categorical RRs when the data were split into 61 categories



Illustrative Example

In Examples 1 and 2 in the manuscript, the observed RRs were smooth and approximately linearly related to the exposure. In the following example (Example 3), the observed RRs are less smooth and more non-linear (Figure 7S) . Figure 8S shows that fixing the RR=1 for the lowest exposure group, or fixing the RR=1 for the second lowest exposure group, etc. substantially changes the fitted continuous linear regression model “with fixed intercept” (i.e., with the fitted model forced to pass through one at the first exposure, or one at the second exposure, etc.) even when the fitted models are rescaled back to the original scale. Thus, the somewhat arbitrary choice of which group to use as the comparison group substantially impacts the slopes of the predicted RRs. Figure 9S continues Example 3 and shows that, regardless of which exposure has its RR fixed equal to one, if the intercept in the fitted models is estimated instead of being fixed, then the slopes of the predicted RRs are all the same when they are rescaled back to the original scale.

Figure 7S. Example 3 in which the observed RR's are less smooth than in Examples 1 and 2 and not linearly related to the exposures

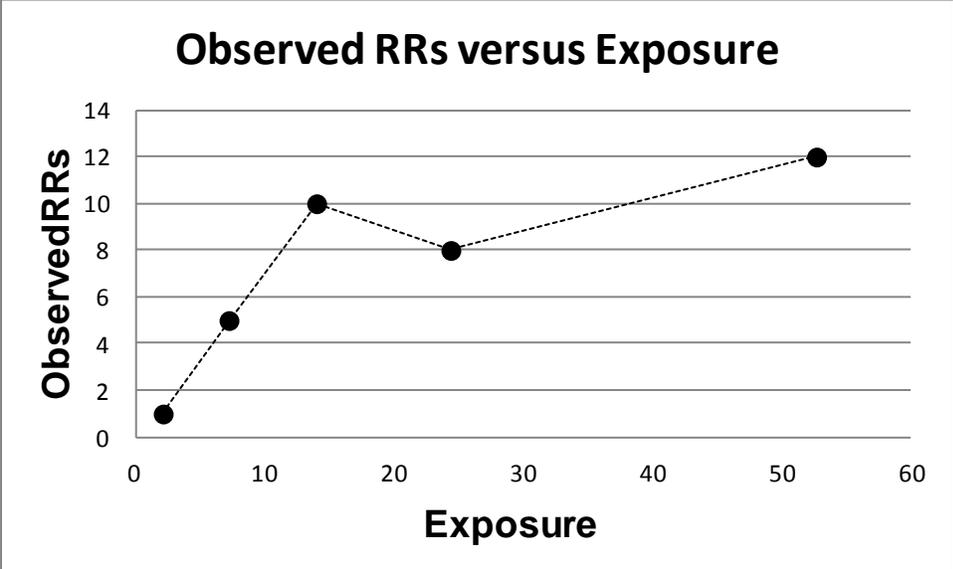


Figure 8S. Third Example: Substantial change in the predicted RRs caused by fixing the intercept to be one at different specified exposures(i.e., forcing the fitted model to pass through a RR=1 at a specified exposure)

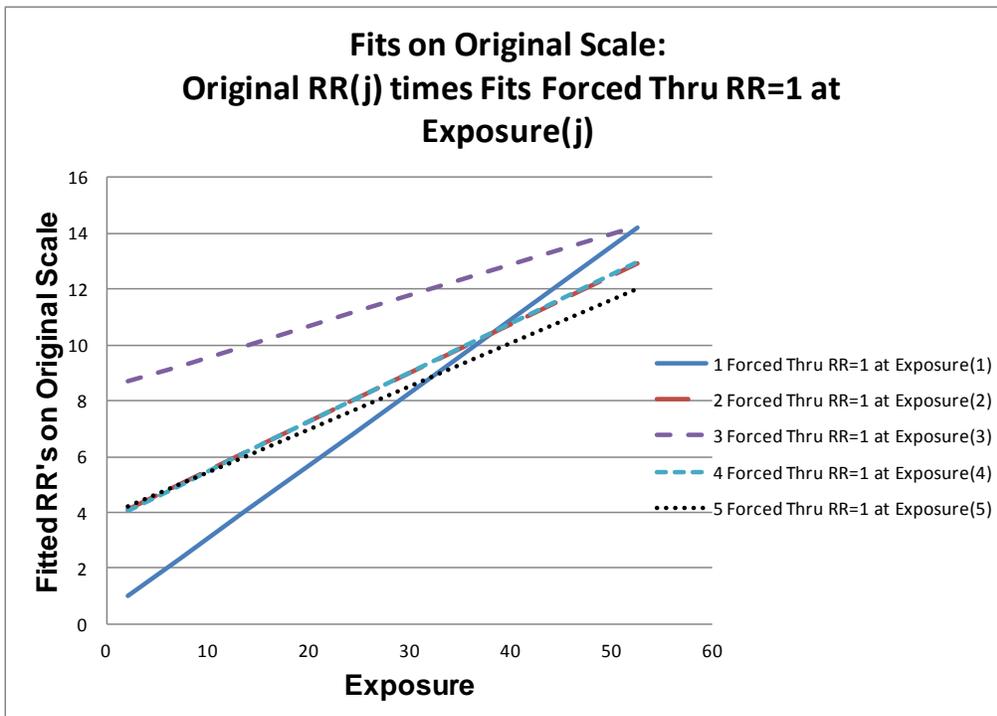
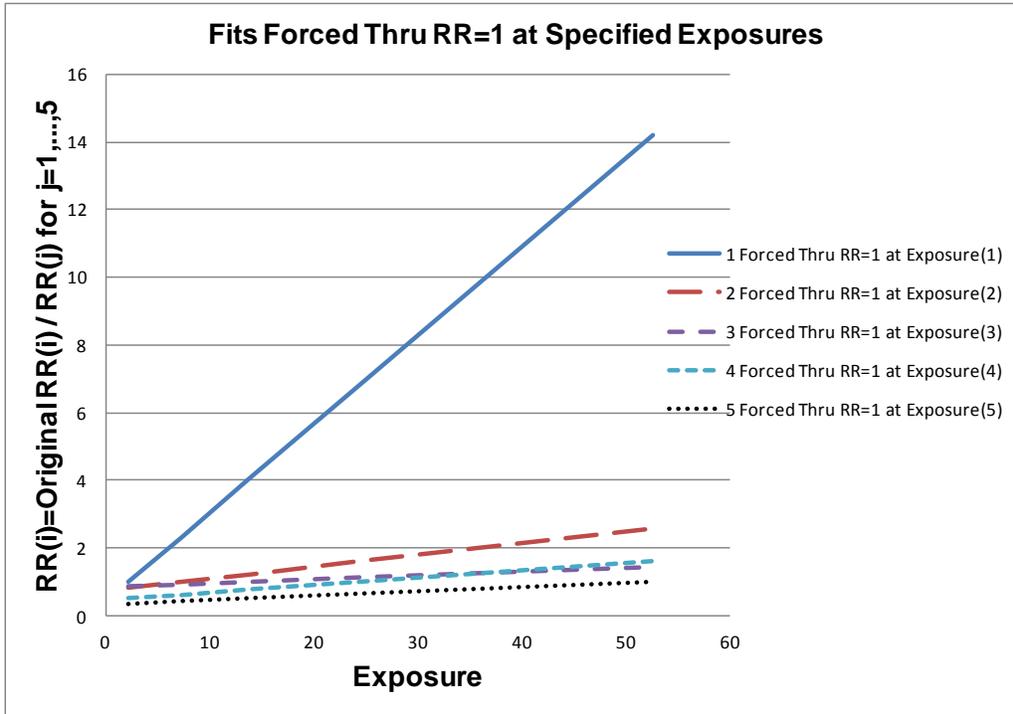


Figure 9S. Continuation of Third Example: Insensitivity of predicted RRs when the intercept is estimated as opposed to being fixed equal to one at different specified exposures(i.e., benefit of not forcing the fitted model to pass through a specified RR at a specified exposure)

