II. Thresholds and Other Non-linearities in the Relationship between Hexavalent Chromium and Lung Cancer

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Park RM, Stayner LT. A Search for Thresholds and Other Non-linearities in the Relationship between Hexavalent Chromium and Lung Cancer. *Risk Analysis* 2006; 26:79-88.

Traditional cumulative exposure metric assumptions:

a) Damage (effect) is immediate

b) Subsequent induced risk is linear in current exposure intensity

c) Effects are irreversible over subsequent period of follow-up

Alternate Exposure metrics

Lagging (in Cr(+6) analyses, assumed 5 yr lag)

$\Sigma \{[\max(0, Cr6_j - \tau)] \times [duration_j]\}$, τ – threshold level (e.g., 0.050 mg/m^3)

$\Sigma \{[(Cr6_j)^a] \times [duration_j]\}$, a – dose-rate exponent (e.g., 0.2 – 5.0)

$\Sigma \{[Cr6_j \times 0.5^{(t-tj)/T1/2}] \times [duration_j]\}$, $T_{1/2}$ – half-life

Table 1 Hexavalent Chromium – Lung Cancer Exposure Response: Test for Intensity Threshold

Threshold $\mu g/m^3$		Model: Cumulative Chromium		Model: Cumulative Chromium by Race	
		Model Deviance	Exposure[1] Δ-2ln(L), 1 df	Model Deviance	Exposure Δ-2ln(L), 2 df
as CrO_3	as Cr^{+6}				
0	0	1930.46	16.28[2]	1923.66	23.08[2]
1	0.5	1930.46	16.27	1923.70	23.04
2	1.0	1930.47	16.27	1923.75	22.99
5	2.6	1930.49	16.24	1923.92	22.81
10	5.2	1930.59	16.14	1924.30	22.44
20	10.4	1931.24	15.50	1925.44	21.30
30	15.6	1931.69	15.05	1926.32	20.42[4]
50	26.0	1932.79	13.94	1928.12	18.62
55	28.6	1933.15	13.59[3]	1928.61	18.13
60	31.2	1933.50	13.24	1929.11	17.63
100	52.0	1935.21	11.52	1931.45	15.28

1.Change in -2ln(likelihood) with addition of exposure term to model
2.MLE for threshold
3.Upper 95% CI for threshold: 55 $\mu g/m^3$ CrO_3, one-sided confidence interval.
4.Upper 95% CI for threshold: 30 $\mu g/m^3$ CrO_3, one-sided confidence interval.

Table 2 Hexavalent Chromium – Lung Cancer Exposure Response: Test for Non-Linear Intensity Dependence (Dose-rate effect)

	Model: Cumulative Chromium			Model: Cumulative Chromium by Race	
(intensity)[a] a	Model Deviance	Exposure[1] Δ-2ln(L), 1 df		Model Deviance	Exposure Δ-2ln(L), 2 df
.25	1931.80	14.94		1923.59	23.15
.50	1930.80	15.94		1922.91	23.83[2]
.75	1930.34	16.39		1922.96	23.78
.80	1930.32	16.41[2]		1923.05	23.69
.85	1930.32	16.41		1923.17	23.57
.90	1930.35	16.39		1923.31	23.42
1.00[3]	1930.46	16.28		1923.66	23.08
1.20	1930.89	15.85		1924.56	22.18
1.50	1931.82	14.91		1926.12	20.62

1.Change in -2ln(likelihood) with addition of exposure term to model
2.MLE for x; lower 95% CI for a < .25; upper 95% CI for a > 1.50.
3.Linearity, or constant dose-rate effect

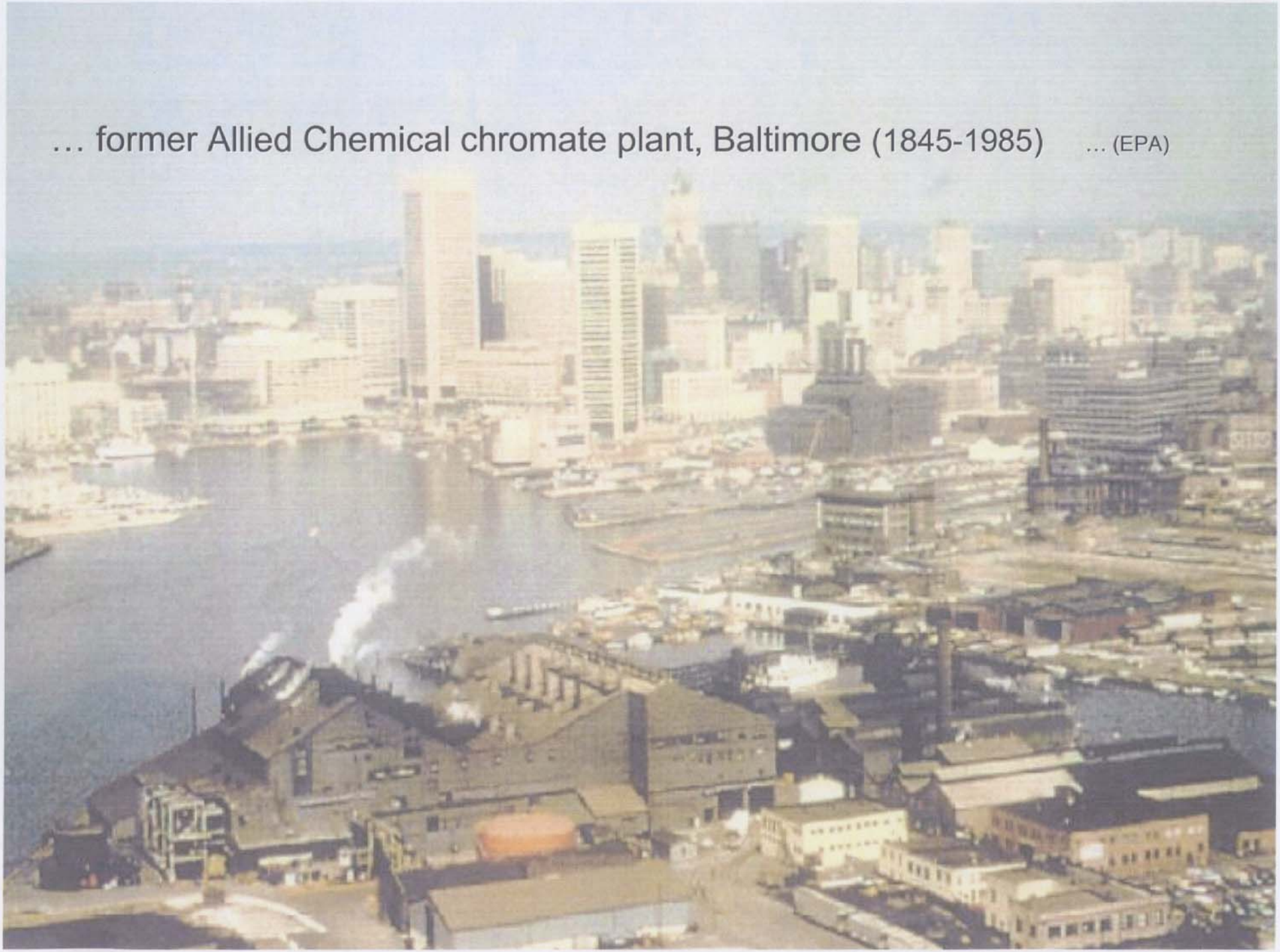
Table 3 Hexavalent Chromium – Lung Cancer Exposure Response: Test for Declining Burden

	Model: Cumulative Chromium			Model: Cumulative Chromium by Race	
Half-life, yrs	Model Deviance	Exposure[1] Δ-2ln(L), 1 df		Model Deviance	Exposure Δ-2ln(L), 2 df
1	1942.18	4.555		-[2]	
2	1938.33	8.408		-[2]	
5	1934.71	12.03		1930.61	16.12
8	1933.14	13.59[3]		1928.42	18.31
10	1932.55	14.19		1927.49	19.25
14	1931.84	14.89		1926.34	20.39[4]
20	1931.35	15.39		1925.48	21.26
40	1930.85	15.89		1924.52	22.22
∞	1930.46	16.28[5]		1923.66	23.08[5]

1.Change in -2ln(likelihood) with addition of exposure term to model
2.Unable to fit model
3.Lower 95% CI for halflife = 8 yr, one-sided confidence interval.
4.Lower 95% CI for halflife = 14 yr, one-sided confidence interval.
5.MLE for halflife

Conclusions

- Cumulative exposed (lagged) is an appropriate exposure metric for Cr(+6)
- The data are consistent with at most a small exposure intensity threshold (< 20 $\mu g/m^3$) and the best estimate is zero-threshold
- If there is a dose-rate effect, it appears to be negative (diminishing incremental risk with incremental intensity)
- The risk arising from prior Cr(+6) exposure does not diminish over time.


… former Allied Chemical chromate plant, Baltimore (1845-1985) … (EPA)