

NIOSH Cr(VI) Criteria Document Update Public Meeting

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I. Hexavalent Chromium and Lung Cancer in the Chromate Industry: A Quantitative Risk Assessment

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Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PSJ. Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. *Risk Analysis* 2004; 24:1099-1108.

Background

- Chromic acid, pigments and stainless steel; from welding stainless steel, electroplating, wood preservation... suspect carcinogen is hexavalent chromium, Cr(+6), a strong oxidizing agent.
- Population: chromate chemical workers employed at an Allied Chemical plant in Baltimore, MD, previously studied by Hayes et al. (1979), Braver et al., (1985) and Gibb et al. (2000).
- Purpose: describe the exposure-response for lung cancer mortality and estimate excess lifetime risk.

Methods

- Extensive environmental assessment since 1950
- Smoking at hire information
- Descriptive analyses by standardized mortality ratios (SMRs) and standardized rate ratios (SRRs)
- Models of SMRs using Poisson regression fit with log-linear or linear relative rate model forms, incorporating external U.S. rates
- Excess lifetime risk by actuarial method (BEIR IV) that accounts for competing risks of death

Methods... Exposure Assessment

- 70,000 gravimetric samples, largely area and short-term breathing zone, 1950-1985, designed to characterize typical exposures.
- Sampling for total particulate, analyzed for soluble Cr(+6), using one colorimetric method (reported as CrO₃).
- All sampling and sample analyses conducted by the employer.
- Unique exposure characterization far exceeding that available in most occupational studies.

Methods... Smoking Specification

- Smoking at hire for 91% including cigarette usage for 70%
- Smoking analyzed categorically (smoker: yes, no, unknown), traditional approach.
- Calculated smoking cumulative exposure from information at hire: assuming started at age 18 and smoked for life.
- Smoking variable fit as piece-wise linear terms with one internal knot (at 30 pack-years), based on inspection of cubic spline representations of cumulative smoking.

Methods... Rate Classification Table

All observation time classified in:

16 age (<20, 20-24, 25-29, 30-34, ..., 85+)

9 calendar (1950-54, 1955-59, ..., 1990-94)

3 race categories (0=nonwhite, 1=white, 2=unknown)

50 levels of time-dependent cumulative Cr(+6) exposure

10 levels of time-dependent cumulative smoking

10 levels of employment duration

Unit of observation: 30 days

Methods... Poisson regression modeling

- Observation time replaced by *expected*:
expected = person-yr. \times U.S. (age, yr, race) rate
- Model **standardized mortality ratios** (rather than rates).
- Intercept an estimate of $\ln(\text{SMR})$ for the non exposed population.
- Age and race terms: allow departures from reference rates (healthy-worker and healthy-worker-survivor effects).
- Effects estimated for chromium and smoking based on internal comparisons.

Methods... Excess lifetime risk

... proportion of deaths in an exposed population that are attributable to that exposure

Calculated with actuarial method (BEIR IV) accounting for competing causes of death assuming 45 years Cr(+6):

Lifetime risk (LTR)	$\sum_i \{ [R_{gt}/R_{+i}] S(1,i) [q_i] \}$
Excess lifetime risk	LTR (exposed pop.) – LTR (reference pop.)

where,

R_{+i} = all-cause age-specific mortality rate

q_i = Pr(death in interval i given alive at the start of interval i)

$$S(1,i) = (1-q_1) \times (1-q_2) \times \dots \times (1-q_{i-1})$$

Results...Study Population

- 2372 men hired August 1, 1950 - December 31, 1974
- Follow-up: date of hire – 12-31-1992 (or death)
- 122 lung cancer deaths (vs. 66 in Mancuso (Ohio) study)
- 1205 white (51%)
848 nonwhite (36%) – believed mostly African Americans
304 with unknown race (13%)
- duration of employment:
mean : 3.1 yr.
median: was 0.39 yr or 4 mos.
- final cumulative Cr(+6) exposure:
average 0.134 mg/m³-yr
maximum: 5.3 mg/m³-yr
- 45 yrs at OSHA PEL(2003): 4.5 mg/m³-yr

Table 1 SMRs and SRRs by Poisson regression for all workers by levels of Cr(+6) cumulative exposure (mg/m³-yrs)

	cum. exposure	P-yrs	Obs	Exp	SMR	95%CI	SRR	95%CI
All Workers (includes 4 lung cancer cases with unknown race)								
1	[0.000-0.028]	51348	72	47.93	1.50	1.18-1.88	1.0	-
2	(0.028-0.094]	7837	14	7.64	1.83	1.03-2.97	1.29	0.69-2.22
3	(0.094-0.372]	6859	12	6.09	1.97	1.06-3.31	1.38	0.71-2.46
4	(0.372-1.095]	3841	12	5.13	2.34	1.25-3.93	1.70	0.87-3.03
5	(1.095-5.260]	950	12	1.90	6.32	3.39-10.60	4.53	2.32-8.13
	Total		122	68.68	1.78	1.50-2.11		

Table 2 SMRs and SRRs by Poisson regression for white workers by levels of Cr(+6) cumulative exposure (mg/m³-yrs)

	cum. exposure	P-yrs	Obs	Exp	SMR	95%CI	SRR	95%CI
White Workers								
1	[0.000-0.028]	27962	45	27.32	1.65	1.21- 2.18	1.0	-
2	(0.028-0.094]	4088	12	3.93	3.06	1.64- 5.13	1.85	0.92-3.43
3	(0.094-0.372]	3409	6	2.98	2.01	0.80- 4.08	1.21	0.46-2.70
4	(0.372-1.095]	2188	4	3.22	1.24	0.39-2.89	0.86	0.26-2.15
5	(1.095-5.260]	495	4	1.03	3.87	1.20- 8.98	2.55	0.76-6.38
	Total		71	38.48	1.85	1.45-2.31		

Table 3 SMRs and SRRs by Poisson regression for *nonwhite* workers by levels of Cr(+6) cumulative exposure (mg/m³-yrs)

	cum. Cr(+6)	P-yrs	Obs	Exp	SMR	95%CI	SRR	95%CI
Nonwhite Workers								
1	[0.000-0.028]	16384	24	16.16	1.49	0.97-2.16	1.0	-
2	(0.028-0.094]	3118	2	3.31	0.60	0.10-1.86	0.41	0.07-1.41
3	(0.094-0.372]	3125	5	2.93	1.71	0.61-3.67	1.24	0.41-3.04
4	(0.372-1.095]	1589	8	1.87	4.23	1.96-7.98	3.03	1.24-6.64
5	(1.095-5.260]	434	8	0.85	9.41	4.30-17.5	6.76	2.76-15.0
	Total		47	25.12	1.87	1.39-2.46		

Methods... Model Specification

Loglinear relative rate model:

$$\begin{aligned} RR &= \exp [a_0 + a_1 I(w) + a_2 I(u) + a_3 (\text{Age}-50) + a_4 \text{Smk1} + a_5 \text{Smk2} + b \text{Cr6}] \\ &= \exp [a_0] \times \exp [a_1 I(w)] \times \exp [a_2 I(u)] \times \dots \times \exp [a_5 \text{Smk2}] \times \exp [b \text{Cr6}] \end{aligned}$$

(not very biologic)

Linear relative rate model

$$RR = \exp [a_0 + a_1 I(w) + a_2 I(u) + a_3 (\text{Age}-50)] \times [1 + a_4 \text{Smk1} + a_5 \text{Smk2} + b \text{Cr6}]$$

where,

$I(\cdot)$ are indicator variables (0,1) for race (w=white, u=unknown)

Smk1 is pack-yrs up to 30; =30 if pack-yrs >30 (lagged 5 yrs)

Smk2 is pack-yrs greater than 30

Cr6 is cumulative exposure (mg/m³ yrs) lagged 5 yrs

Table 4 *Cr(+6)-lung cancer exposure-response: linear relative rate models with piece-wise linear terms for smoking in linear or log-linear component of model*

models ¹	parameter estimate	deviance	Δ -2ln(L) (df)	p
Model: linear relative rate in smoking and chromium; loglinear rate in race, age				
Intercept	-1.636	1930.51		
Smoking < 30 pack-yr	0.402			
Smoking > 30 pack-yr	0.031			
Cumulative Cr(+6)	10.95		16.25 (1)	< 0.0001
SMR(0)=0.195				
Model: linear relative rate in chromium; log-linear rate in smoking, race, age				
Intercept	-0.786	1931.60		
Smoking < 30 pack-yr	0.061			
Smoking > 30 pack-yr	-0.006			
Cumulative Cr(+6)	1.444		15.05 (1)	0.0001
SMR(0)=0.456				

Final model form for standardized rate ratio (RR):

$$RR = \exp [a_0 + a_1 I (w) + a_2 I (u) + a_3 (\text{Age}-50) + a_4 \text{Smk1} + a_5 \text{Smk2}] \times [1 + b \text{Cr6}]$$

Cr(+6) effect estimate is relative to a background rate that includes the effects of smoking; will use this because regulation isn't specific to smoking status

Table 5 Final model of Cr(+6)-lung cancer exposure response

Model	parameter estimate	$\Delta-2\ln(L)$ (df)	SMR	RR	RR, 95% CI	Reference
Race: nonwhite men	-0.786		0.46			US NW men
Race: white men	-0.901		0.41			US W men
Race: unknown	-1.515		0.22			US men
Age	-0.082			0.92		5 yr of age
Smoking < 30 pack-yr	0.061			1.06	1.04,1.09	pack-yrs
Smoking > 30 pack-yr	-0.006			0.99	0.97,1.01	pack-yrs
Cumulative Cr(+6)	1.444	15.05 (1)		2.44	1.54,3.83	mg/m ³ -yr
(deviance: $-2\ln(L) = 1931.60$)						

Model with exposure-race interaction:

$$RR = e [a_0 + a_1 I(w) + a_2 I(u) + a_3 (\text{Age}-50) + a_4 \text{Smk}1 + a_5 \text{Smk}2] \times [1 + b_1 \text{Cr}6\text{NW} + b_2 \text{Cr}6\text{W}]$$

where,

Cr6NW is cumulative Cr6 in workers known to be nonwhite

Cr6W is cumulative Cr6 in all other workers

Table 6 Model of Cr(+6)-lung cancer exposure response with exposure-race interaction

Model ¹	Parameter estimate	$\Delta-2\ln(L)$ (df)	SMR	RR	RR, 95% CI	Reference
Race: nonwhite men	-1.121		0.33			US NW men
Race: white men	-0.834		0.43			US W men
Race: unknown	-1.557		0.21			US men
Age	-0.100			0.90		5 yr of age
Smoking < 30 pack-yr	0.064			1.07	1.04,1.07	pack-yrs
Smoking > 30 pack-yr	0.001			1.00	0.98,1.02	pack-yrs
Cum. Cr(+6), NW men	4.312	25.63 (2)		5.31	2.78,10.1	mg/m ³ -yr
Cum. Cr(+6), W men	0.176			1.18	0.43,1.92	mg/m ³ -yr

(Model deviance: $-2\ln(L) = 1921.02$)

Interpretation

- ┆ Interaction with race unlikely to be biological or the result of uncontrolled confounding from smoking, life-style...
- ┆ History: coke-oven workers
- ┆ Exposure misclassification, two speculations:
 - 1) total particulate soluble Cr(+6) may be non optimal when multiple forms of chromate, different solubilities and size distributions, across process areas
 - 2) assignment of average exposure in exposure zones when actual exposures differed by race within zones could generate important exposure-race interactions..

Excess lifetime risk calculation...

- Used model without Cr(+6)-race interaction because unlikely to be biological, more likely from some misclassification
- Two models had very similar fit; used both

Table 7 *Excess lifetime risk (BEIR IV) calculated using final model and competing model of Cr(+6) exposure-response*

Cr(+6) (as CrO ₃ , mg/m ³)	Excess Lifetime Risk (45 yrs)			
	Linear relative rate model		Log-linear model	
	Excess risk ³	95% CI	Excess risk	95% CI
0.000	0.000	-	0.000	-
0.001	0.003	0.001 - 0.006	0.003	0.001 - 0.004
0.002	0.006	0.003 - 0.012	0.005	0.003 - 0.008
0.005 ¹	0.016	0.006 - 0.030	0.014	0.007 - 0.020
0.010	0.031	0.012 - 0.059	0.028	0.013 - 0.043
0.020	0.060	0.023 - 0.113	0.057	0.025 - 0.093
0.050	0.141	0.057 - 0.251	0.145	0.056 - 0.264
0.100 ²	0.255	0.109 - 0.416	0.281	0.096 - 0.516

1. Current OSHA PEL

2. Previous OSHA PEL

Conclusions

- Estimate of excess lifetime risk of lung cancer for workers exposed at the previous OSHA PEL, 255 per thousand, is very high compared to that usually permitted in occupational settings.
- Estimate is within range of risk assessments by OSHA, EPA and Cal EPA.
- Excess lifetime risk linearity implies rotating workers through high exposure environments would not reduce the overall burden of chromium induced lung cancer death.
- New OSHA standard for hexavalent chromium, 0.005 mg/m^3 , permits about 15/1000 excess lifetime risk for lung cancer death.
- NIOSH REL is 0.0002 mg/m^3 or $0.2 \text{ } \mu\text{g/m}^3$, 25-fold lower than PEL.