ZCFT 84-80-RJS November 21, 1984

MOSS LANDING MAGNESIA AND BRICK PLANTS - CHROMIUM AIR EMISSIONS SURVEY

R. J. Schlager

KAISER ALUMINUM & CHEMICAL CORPORATION
Center for Technology

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CHROMIUM AIR EMISSIONS SURVEY

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Copies to:

J. G. Shepherd (5)	- Moss Landing
L. R. Barsotti	- CFT 20
A. BeLue	- CFT 20
T. A. Lowe	- CFT 08
E. B. Paille	- KB 1237
J. C. Schwegmann	- KB 1241
J. O. Thompson Library	- Moss Landing

SAMPLING PROCEDURES

A standard test method for determining chromium emissions from stationary sources has not as yet been written by either EPA or the State of California. Both agencies have, however, sampled sources for chromium emissions based on modifying EPA Method 5 techniques. Contacts were made with the two agencies (Mr. Joe Noll of EPA, and Mr. Dean Simeroth of the State of California Air Resources Board) to discuss the sampling methods employed. The sampling method used in the present study used suggestions of the two agencies in addition to incorporating the experiences of CFT in analyzing samples for chromium. The method used in collecting the samples was basically EPA Method 5 with several modifications. The probe liner was glass to avoid any contamination from metal liners. Filter material was Teflon, manufactured by Membrana Inc. to avoid possible blank levels of chromium in other filter media. The 1.0 µm pore size filters exceed the performance criteria for filters specified in EPA Method 5. A nylon brush with Teflon tubing rod was used to clean the probe after each test. Probe washes were made using pH 2 sulfuric acid, since laboratory testing at CFT has shown this to preserve the oxidation state of chrome-containing particulate. 100-ml of distilled water was used in each of the first two impingers instead of the 200-ml amount specified in Method 5. This was done to improve the sensitivity of measuring small amounts of Cr in these solutions.

Except for the modifications noted above, EPA Method 5 procedures were followed in isokinetically sampling the sources. EPA Method 1 (as modified in Federal Register, V.48, no 191, p. 45034, 9/30/83) was followed to locate traverse points. Fyrite test kits were used in the O_2 and CO_2 determinations.

ANALYTICAL PROCEDURE

Samples collected in each test were recovered from the sample train and placed into four containers: probe and nozzle rinse, filter, first impinger catch, and second impinger catch. Each of the four fractions were analyzed separately. All impinger samples were analyzed for Cr^{+3} and Cr^{+6} content, while solids were analyzed for pH 2 sulfuric acid soluble Cr^{+3} and Cr^{+6}, and pH 2 sulfuric acid insoluble Cr^{+3}. The analytical methodology was a colorimetric diphenylcarbazide procedure and is found in Appendix A.

TEST RESULTS

Source conditions for each of the four stacks tested are given on Table I. Analytical results for the samples are shown on Table II. Chemical analysis of the impinger samples are not shown since all samples showed less than quantifiable levels of chromium (less than 0.00001 mg Cr^{+3} or Cr^{+6} per ml of impinger solution). Cr^{+6} in particulate samples was also not found at quantitation levels (less than 0.005 mg Cr^{+6} per filter, and less than 0.001 mg Cr^{+6} per 100-ml probe and nozzle rinse). Table III shows calculated grain loadings and mass loadings

SUMMARY

Four sources were tested at the Moss Landing facility for chromium air emissions. Chemical analysis of the samples show that no Cr^{+6} was detected in any sample. Cr^{+3} emissions were quantified for the Magnesia Plant Kiln 5, Brick Plant Kiln 2, and Brick Plant chrome drier. No detectable amounts of chromium were being emitted from Kiln 2 at the Magnesia Plant.

* * * * * * * * *

INTRODUCTION

Recent interest in toxic air pollutants at the State and local levels prompted a chromium emissions survey at Kaiser Aluminum & Chemical Corporations (KACC) Moss Landing Magnesia and Brick Plant. Four sources were identified for testing at the Moss Landing facility - kilns #2 and #5 at the Magnesia Plant, and tunnel kiln #2 and the "chrome drier" at the Brick Plant. The sources were tested on September 12, 13, 17, and 19, 1984. Each source was tested twice.

Regulatory agency visitors during portions of the testing were Mr. Kenneth A. Kitts and Mr. Bob Nishimura of the Monterey Bay Unified Air Pollution Control District, and Mr. Cliff Popejoy of the State of California Air Resources Board.

KACC's Center for Technology (CFT) and the Moss Landing Plant Technical Department performed the source testing, and the CFT Analytical Department provided sample analysis.

for the chromium emissions for the four sources. Samples identified as "insoluble" Cr on the Tables result from the way the particulate samples were prepared during analysis. In the analytical workup, Cr^{+6} and soluble Cr^{+3} were extracted from the particulate matter using dilute sulfuric acid (pH 2). The extract was analyzed for Cr^{+3} and Cr^{+6} content, and the residual particulate matter underwent additional analysis for insoluble Cr^{+3} determination. The "insoluble" values listed in the Tables are therefore the Cr^{+3} content of the particulate matter after dilute acid extraction to remove Cr^{+6} and soluble Cr^{+3}. Results of the chemical analysis of the field blank samples are shown in Table IV. Process data for the sources tested are given in Table V.

Sample data sheets and calculations are given in Appendix B. Calibration data for the EPA Method 5 meter case and pitot tube is given in Appendix C.

RJS:dn

Table 1 - MOSS LANDING MAGNESIA AND BRICK PLANT STACK GAS PROPERTIES

Test No.	Date	Source	Stack Gas Conditions						
			Temp, °F	Static Press.[1]	ACFM	SCFM(dry)	% H_2O	% O_2	% CO_2
1	9/12/84	Magnesia-Kiln #2	80	-29.0	16,300	13,900	4.9	3.0	12.3
2	9/12/84	Magnesia-Kiln #2	87	-29.0	16,500	13,900	5.5	4.0	12.8
3	9/13/84	Magnesia-Kiln #5	146	+0.05	5330	3420	26.5	5.5	7.3
4	9/13/84	Magnesia-Kiln #5	148	+0.05	6020	3850	26.4	5.0	7.5
5	9/17/84	Brick-Kiln #2	792	+0.20	14,900	5620	10.4	2.5	5.0
6	9/17/84	Brick-Kiln #2	778	+0.20	15,400	5860	10.9	3.5	5.0
7	9/19/84	Brick-Cr Drier	113	+0.10	6980	5870	9.2	19.5	-
8	9/19/84	Brick-Cr Drier	110	+0.10	6800	5800	8.2	19.5	-

Note: 1. In inches of water

Table II - ANALYTICAL RESULTS - MOSS LANDING MAGNESIA AND BRICK PLANT SAMPLES

Test No.	Source	Filter Catch-mg Cr		Probe + Nozzle Rinse-mg Cr	
		Cr^{+3}	Insoluble	Cr^{+3}	Insoluble
1	Magnesia-Kiln #2	ND	ND	ND	ND
2	Magnesia-Kiln #2	ND	ND	ND	ND
3	Magnesia-Kiln #5	0.01	0.10	ND	ND
4	Magnesia-Kiln #5	0.01	0.30	ND	ND
5	Brick-Kiln #2	0.01	3.22	0.36	0.23
6	Brick-Kiln #2	0.06	1.88	0.09	0.21
7	Brick-Cr Drier	0.01	0.65	0.22	4.60
8	Brick-Cr Drier	0.02	0.91	0.31	7.20

Note: ND - not detected at method quantitation levels
- less than 0.005 mg Cr^{+3} per filter
less than 0.01 mg insoluble Cr per filter
less than 0.001 mg Cr^{+3} per 100-ml probe and nozzle rinse
less than 0.05 mg insoluble Cr per 100-ml probe and nozzle rinse

Table III - MOSS LANDING MAGNESIA AND BRICK PLANT TEST RESULTS

Test No.	Source	Sample Volume (scf)	grains/scf		lb/hr		% Isokinetic
			Cr^{+3}	Insoluble	Cr^{+3}	Insoluble	
1	Magnesia-Kiln #2	31.490	ND	ND	ND	ND	97.8
2	Magnesia-Kiln #2	30.608	ND	ND	ND	ND	95.4
3	Magnesia-Kiln #5	20.963	7.3×10^{-6}	7.3×10^{-5}	2.2×10^{-4}	2.2×10^{-3}	96.4
4	Magnesia-Kiln #5	29.314	5.3×10^{-6}	1.6×10^{-4}	1.7×10^{-4}	5.2×10^{-3}	94.7
5	Brick-Kiln #2	20.671	2.8×10^{-4}	2.6×10^{-3}	1.3×10^{-2}	1.2×10^{-1}	104.5
6	Brick-Kiln #2	21.598	1.1×10^{-4}	1.5×10^{-3}	5.4×10^{-3}	7.5×10^{-2}	105.0
7	Brick-Cr Drier	20.125	1.8×10^{-4}	4.0×10^{-3}	8.9×10^{-3}	2.0×10^{-1}	93.4
8	Brick-Cr Drier	37.322	1.4×10^{-4}	3.3×10^{-3}	6.8×10^{-3}	1.7×10^{-1}	94.6

Note: ND - Not detected at method quantitation levels given in Table II.

Table IV - FIELD BLANK ANALYTICAL RESULTS

Sample	Total Found - mg Cr^{+3}	Total Found - mg Cr^{+6}	Total Found - mg Insoluble	mg/ml
Distilled Water - 9/10/84	<0.002[1]	<0.002[1]	-	<0.00001
Distilled Water - 9/19/84	<0.002[1]	<0.002[1]	-	<0.00001
4" Teflon Filter- 9/11/84	<0.005	<0.005	<0.01	-
4" Teflon Filter- 9/19/84	<0.005	<0.005	<0.01	-
Probe Rinse - 9/10/84	<0.001[2]	<0.001[2]	-	<0.00001
Probe Rinse - 9/19/84	<0.001[2]	<0.001[2]	-	<0.00001

1. Using 200-ml as an average volume of impinger solution plus rinses.

2. Using 100-ml as an average volume of probe rinsings.

Table V - MOSS LANDING PLANT PROCESS DATA

	Magnesia Plant		Brick Plant	
	Kiln 2	Kiln 5	Kiln 2	Cr Drier
1. Process Weight Rate (tons/hour)	13.4	2.5	1.6	8.0
2. Fuel Type	Oil	Gas	Gas	Gas
3. Fuel Rate (10^6 BTU/hour)	60	17.9	10.2	2.6

Appendix A (Analytical Procedures for Chromium Analysis) and Appendix B (Data Sheets and Calculations) to the report "Moss Landing Magnesia and Brick Plants-Chromium Air Emissions Survey" were provided to the Scientific Review Panel, and are available upon request from the Toxic Pollutants Branch of the California Air Resources Board.*

* See note on page ii.

EXHIBIT 4

The report entitled "Evaluation of the Potential Health Effects of Trivalent Chromium Compounds in the Refractories Industry" was provided to the Scientific Review Panel, and is available upon request from the Toxic Pollutants Branch of the California Air Resources Board.*

Only the Table of Contents and Executive Summary of the Report are reproduced here.

* See note on page ii.

REPORT

EVALUATION OF THE POTENTIAL HEALTH EFFECTS OF TRIVALENT CHROMIUM COMPOUNDS IN THE REFRACTORIES INDUSTRY

THE REFRACTORIES INSTITUTE

[illegible] 1[illegible], 1983

[illegible]d L. Joiner
[illegible]rry D. Rench
[illegible] Anne Zanetos
[illegible] E. Breuning

BATTELLE
Columbus Laboratories
505 King Avenue
Columbus, Ohio 43201

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DISCLAIMER

This report was prepared by Battelle Columbus Laboratories, Columbus, Ohio. The statements contained herein are based upon general information available from a random examination of the refractories industry, certain testing of raw materials and products, and from other data sources. Neither The Refractories Institute, any member of The Refractories Institute, Battelle Columbus Laboratories, nor any person acting on behalf of any of them assume any liability with respect to the use of or for possible or actual damage resulting from the use of any information disclosed in this report.

EXECUTIVE SUMMARY

The Refractories Institute commissioned Battelle Columbus Laboratories in the summer of 1981 to conduct an independent investigation to determine the effects of exposure to chromium compounds on human health and the environment. Battelle's study included a critical review of selected publications relating to chromium toxicity, a comprehensive survey of all 30 refractory plant locations in the United States, site visits to a representative group of manufacturing plants, and an analytical assessment to determine if trivalent chromium compounds used in manufacturing refractories were converted to hexavalent materials during the manufacturing process. The key findings are summarized below:

(1) The principal forms of chromium used in making refractory brick do not appear to be linked with cancer. This group of materials, identified as trivalent chromium compounds from their chemical structures, have been used for decades to strengthen the heat resistance of furnace brick produced for extremely high temperature applications. The chromium content of these chrome-bearing refractories ranges from 30 to 90 percent of their total volume. The conclusion that exposure to trivalent chrome compounds does not cause cancer is supported by negative findings drawn from a variety of sources. These include *in vivo* and *in vitro* bioassays, laboratory studies into the effects of trivalent chromium on animals, and epidemiologic studies on human exposures.

(2) A second type of chromium compound, chromic acid, is used in limited quantities for specific products at several refractory-making plants. It is also known as hexavalent chromium, and it is sometimes used as an additive by the refractories industry. Less than 550 of the 4,300 refractory workers in chrome-using facilities are potentially exposed to hexavalent compounds (325 of these exposed to trivalent and hexavalent, and 225 more to hexavalent alone). Hexavalent compounds have been consistently linked to an increased risk of lung cancer in exposed workers.

Additional support for this relationship has been provided by similar findings in laboratory animal experiments.

(3) Active programs of occupational health have been established in most of the plants surveyed. Their concerns vary, but typically include: instruction in special work safety practices, the use of personal protective equipment to limit exposure to particulates, monitoring of chromium concentrations in the workplace, and installation of equipment to control dust levels in their plants. In addition, most plants require pre-employment physical exams as periodic medical check-ups.

(4) Those refractories plants using chrome are usually well within OSHA's exposure limits for chromium compounds, according to monitoring data retrieved during site visits. These limits, which concern dust levels, are based on total chromium compounds present, but do distinguish between hexavalent and total chrome content. Of the 4,300 workers employed at the plants using chrome, no more than 1,725 are potentially exposed to trivalent compounds, fewer than 325 work with trivalent and hexavalent compounds, and less than 225 work exclusively with hexavalent compounds. In those plants where employees do work with hexavalent chrome, adequate exposure control measures appear to be in place.

(5) Trivalent chromium is not transformed into significant quantities of hexavalent chrome during the manufacture of chrome-bearing refractory products. These refractory products, when they are shipped from the plant, usually contain trivalent chrome only. This conclusion, which confirms a long-standing impression among industry mineralogists, was substantiated by analytical laboratory studies using both raw materials and finished products from various plants.

(6) The analyses of raw materials and finished refractory products revealed that the trivalent chromium raw materials, such as chromite, are not subjected to conditions which favor the formation of hexavalent chrome compounds during the production of refractories.

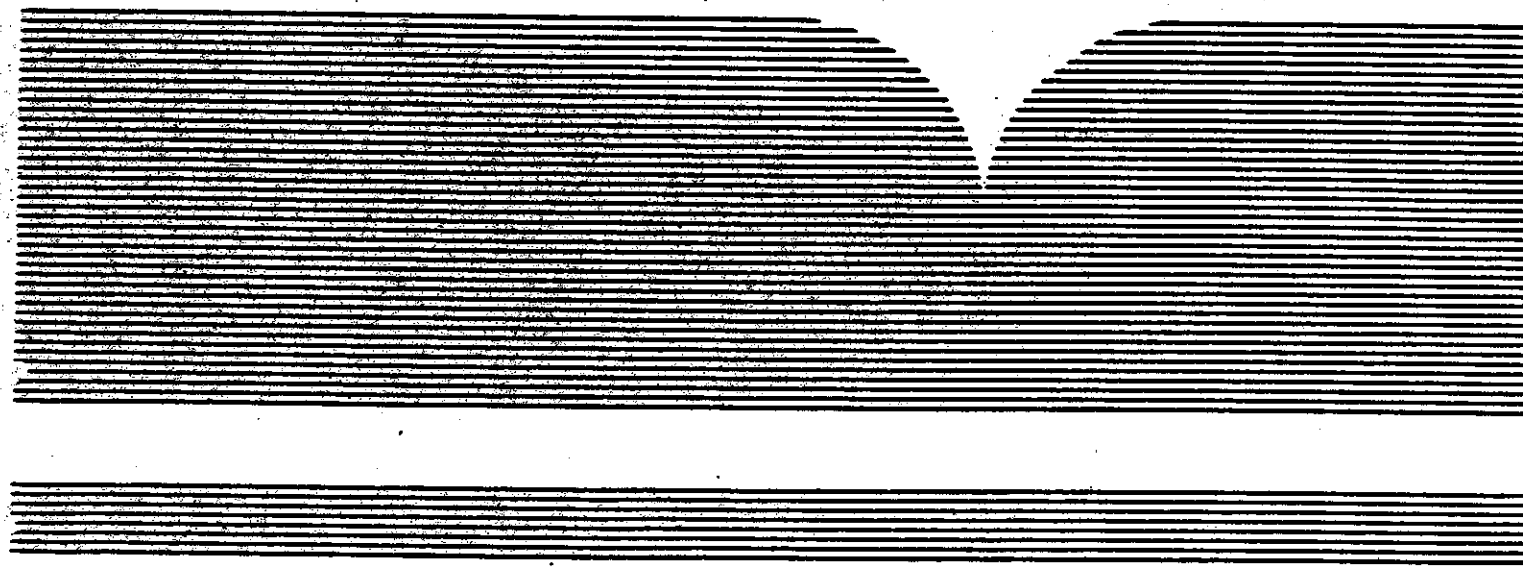
EXHIBIT 5

PB83-252205

HEALTH ASSESSMENT DOCUMENT FOR CHROMIUM

U.S. Environmental Protection Agency
Research Triangle Park, NC

Jul 83



U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
NTIS

TABLE 3-6

Sources and Estimates of United States Atmospheric Chromium Emissions in 1970[a]

Source	Chromium Emissions, metric tons/year		
	GCA Estimates		Goldberg
	Uncontrolled	Controlled	Controlled
Industrial Sources:			
refining	18,700	11,200	3,800
steel and alloy	2,407	595	NR
material handling	1,100	750	NR
chemical processing	835	106	NR
refractory	4,784	1,650	6
Inadvertent Sources:			
coal combustion	7,900	1,420	7,030
oil combustion	336	336	69
cement production	NR	254	NR
incineration	NR	143	NR
Asbestos Mining	9	0	7
Total	36,100	16,500	10,900

[a]Source: GCA Corporation, 1973; Goldberg, 1973
NR = Not reported

EXHIBIT 6

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Office of Air Quality Planning and Standards
Research Triangle Park, North Carolina 27711

DEC 1 2 1984

Dr. Robert Drake
2721 Oak Valley Drive
Vienna, Virginia 22180

Dear Dr. Drake:

As you may know, the United States Environmental Protection Agency (EPA) is considering adding chromium to the list of hazardous air pollutants under Section 112 of the Clean Air Act, as amended, August 1977. A preliminary assessment has identified 11 categories of stationary sources as potential emitters of significant quantities of chromium to the atmosphere.

In addition to the previously identified 11 source categories, EPA is attempting to gather information on other sources of chromium emissions to determine if they may require further study as separate source categories. Included among these other sources are glass melting furnaces.

Because there are limited data and available information, especially with respect to the quantities and forms of chromium actually emitted, EPA has undertaken a program to develop additional background information on each source category. A major element of the program consists of locating and visiting a number of representative plants within each source category. From these visits, one or more plants may be selected as candidates for emission testing. The tests will be performed to quantify the amount and form (trivalent or hexavalent) of chromium discharged from chromium emitting facilities and air pollution control devices.

As we have discussed previously on the telephone, I have contacted the State of California Air Resources Board and requested available information on the use of chromium additives in Gallo Glass Company's glass melting furnaces in Modesto, California. I am enclosing a copy of that request in this letter for your information, along with a copy of the questionnaire that was sent to the State detailing the type of information we are interested in obtaining.

Any similar information of this type which the members of the Glass Packaging Institute may be able to provide to EPA would greatly help in determining the need to include glass melting furnaces as a separate source category in this study.

If you have any questions regarding this request, please contact me at (919) 541-5601.

Sincerely,

Peter Schindler

Peter J. Schindler
Industrial Studies Branch
Emission Standards and
Engineering Division

Enclosure

TABLE 1. Chromium Sources, Emissions and Risk

Source Category	No. of Sources	Emissions Mg/yr	Max. Risk Lifetime	Annual Incidence
Chrome Plating	9,750	50	6.5X10-5	20
Refractory Prod.	35	90	1.6XI0-1	10*
Chemicals Prod.	3	450-900	2.0X10-2	12
Steel Prod.	112	2,870	9.0X10-4	11
Municipal Incin.	129	25	2.8X10-4	3.5
Sewage Sludge Incin.	141	30	1.0X10-3	0.8
Ferrochrome Prod.	x 2	43-	2.8X10-4	0.05
Cement Production	163	15	5.6X10-4	0.4
Ore Refining	x 3	3	3.8X10-5	0.006
Coal & Oil Combustion				
Power Plants	1,100	560	4.1X10-5	3
Industrial Boilers	165,000	840	8.0X10-4	200
Comm. & Res. Heating	16,800,000	323	N.A.**	70
Cooling Towers	Many	296-527	N.A.***	N.A.

*For 16 of 35 plants only

**Not available, but likely to be lower than other combustion sources.

***Not available; dispersion model for aerosols being developed.

Note--All emissions are assumed to be as potent as Cr+6. This will likely overestimate risk. See text.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

(6)

NOV 19 1984

Mr. Al Jenkins
State of California Air Resources Board
Post Office Box 2815
Sacramento, California 95812

Dear Mr. Jenkins:

I would like to thank you for providing the emission testing reports and related information on the glass melting furnaces at the Gallo Glass Company in Modesto, California, as requested by Mr. Ron Myers in October. After reviewing the contents of the test reports, we have determined that there is need for some of the information that has been omitted from the test reports due to Gallo's proprietary concerns.

This letter is to request a copy of Table 1 on page 3 of Test Report No. C-84-016, "Emissions from Glass Melting Furnaces at Gallo Glass Company," dated August 1984, which contains process weight rates and other operating conditions for the furnaces. Enclosure 1 details a further request for information which may be available on all five glass melting furnaces at Gallo in addition to that data provided in Table 1. This information would help greatly in EPA's investigation of this source category for chromium emissions.

Enclosure 2 summarizes Agency and Emission Standards and Engineering Division policies and procedures for handling privileged information and describes EPA contractor commitments and procedures for use of confidential materials. EPA has contracted with Midwest Research Institute (MRI) (Contract No. 68-02-3817) to obtain information pertinent to stationary categories which emit chromium. Thus, MRI has been designated by EPA as an authorized representative of the Agency. It is EPA's policy that compliance by an authorized representative with the requirements detailed in Enclosure 2 provides sufficient protection for the rights of submitters of privileged information.

Your efforts to provide EPA with this requested information at your earliest convenience would be greatly appreciated. If you have any questions regarding this request, please contact Mr. Peter Schindler at (919) 541-5501.

Sincerely,

Stanley T. Cuffe, Chief
Industrial Studies Branch

CONCURRENCE Emission Standards and Engineering Division

SYMBOL		SSS		ESB			
SURNAME	Jenkins	Schindler		Cuffe			
DATE		11/14/84		11/19/84			

EPA Form 1320-1 (12-70)

OFFICIAL FILE COPY

ENCLOSURE 1

Please provide all of the information which may be available concerning these topics:

- Average feed rate and average product pull rate at each furnace during a melt cycle.
- Feed rate of $Na_2Cr_2O_7$ or other chromium-containing additive (lb/ton of virgin feed).
- Cullet ratio-percent recycled from product.
- Percent chromium in finished product.
- Individual furnace stack parameters
  - diameter
  - temperature
  - gas flow rate
  - height
  - height of tallest building within one stack height
- Any other emission test results on chromium from glass furnaces at Gallo or other plants.

STATE OF CALIFORNIA
AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

GEORGE DEUKMEJIAN, Governor

June 18, 1985

Ms. B. J. Kirwan
McClintock, Kirwan, Benshoof,
Rochefort, and Weston
611 West Sixth Street, Suite 2100
Los Angeles, CA 90017

Dear Ms. Kirwan:

Comments on Draft Chromium Report

Thank you for the comments and suggestions of the Ad Hoc Environmental Group of the glass industry on the Draft Chromium Report. We have referred their comments on Part B to the Department of Health Services (DHS) for response. Their comments, the DHS response, and this letter will be included in Part C of the Report to the Scientific Review Panel on Chromium. You will received a copy of that report. I am responding to their comments in the same sequence in which they appear in your letter.

Page 4, paragraph 2: Several people commented, as you did, that estimation of excess cancer burden based on the assumption that all ambient chromium is hexavalent is confusing or inappropriate. Consequently, to reduce the possibility of confusion, we have, in revising the report: 1. removed the table entitled "Excess Cancer Burden . . ." (overview, page 9); 2. deleted discussions of excess cancer risk presented which are based on the assumption that all ambient chromium is hexavalent; and 3. provided an estimate of a range of excess cancer risk from ambient hexavalent chromium based on measured chromium(VI) concentrations.

Please note that the Department of Health Services has revised the upper-bound dose-response relationship, and that the ranges of excess cancer risk presented in the overview have been changed accordingly.

Page 5, paragraph 2 and 3: We understand your sensitivity to possible public perception that all chromium may be "toxic." We have endeavored throughout the draft report to maintain a distinction between chromium(VI) and other forms of chromium, whenever technical data allowed such a distinction to be made. In cases where a lack of adequate data on the form or state of chromium in a particular usage or emission precludes its classificaton as chromium(IV) or chromium(III), we have so indicated, and used the more general term "chromium" or "total chromium."

In the draft Report, we present the required estimates of usage and emissions of chromium (differentiated as to its oxidation state, wherever possible). Estimation of cancer risk due to chromium(VI) is based directly on measured ambient air concentrations of total and hexavalent chromium and subsequent exposure assessment. The fact that current limited knowledge of certain sources does not permit the classification of chromium emissions as hexavalent or otherwise, does not affect the estimation of cancer risk from measured ambient chromium exposure, nor does it "increase it... beyond the facts," as you state. In the Draft report, the emission estimates and the exposure assessment used to estimate excess cancer risk are independent.

We believe the information presented in the draft report on usage and emissions of chromium, and specifically on chromium(VI), is adequate along with the exposure assessment and DHS health effects information, to justify listing chromium(VI) as a toxic air contaminant. A major part of any control effort for chromium(VI) will be a refinement of the emissions inventory, including direct measurement of emissions to detect and measure mass emissions of chromium(VI) from various source types.

Page 6, paragraph 3: Thank you for the information that there are six green glass manufacturers in California. We will change our report to reflect this fact. Your statement that, "At this time, all green glass colorant used is iron chromate or trivalent chrome," is unclear. Typically, iron chromite, which contains chromium in the trivalent state, or hexavalent chromium, are used as green-glass colorants. If iron chromate is being used in California, we would appreciate further information on its usage, because ARB source tests indicate that processes using chromate colorants have a greater potential for hexavalent chromium emissions.

Page 7, paragraph 1: The data concerning chromium(VI) emissions from a large green glass manufacturer and cited in the

report are from a final ARB report (given as ref. I-19 in the Draft Chromium Report) which received public review and which was modified to address the comments received. Further testing of that large green glass manufacturer is scheduled because formulation changes have occurred which may affect chromium(VI) emissions. Based on information supplied by industry, the information gathered in April, 1984 on chromium(VI) emissions from that large green glass manufacturer may not represent current emissions; however, we believe that the 1984 test data are technically supportable, and are representative of emissions from the plant at the time of the tests.

Page 7, paragraph 2: The ARB's interest in potential chromium(VI) emissions from clear glass plants is supported by EPA or EPA-sponsored reports indicating that greater than trace levels of chromium(VI) had been measured in the emissions of clear glass plants; these were cited as references 20 and 21 of Section I of Part A of the Draft Report on Chromium.

Subsequent to the issuance of the draft chromium report, data became available on chromium (hexavalent and total) emissions from a clear glass plant in California. As you indicated, emissions of chromium(VI) were very low in this test. We will indicate this in the revised report. Any decisions on the source types to be evaluated for controls will be made during the control development phase. We expect additional data from ARB and industry emissions testing of glass plants will be available if we do proceed to a control development phase for hexavalent chromium .

Page 7, paragraph 3: The emissions listed in Table I-1 for refractory production were trivalent chromium. We have estimated maximum chromium(VI) emissions based on the detection limits of the source test performed for chromium(VI) at Kaiser plant, and will indicate in the Report that emissions of chromium(VI) are less than that amount.

Page 8, paragraph 2: Estimates of chromium(VI) emissions from glass manufacturing were not included in Table I-1 of the Draft Report because there is insufficient evidence available to make an accurate estimate of statewide emissions, not because the source category is believed to be insignificant. We have clarified this in the report.

We note that in the letter from Peter J. Schindler of the U.S. EPA to Mr. Robert Drake (dated December 12, 1984) which you attached to your comments as exhibit 6, Mr. Schindler states:

"In addition to th previously identified 11 source categories, EPA is attempting to gather information on other sources of chromium emissions to determine if they may require further study as separate source categories. Included among these other sources are glass melting furnaces."

We believe the omission of the glass industry in Table 3-6 of the "Health Assessment Document for Chromium" reflected a lack of information by EPA on emissions from the industry and is not an implicit statement that glass plants do not have the potential to emit chromium, or that these emissions are, or are not, significant.

Page 9, paragraph 2: An EPA sponsored test, cited as reference 20 in Part I, indicates that chromium was emitted from a green glass furnace in which chromium(VI) colorants were used; the oxidation state of the chromium was not specified. Because the information is not specific to chromium(VI), and because ARB testing of a California green glass plant using chromium(VI) colorants showed significant chromium(VI) emissions, reference to the EPA sponsored work in regard to this point has been removed from the report.

Page 9, 10 (conclusion): The best available emission data and usage information on chromium(VI) have been used in the report. Where data were insufficient to permit classification of chromium emissions as hexavalent, total chromium was reported, and deficiencies or uncertainties in the data identified in the report. Any control decisions will be made during a control development phase, if chromium(VI) is identified as a Toxic Air Contaminant by the Air Resources Board.

Again, thank you for your comments. You may contact Cliff Popejoy at (916) 323-8503 if you have further questions.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: Peter D. Venturini

Chevron U.S.A. Inc.
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May 14, 1985

W. T. Danker
Manager, Environmental Programs
Environment, Safety, Fire and Health

COMMENTS ON ARB/DHS
DRAFT REPORTS ON CHROMIUM

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA

Dear Sir:

Chevron has reviewed the draft reports on Chromium and we appreciate the opportunity to comment prior to submitting the reports to the Scientific Review Panel. The following summarizes our major observations on both "Part A - A Review of Chromium Uses, Emissions and Public Exposure" and "Part B - Health Effects of Chromium." More detailed comments prepared by our experts at Chevron Research Company and the Chevron Environmental Health Center are included as attachments.

PART A

The overly concervative assumptions made in the selection and handling of exposure data result in an estimated exposure level of hexavalent chromium that may be as much as a factor of six too high. When this overly concervative exposure estimate is coupled with the Department of Health Service's dose response data, the result is an estimated population risk that is also a factor of six too high (See items 1 and 2 on Attachment I).

PART B

The epidemiology studies used as a basis for the Department of Health Service's risk assessment may be adequate for a qualitative evaluation of health risk, but each of the studies sited has at least one major defect which seriously limits its use as a basis for quantitative risk assessment (See Attachment II). Therefore, we believe:

1) It is premature to produce statistical estimates of risk based on current data, and

2) Risk management decisions should not be made until sufficient data is available to make a quantitative risk assessment.

We hope these comments will be of value in revising your draft documents. If you have any questions, please contact Mark Nordhiem at (415) 894-6107.

Sincerely,

W.T. Danker/mwn

ATTACHMENT I

CHEVRON COMMENTS ON THE AIR RESOURCES BOARD DRAFT "PART A" REPORT ON CHROMIUM

1. The Air Resources Board Staff report recommends that only hexavalent chromium be listed as a Toxic Air Contaminant since there is insufficient evidence that trivalent chromium causes cancer. However, annual ambient concentration estimates used to predict excess cancer rates are based on measurements of total chromium. At the same time, the Part A report states that recent ambient data show hexavalent chromium represents up to one-third of the total chromium present in the air. Therefore, the estimated ambient concentrations of hexavalent chromium and the resulting predicted cancer rates are unrealistically high by at least a factor of three.

2. The ARB measured chromium in nine cities during 1982-1983. However their program did not cover a full year. For this reason, the annual ambient concentration estimates for chromium are based on 1977 monitoring data from EPA's National Aerometric Data Bank. These measurements were originally obtained from various public agencies, which probably used a variety of collection and analysis methods. For the three cities included in both data bases, average chromium levels measured by CARB are a factor of two lower. Therefore, using the EPA data results in predicted cancer rates that may be a factor of two high. When this effect is combined with the effects of item one above, the result is a cancer risk estimate that may be a factor of six too high.

3. The relative magnitude of hexavalent chromium emissions from various sources needs to be better defined before an effective control program can be devised. Cooling tower emissions illustrate this point. According to the draft report, they may be responsible for as little as 0.6% or as much as 20% of total chromium emissions from stationary sources. A more precise estimate is required to determine whether controls should be considered for this source category.

ATTACHMENT II

CHEVRON COMMENTS ON THE DEPARTMENT OF HEALTH SERVICES DRAFT "PART B" REPORT ON CHROMIUM

Following a review of the DHS/EPA risk assessment for chromium, we are concerned that the epidemiology studies cited by both the DHS and EPA are inadequate for the quantitative estimation of cancer risk associated with ambient airborne concentrations of chromium. Each of the studies selected has at least one characteristic (such as questionable quantitation and speciation of airborne chromium levels, concurrent exposure of the cohort to known carcinogens, and poor cohort definition) which seriously limits their utility for quantitative risk assessment. Most of these characteristics tend to overestimate the risk. The use of questionable data as the basis for a risk assessment can only result in estimates of dubious accuracy. For this reason, we believe it is both premature to perform rigorous mathematical estimates of risk based on the available data and misleading to present such estimates to risk managers as accurate. Our concerns for each of the studies cited are outlined below.

Pokrovskaya, et. al.:

1. In reviewing this study EPA concludes "although this study showed a significant increase of lung cancer mortality over the control group, the validity of the data is questionable because the study cohort is not clearly defined." Thus, it is inappropriate to use this data for a rigorous risk assessment.

2. In addition to chromium, the study's authors reported that workers were exposed to other potentially carcinogenic substances including benzo (a) pyrene and furnace gases. No attempts were made to account for these confounding factors.

Axelsson, et. al.:

1. The authors of this study concluded that there was no association between employment in the ferrochromium industry and risk of respiratory cancer. Thus this data is theoretically useful only in calculating an upper-bound estimate of potency.

2. Because of the confounding effects of smoking and exposure to asbestos (two of the four cases of respiratory cancer observed were diagnosed as mesotheliomas), no definite conclusions should be drawn from this study.

Langard, et. al.:

1. Ambiguity exists over the authors' classification of the observed cases of "lung cancer." This raises questions as to the authors' comparisons of observed and expected cases. If the observed number of "lung cancer" cases includes mesotheliomas, then the stated "lung cancer" risk due to chromium may instead be a partial reflection of the asbestos exposure believed to have also occurred in this cohort.

2. Measurements of airborne chromium levels were not taken until 1975, and may seriously underestimate the actual ambient levels to which most of the workers were exposed. EPA states that "These concentrations are used in our potency caluclations, with the understanding that the potency so estimated can only be considered an upper-bound estimate" (emphasis added).

3. As in the Pokrovskaya study, these ferrochromium workers may have been exposed to two other carcinogens, asbestos and polycyclic aromatic hydrocharbons.

Mancuso:

1. In reviewing this study, the EPA concludes that the observed association between chromium exposure and lung cancer is "based on very small numbers, and thus the findings of a dose-response is probably questionable."

2. Two factors that may result in an overestimation of the risk association with exposure to chromium from the application of this study's results are:

   a. The 1949 industrial hygiene data used in this study may underestimate the workers' exposure.

   b. An implicit assumption was made that the smoking habits of chromate workers were similar to those of the general white male population.

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

June 13, 1985

Mr. W. T. Danker
Manager, Environmental Programs
Chevron U.S.A., Inc.
575 Market Street/P. O. box 7643
San Francisco, CA 94120-7643

Dear Mr. Danker:

Comments on Part A of the Draft Chromium Report

Thank you for your comments and suggestions on the Draft Chromium Report. The Department of Health Services will prepare responses to your comments on Part B. Those responses, this letter, and your comments will be included in Part C of the Report to the Scientific Review Panel. We will send you a copy of that report. Briefly, our response to your comments in Attachment I to your letter are as follows:

1. Several people commented, as you did, that the application of dose-response data for hexavalent chromium to total ambient chromium concentrations provides estimates of excess cancer risk which, because they represent worst case or upper bound estimates, are unrealistically high. We have revised the overview to include estimates of excess cancer risk which reflect current knowledge of ambient hexavalent chromium concentrations. The resulting risk estimates are approximately one-third the value of the upper-bound estimates.

Please note that the Department of Health Services has revised the upper-bound dose response relationship, and that the ranges of excess cancer risk have been changed accordingly.

The ARB is working to better characterize ambient levels of chromium(VI) in California. As more temporally and spatially specific data on chromium(VI) concentrations becomes available, it will be possible to make a better estimate of the health impact of ambient chromium(VI).

2. Ambient concentrations of total chromium measured by the ARB in 1982-83 are lower than those in the EPA National Aerometric Data Bank for 1977 because different sampling methods were used. The EPA data is from samples collected using high-volume samplers, which collect particulate matter less than 50 micrometers (um) in diameter; ARB data is from samples collected using dichotomous samplers, which collect particulate matter less than 10 um in diameter (inhalable particulate).

The difference between EPA and ARB data is indicative of a difference in sampling techniques which provide information on the particle size distribution of chromium particulate, rather than of differences in ambient chromium concentrations.

3. We agree that an improved emissions inventory will be an important part of any control program for hexavalent chromium. A decision on whether or not to require controls on specific source types will be made during the control measure development phase.

Again, thank you for your comments. If you have any questions, please contact Cliff Popejoy of my staff at (916) 323-8503.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: Peter D. Venturini

Diamond Shamrock

May 14, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
Sacramento, CA 95812

RE: March 1985 Draft
Report to the Scientific Review Panel on Chromium

Dear Mr. Loscutoff:

This letter is submitted to forward comments on the above-referenced draft Report to the Scientific Review Panel on Chromium. These comments should be considered as being additional to those previously submitted by our Mr. Ralph Temple.

If you have any questions on these comments, please let me know at (214) 922-2739 on the letterhead address.

Sincerely,

Mel Skaggs

M. M. Skaggs, Jr.
Technical Manager, Environmental Affairs

/kdv

MAY 16 RECD

COMMENTS ON PART A, SECTION III.
AMBIENT CONCENTRATIONS IN THE COMMUNITY

1. "Non-Detectable" Data Handling: All ambient samples which contained non-detectable chromium levels were entered into the analysis as positive values. These data points were assumed to be equal to "one-half of the lowest non-zero concentration measured" (Page III-1). This assumption forces the data set minimums to be 4 ng/m3 of chromium. This method appears to have little merit or statistical support, particularly where the data is then fed into a linear carcinogenicity model.

2. Chromium Valence State: This report bases its cancer incidence assessment on the assumption that ambient chromium is entirely hexavalent in form. This assumption is invalid, particularly in light of the unreported S.C.A.B. data reported on Page III-8. This non-peer reviewed data is quoted as showing that only approximately one-third of the ambient chromium is hexavalent. Thus, the total chromium figures from Table III-1, III-2, III-3, III-4, III-5 and III-6 should be evaluated in this context.

3. Synergism of Assumptions-Cancer Risk: The two assumptions objected to above operated synergistically to bias the entire analysis. To see the problems with these paired assumptions, one should examine the application of these assumptions to the zero ambient chromium theoretical condition. In this case, while absolutely no chromium would be present, the model would be based on uniform assumed values of 4 ng/m3 (all hexavalent). Application of these assumed values to Figure A (Page 8) would result in an "estimated excess cancer burden" of 130 to 18,000 cases. Thus, despite an absence of environmental chromium in this hypothetical case, the model used would predict major public health impacts.

4. Monitoring Site Location: The monitoring sites at which the ambient chromium data were collected were not justified by modelling or other means as being appropriately located to be representative of the public exposure in their respective areas. Without such siting qualification, the assumptions of population exposure made on Page III-8 through III-19 are invalid. Impacts from intermittent local sources, which would normally disqualify air quality monitoring sites, were in fact used to explain away data variabilities. Thus, without a clearer examination of the monitoring site locations, nearby sources, and local meteorology, one should disallow much of the data as not being representative of the nearby populated areas.

5. Data Accuracy: Page III-19 states that "the accuracy of the chromium measurements is undocumented". Any data presented without adequate quality controls should be removed, as should any data not subjected to prior peer review.

STATE OF CALIFORNIA
AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

GEORGE DEUKMEJIAN, Governor

June 17, 1985

Mr. M. M. Skaggs, Jr.
Technical Manager, Environmental Affairs
Diamond Shamrock Corporation
717 North Harwood Street
Dallas, TX 75201

Dear Mr. Skaggs:

Comments on Draft Chromium Report

Thank you for your comments on the Draft Chromium Report. Your comments and our responses will be included in Part C of the Report on Chromium to the Scientific Review Panel. We will send you a copy of that report. Our responses to your numbered comments are as follows:

1. Non-Detectable Data Handling

The replacement of zero values in the EPA National Aerometric Data Bank data used for the exposure assessment with a value one-half of the lowest reported non-zero concentration was done to provide a better estimate of average concentrations than would be the case if the zero values were either eliminated from consideration, included as zero, or included as being equal to the lowest non-zero concentration measured during the year. The percentage of observations at each site reported as zero ranged from 3 to 77. The overall average percentage of concentrations reported as zero was 27. Two-thirds of the sites (10 of 15) had 33 percent or fewer zero values, and one-third of the sites (5 of 15) had fewer than 10 percent zero values.

2. Chromium Valence State

Several people commented, as you did, that the application of dose-response data for hexavalent chromium to total ambient chromium concentrations provides estimates of excess cancer risk, which, because they represent worst case or

upper-bound estimates, are invalid. We have revised the overview to include estimates of excess cancer risk which reflect the current knowledge of ambient hexavalent chromium concentrations. The resulting risk estimates are approximately one-third the value of the upper-bound estimates.

Please note that the Department of Health Services has revised the upper-bound dose-response relationship, and that the ranges of excess cancer risk have been changed accordingly.

The data on hexavalent chromium concentrations in the South Coast Air Basin which were used to estimate risk from ambient chromium(VI) were based on ARB method 106, Procedure for the Sampling and Analysis of Atmospheric Hexavalent Chromium(VI). We have included a copy of Method 106 in Appendix D of Part A. A limited interlaboratory study of this method has shown agreement within 25 percent. Method development for chromium(VI) analysis is presently being done by the Inorganic Toxics Analytical Subcommittee of the Toxics Air Monitoring Technical Advisory Committee (TAMTAC) which is comprised of technical representatives of Federal, State, and local air quality and public health agencies.

3. Synergism of Assumption Cancer Risk

The two assumptions which you object to were discussed above; in summary, we believe the use of one-half the lowest non-zero concentration measured for observations reported as zero yeilds the best estimate of concentration possible using existing information. In addition, data on ambient hexavalent chromium concentrations were used to estimate a range of risk from hexavalent chromium. Because estimates of hexavalent chromium emissions indicate that hexavalent chromium is emitted to the atmosphere of California, the "hypothetical case" of "zero ambient chromium" is unlikely. Efforts are underway to better characterize ambient chromium(VI) concentrations at sites throughout the state. As additional data become available, we will be able to better assess the public health impact of ambient chromium(VI).

4. Monitoring Site Location

The monitoring sites at which the EPA NADB data were collected were established to provide data reflecting population-oriented chromium concentrations.1/

Discussions of peak-to-mean ratios of TSP chromium and of di-chot fraction chromium were incuded in the report to provide an indication of the homogeneity of source areas.

Because chromium(VI) at the levels observed in ambient air is expected to have a chronic effect, the lifetime exposure or dose to the individual is used to estimate health impact. Therefore, intermittent sources of chromium(VI) are significant and should be considered in estimating population-oriented exposure. Based on these factors, we believe the data is representative of population exposure, and its use is appropriate.

5. Data Accuracy

While the absolute accuracy of the EPA database is not documented, certain procedures have been implemented to provide for reliable data. The chromium data were originally sampled and analyzed by a number of different agencies; these agencies presumably applied acceptable quality assurance practices during the collection and analysis phases. Additionally, after the data were received by EPA, they were subjected to several checks[2/] to assure accuracy and completeness: edit checks, to determine whether the data met minimum completeness requirements; data validation, to determine whether the data reflect true or realistic situations based on guidelines values, reasonable range checks, etc.; and certification, review of data after validation. We feel that the EPA data used to assess exposure was collected using adequate quality controls, and that review by various agencies represents sufficient peer review.

Thank you again for your comments. If you have any questions, please contact Cliff Popejoy, at (916) 323-8503.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Peter D. Venturini

Attachment

References

1. U.S. EPA, December 1984, Aeros Manual Series, V5: Aeros Manual of Codes, 3rd ed. EPA-450/2-76-005B. U.S. EPA National Air Data Branch, Research Triangle Park, NC.

2. U.S. EPA, February 1976, Aeros Manual Series, V1: Aeros Overview, EPA-450/2-76-001, U.S. EPA, Office of Air and Waste Management, Research Triangle Park, NC.

PACIFIC GAS AND ELECTRIC COMPANY

PG&E

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H. M. HOWE
CHIEF SITING ENGINEER

May 13, 1985

Mr. William V. Loscutoff, Chief
Toxics Pollutants Branch
Re: Chromium
California Air Resources
Board (ARB)
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Comments on Draft Chromium
Risk and Exposure Assessment

PGandE supports the draft assessment's apparent conclusion that only hexavalent chromium could be considered for possible identification as a toxic air contaminant at this time. However, PGandE suggests that conclusion should be more clearly stated, and the rest of the report should be more consistent with that conclusion.

In August 1984, the Environmental Protection Agency (EPA) final chromium risk assessment concluded on page 2-11 that trivalent compounds have not been reported to be carcinogenic by any route of administration. In its Part B report, the Department of Health Services (DHS) concluded that there is inadequate data to confirm or refute the carcinogenic potential of trivalent chromium. Nevertheless, the Part B summary concludes "The DHS recommends that the ARB take the increased carcinogenic risk from exposure to chromium$_3$ (emphasis$_1$ added) as$_3$ falling in the range of 3.0×10^{-3} to 9.3×10^{-1} per $\mu g/m^3$." That recommendation is the most important part of this entire assessment. PGandE suggests that it be clarified that the DHS is not recommending applying hexavalent chromium based risk estimates to all chromium compounds.

The EPA assessment also concluded that hexavalent chromium compounds have not induced lung tumors by inhalation (page 2-11). We understand the health protective concerns which have caused the DHS to nevertheless recommend that hexavalent chromium be regulated as if we were certain it

created the upper bound health risks implied by some epidemiological studies. But the overview table entitled "Estimated Excess Cancer Burden to Selected California Populations" fails to acknowledge that the actual risk may be zero. This is particularly misleading since one of the "health conservative" estimates is labeled as "low." It should be clarified that this is the lower upper bound, not an absolute lower bound, estimate. A footnote should also be added acknowledging the uncertainties of these health protective risk extrapolations and the possibility that the risk might actually be zero.

PGandE is disappointed that the "best" burden estimate is based upon an assumption that all ambient chromium is hexavalent when the only data cited indicates that only one-third of the ambient may be hexavalent. The ARB should either delay finalizing the report until it has better data or should base its "best" estimate on the best data available. In any event, it is clearly inappropriate to apply the 100% hexavalent assumption to any "low" estimate.

Table I-1 in Part A lists sources of chromium emissions. PGandE suggests that the ARB expand that table to include HIGH, BEST, and LOW estimates of the fraction of total chromium emissions from each source believed to be hexavalent. Absent data to the contrary, PGandE suggests that the ARB should rely upon the conclusion, implied on page 2-3 of the final EPA assessment, that oil combustion sources are unlikely to be sources of hexavalent chromium.

PGandE appreciates this opportunity to comment on the draft chromium assessments. Please call Mr. J. T. Holcombe at (415) 972-6910 if you have any questions regarding these comments.

Sincerely,

Hal Lowe

EPA-600/8-83-014F
August 1984

Health Assessment Document for Chromium

Final Report

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

2. SUMMARY AND CONCLUSIONS

2.1. INTRODUCTION

Trivalent Chromium (Cr III) is considered an essential micro-nutrient at relatively low levels, largely because chromium deficiency results in a buildup of glucose in the blood. At much higher levels, certain hexavalent chromium (CrVI) compounds are known to be carcinogens. Thus, chromium is unique among the metallic elements, given its paradoxical roles in both nutrition and carcinogenesis. The seemingly contradictory information on the effects of chromium is being clarified through increasing understanding of the role of the differing oxidation states and types of chromium compounds, which apparently determine the relative risks and benefits to human health of chromium in its various forms.

In the ambient environment, however, most of the monitoring information has provided only total elemental chromium levels. Outside of occupational settings, only limited information exists on the types of chromium compounds to which the public is exposed, although the trivalent form is known to be predominant. The assessment which follows focuses on several key areas which bear on the kind and extent of effects associated with chromium compounds: sources and concentrations of important chromium compounds (particularly Cr(III) and Cr(VI)); measurement methods; pharmacokinetics and essentiality; toxic effects in man and animals; and carcinogenic risks.

2.2. FORMS, SOURCES AND CONCENTRATIONS OF CHROMIUM

Chromium is a metallic element which occurs in nature primarily as the mineral chromite; elemental chromium does not occur naturally. Chromium exists

in four oxidation states, but only two of them, Cr(III) and Cr(VI), appear to be important, owing to their predominance and stability in the ambient environment. All forms are influenced greatly by pH, which affects the solubility and subsequent reactivity of chromium ions. Trivalent chromium is chemically basic, while hexavalent chromium is acidic.

Trivalent chromium is the most stable oxidation state, and the most important chemically. Its foremost characteristics are its ubiquitousness in the environment as part of the earth's crust, and its tendency to form kinetically inert hexacoordinate complexes. It reacts with aqueous hydroxides to form insoluble chromium hydroxide. Hexavalent chromium is the second most stable state, but the most important toxicologically. It occurs rarely in nature, apart from man's intervention, because it is readily reduced to Cr(III) in the presence of organic matter. It is quite soluble, existing in solution as a complex anion. However, in certain soils and natural waters, it can remain unchanged for protracted periods of time.

Chromite ore is not mined in the United States, but Cr(VI) chemicals are produced from imported ores, amounting to 21% of total U.S. chromium consumption. Metallurgical processes constitute approximately 60%, and refractory uses about 18%. Little direct information exists on the speciation of chromium compounds in the environment, because of the limitations of existing measurement methods (as described below). Accordingly, knowledge of chromium chemistry and its sources must be relied on in estimating the relative ambient contribution of different species. Direct sources include chemical and refractory plants; indirect sources include fossil fuel combustion, waste incineration and cement plant emissions.

Some source categories are likely to emit both trivalent and hexavalent forms of chromium. These are steel, refractory, chemicals manufacturing, as well

as sewage sludge and municipal incineration. Cooling towers and chrome plating facilities emit hexavalent chromium, and chromium ore refining, ferro-chromium production, cement production, and coal and oil combustion are likely to be sources of trivalent chromium. Maximum annual average ambient (total) chromium levels within 20 kilometers of these sources range from approximately 0.01-13.50 $\mu g/m^3$.

Background ambient air concentrations of total chromium have ranged from as low as 0.005 ng/m^3 (at the South Pole) to 1.1 ng/m^3 in other remote areas of the world. In the United States, recent monitoring of the ambient air in many urban and non-urban areas has shown total chromium concentrations averaging in the range of approximately 0.005-0.157 $\mu g/m^3$. The maximum 24-hour average concentration found for any one site was 0.684 $\mu g/m^3$ in the Baltimore, MD area. Because Cr(III) is highly stable and Cr(VI) reacts over time to form Cr(III), it is assumed that most chromium in ambient air occurs in the trivalent state. Monitoring of both the species and oxidation states of chromium in the ambient air should be a priority for future research.

The chromium concentration in U.S. waters varies with the type of surrounding industrial sources and the type of underlying soils. An analysis of approximately 4,000 tap water samples in representative U.S. cities showed chromium concentrations ranging from 0.4 to 8 ppb. Chromium levels in soil vary with soil origin and degree of contamination from anthropogenic sources. Tests on domestic soil have shown chromium concentrations ranging from an average of 14-70 ppm. Because the amount of chromium in food and food plants is relatively low, and because chromium does not appear to accumulate in mammalian systems, bioaccumulation in the soil-plant-animal system does not appear to be a significant exposure source.

2.3. MEASUREMENT METHODS

One of the main problems in assessing the effects of chromium on human health is the lack of adequate methods to measure the types and amounts of chromium compounds. Prior to 1978, urinary chromium levels fell within the range of 2 to 20 µg/ℓ. In 1971, radio-tracer experiments indicated that approximately 0.5-1% of the chromium was absorbed throught the digestive system. Accordingly, chromium excretion of 10 µg/day would correlate with a chromium intake of 1-2 mg/day. However, few diets contain more than 100 µg/day chromium; this anomaly was resolved by showing that the background collection capabilities of the analytical methods used to measure chromium (atomic absorption) were inadequate for chromium determinations.

Several methods are available for measuring elemental chromium in both environmental and biological samples. These include atomic absorption spectroscopy, instrumental neutron activation analysis, X-ray fluoroescence, and particle-induced X-ray emissions (PIXE). While these methods are sensitive to the ppb level, problems in sample collection, preparation and interferences are shared by all. In biological samples, neutron activation analysis data tend to be lower than atomic absorption and X-ray fluorescence data. In environmental samples, neutron activation analysis data are higher. Generally, a comparison of the results indicates that modified atomic absorption spectroscopy provides relatively reliable analyses. Another problem in chromium determination is the lack of adequate reference materials. Ideally, reference materials should match the samples to be analyzed with respect to chromium levels and each reference composition. Because the materials are not yet standardized, inter-laboratory comparisons are difficult.

Techniques for monitoring hexavalent chromium are also subject to considerable error. For example, although the OSHA colorimetric method is the

most commonly used analytical tool, particularly in occupational settings, low sample recoveries have been reported in chromium levels of less than 10 µg.

2.4. PHARMACOKINETICS AND ESSENTIALITY

2.4.1. Absorption, Transport and Excretion. An understanding of the role of chromium as an essential nutrient and causative agent in toxicity and carcinogenicity requires knowledge of the rates of absorption, mechanisms of absorption, transport and organ distribution of the various chromium-containing compounds. There are three primary routes of entry for chromium into the human body. For most people, the gastro-intestinal (GI) tract is the primary route of uptake, while in occupational exposures the airways and skin are the most important routes of uptake. Rates of uptake in the GI tract depend on a number of different factors, such as the valence state of chromium in the compound, the water solubility of the compound and the passage of time through the tract. Uptake in the airways is also influenced by the particle size distribution of the inhaled aerosols, and on factors which govern the clearance time of the lung.

Limited work on humans has been carried out on the relationship between exposure to trivalent chromium compounds and lung uptake and urinary excretion of chromium. In one study on workers exposed to chromium lignosulfonate, it was demonstrated that while chromium in the chromium lignin was present in the trivalent state, it acted pharmacokinetically like water soluble Cr(VI) compounds. An average of 14 µg/ℓ of urine was excreted, at an atmospheric chromium lignin concentration of 50 µg chromium/m^3. One to two percent of the inhaled chromium was excreted in the urine.

For Cr(VI), the urinary chromium concentrations corresponding to an airborne concentration of 50 µg/m^3 Cr(VI) were 40 µg/ℓ in one study, and 10 to 20

µg/ℓ in another. It was noted that chromium-bearing particles stay longer in the airways in smokers than in non-smokers.

The established normal levels of chromium in whole blood and in serum have declined with time, reflecting the changes and improvements in analytical methods. In the airways and in the GI tract, soluble Cr(VI) compounds are apparently taken up by epithelial cells by simple diffusion through the plasma membrane. After entry, Cr(VI) reduction occurs from the action of enzymatically mobilized electrons, which are available from GSH, NADPH, and NADH. The reducing capacity inside the cell is limited, so that Cr(VI) and Cr(III) exist simultaneously inside the cytoplasm; Cr(VI) is then released from the cell by simple diffusion into the blood stream and taken up into blood cells. In spite of the refined methods of analysis available, a reliable range of normal blood chromium concentrations cannot be given with confidence. When using modern methods for analysis, the whole blood concentration may be suggested to be within the range of 0.5 to 3 ppb, while the serum level is probably below 0.2 ppb.

The chromium concentration in human tissues has been shown to decrease with increasing age. In contrast to this, chromium concentrations in the lung have been shown to increase with age. This increase in chromium content in the lungs may be due to deposition and retention of insoluble chromium-containing particles from the inhaled environmental air, as well as from tobacco smoke.

2.4.2. Essentiality of Chromium. Animal studies have demonstrated that chromium-deficient rodents gain less weight and have a shorter life-span than animals maintained on a diet containing adequate chromium values. Chromium deficiency results in glucose intolerance in rats. This intolerance can be reduced with dietary treatment with Cr(III). In humans, symptoms of chromium deficiency consist of glucose intolerance, weight loss and confusion. Those

prone to chromium deficiency include the elderly, diabetics, pregnant women, malnourished children, offspring or siblings of diabetics and persons with early coronary heart disease. Although the exact level of chromium needed for good health is not known, the average American intake of 50 to 200 µg/day is considered adequate because at such levels symptoms associated with chromium deficiency are not observed. It should be noted that there is a considerable difference between the low levels of intake that are associated with nutritional deficiency and the high levels of exposure which are associated with toxic effects.

2.5. EFFECTS OF CHROMIUM ON BIOLOGICAL SYSTEMS AND HEALTH

2.5.1. Toxic Effects in Man and Animals. The effects of both Cr(III) and Cr(VI) have been studied in man and animals. Both long-term and short-term exposure conditions have been investigated, but most of the long-term exposures have focused on carcinogenic effects (discussed in Section 2.5.2. below).

The relative chemical inactivity of Cr(III) compared with Cr(VI) correlates with various acute toxicity studies on chromium salts. Oral LD_{50} (dose lethal to 50% of recipients) levels in rats have been reported to range from 135 mg/kg to 11,260 mg/kg for Cr(III). As seen in the previous section on pharmacokinetics, the relatively high amounts of Cr(III) which are required to cause death arise from the relative insolubility and poor intestinal absorption of most Cr(III) compounds. Unlike the trivalent compounds, those of Cr(VI) tend to cross biological membranes fairly easily, and are somewhat more readily absorbed through the gut or through the skin. The strong oxidizing powers of Cr(VI) compounds explain much of their irritating and toxic properties.

Exposure to Cr(VI) has been associated primarily with renal damage. For humans no quantitative evidence of acute toxcity through oral ingestion has been

reported. In various animal species, single injections of 2 mg/kg caused cellular and structural damage in the kidneys.

The effects of chromium on the skin were recognized over 150 years ago. Many chromium compounds can damage the skin, but metallic chromium or chromium alloys are chemically inert and are not harmful. The effects of chromium compounds on the skin are caused primarily by direct contact. Most of the effects have occurred in occupational settings, and, as expected, with more men than women reporting effects. Cr(VI) derivatives can cause ulcers of the hands and accompanying perforations of the nasal septum. Allergic contact dermatitis may arise from exposure to either trivalent or hexavalent chromium, although hexavalent chromium is responsible for most of the reported cases. Cr(VI) penetrates undamaged skin, and subsequently reduces to Cr(III) which combines with proteins or other skin components to form a whole skin allergin.

Effects on the upper respiratory tract have been observed in workers in chromium-related industries. The major effects of chromium on this system include ulceration of the nasal septum, with subsequent perforation, and chronic rhinitis and pharangitis. Early studies indicated that approximately one-half to four-fifths of the workers in chromate plants had perforated nasal septa, at levels of exposure that approached 1 mg/m^3. Subsequent work indicated that chromic acid levels exceeding 0.1 mg/m^3 also caused perforated septums in some workers.

Limited work has been reported on reproductive effects of chromium. Cr(VI) and Cr(III) have been found to cross the placental barrier in animals (hamsters and mice) and enter the fetus during mid to late gestation. Fetal uptake of Cr(VI), however, was much greater than that of Cr(III). Developmental effects attributed to both Cr(VI) and Cr(III) differed between hamsters and mice, and included such external abnormalities as cleft palate and skeletal defects, and

(in one study of a Cr(III) compound) neural tube defects. One researcher concluded that Cr(VI) occurred at sufficiently high fetal concentrations to cause direct effects on embryonic structures, but also questioned whether all of the teratogenicity and fetal toxicity associated with exposure to Cr(III) might be attributed to extra-embryonic effects, for example, those on placental tissues.

2.5.2. Genotoxicity, Carcinogenicity and Assessment of Risk.

2.5.2.1. GENOTOXICITY -- In recent years, much evidence has accumulated to show that compounds of chromium possess the ability to cause transformations and mutations, as evaluated in a wide variety of in vitro assays such as the reverse and forward mutation, gene conversion, and DNA modification tests. Genotoxic effects have been demonstrated primarily for chromium compounds containing the Cr(VI) species, including effects such as:

-- Mutagenic responses in bacterial strains.

-- Morphologic changes in mammalian fetal cells.

-- Cytogenic effects on mammalian bone marrow cells.

-- Increased gene conversion in yeast species.

-- Increased transformation frequencies in mammalian cells.

-- Chromosomal damage in cultures of human lymphocytes.

In general, soluble Cr(VI) compounds are less active in the presence of metabolic activating systems. The reduction of Cr(VI) to Cr(III) by cellular agents in metabolic activation systems, in part, explains the reduced mutagenic activity of Cr(VI) in the presence of such activating systems. Some recent evidence implicating both Cr(VI) and Cr(III) in induced mutagenesis has been reported in DNA interaction and DNA polymerase infidelity assays, and several tests with apparently pure Cr(III) samples have found chromosomal aberrations.

STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
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SACRAMENTO, CA 95812

June 18, 1985

Mr. H. M. Howe
Chief Siting Engineer
Pacific Gas & Electric Company
77 Beale Street
San Francisco, CA 94106

Dear Mr. Howe:

Comments on Draft Chromium Report

Thank you for your comments and suggestions on the Draft Chromium Report. We have referred your comments on Part B to the Department of Health Services for response, which, along with your comments and this letter, will be included in Part C of the Report on Chromium to the Scientific Review Panel. We will send you a copy of that report. I am responding to your comments in the same sequence as in your letter.

Page 2, paragraphs 1 and 2: We recognize that the overview table, "Estimated Excess Cancer Burden...," overstates the health impact of ambient hexavalent chromium, because it presents the worst (or upper-bound) case. The table has been removed from the overview. Also, the discussion of excess cancer incidence based on the assumption that all atmospheric chromium is hexavalent has been deleted. We have included an estimate of excess cancer incidence based on ambient chromium(VI) data.

Please note that the Department of Health Services has revised the upper-bound dose-response relationship, and that the ranges of excess cancer risk presented in the overview have been changed accordingly.

Page 2, paragraph 3: Because the fraction of chromium(VI) in total chromium emissions is not known with certainty for some sources, we feel that it is not justified in this report to separately list emissions for hexavalent

chromium. We have included whatever information is available on hexavalent chromium emissions in the discussion of emissions for each source. We have revised the report to reflect, in the discussion of fuel-combustion related emissions, that chromium emitted from oil combustion is probably chromium(III). Further research, including source testing to directly measure chromium(VI) and total chromium emissions from oil combustion and other sources, will be an important part of any control program for chromium(VI).

Again, thank you for your comments. If you wish to discuss these comments, or have further questions on the report, please call Cliff Popejoy at (916) 323-8503.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch

cc: Peter D. Venturini

Western Oil and Gas Association
727 West Seventh Street, Los Angeles, California 90017
(213) 627-4866

May 20, 1985

BY FEDERAL EXPRESS

William V. Loscutoff
Chief, Toxic Pollutants Branch,
Stationary Source Division
Air Resources Board
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Sacramento, California 95814

Re: Comments on Draft Report to the Scientific Review Panel on Chromium

Dear Bill:

The Western Oil and Gas Association ("WOGA"), a trade association whose members conduct much of the producing, refining, transporting and marketing of petroleum and petroleum products in the western United States, thanks you for the opportunity to submit comments on the draft report to the Scientific Review Panel ("SRP") on chromium. WOGA's review of the draft report leads us to the conclusion that while available epidemiologic data may support a qualitative decision to list hexavalent chromium (chromium VI) as a toxic air contaminant, the available data simply are not of sufficient quality to develop quantitative risk estimates or to form the basis for future risk management.

California law directs the Department of Health Services ("DHS") and the ARB to evaluate the health effects of substances considered for listing as toxic air contaminants and states that the evaluation shall include, among other things, an assessment of the quality of data on health effects. (Health & Safety Code Section 39660(c).) WOGA believes that when, as here, the quality of the available data is questionable, the evaluation should recognize that fact and qualify the conclusions drawn in an appropriate manner. In this way, the accuracy and the confidence that can be placed in the risk estimates will be communicated to the reader of the report. This approach also avoids unduly alarming the public by overstating risks in situations such as this, where relatively high risks are predicted on the basis of results of

questionable studies, some of which even showed negative results.

Also, even if chromium VI is listed as toxic air contaminant, as recommended in the draft report, it should not be a foregone conclusion that regulation of emission sources will be required. WOGA asks that the statement on page 10 of the Overview that the identification of chromium VI as a toxic air contaminant will lead to the adoption of toxic control measures be changed to read that identification may lead to the adoption of such measures. This will conform to the statute, which requires that after a substance is listed as a toxic air contaminant, the staff must assess the "need and appropriate degree of regulation" (Section 39665(a)). It will also reflect comments made by ARB members at the January 25, 1985 public hearing on benzene at which it was stated that the Board members did not feel compelled to adopt regulations to control benzene simply because it had been listed as a toxic air contaminant.

With these general thoughts in mind, WOGA submits the following comments on Parts A and B of the draft report.

Part A -- A Review of Chromium Uses, Emissions and Public Exposure.

WOGA's primary concern is with the estimates of average ambient concentrations of chromium in California and their use in the draft report. It appears that the average ambient levels used are too high and that total chromium exposures are given instead of just hexavalent chromium. The end result is that, based on these factors alone, the population risk estimates are six times higher than they should be.

The draft report recommends that only chromium VI be listed a toxic air contaminant, but the ambient exposure data used is for total chromium and therefore the resulting population risk estimates are based on total chromium. The draft report indicates that a maximum of one-third of total chromium is hexavalent chromium, based upon measurements conducted by the ARB in the South Coast Air Basin last year. There is further support for this fact in the Langard study

relied on by the Department of Health Services.[1] That study found that hexavalent chromium comprised approximately 11 to 33% of total chromium emissions in the industrial setting studied.

It also appears the ambient concentrations given for total chromium are too high. The report uses 1977 monitoring data from the Environmental Protection Agency's ("EPA") national aerometic data bank. The staff report states that these measurements were taken throughout California by various public agencies (federal, state and local). The data were collected at different times, by different agencies and, presumably, analyzed by different laboratories. The draft report states that "the accuracy of data contained in the EPA database is not documented." (Draft report at III-1.) The draft report then references more recent data collected by the ARB. The ambient levels recorded by ARB are approximately one-half of those shown by EPA. WOGA believes that this more recent data is more reliable and should have been used in place of the more questionable EPA database.

The use of the EPA database and total, rather than hexavalent, chromium significantly overstates actual exposures to chromium VI. If chromium VI exposure levels were used to develop the population risk estimates, the estimates would be approximately one-third of those shown in the staff report. Likewise, if the more recent ARB ambient monitoring data were used in place of the EPA data, the population risk estimates would be one-half of those estimated by the ARB staff. When both factors are combined, the resulting population risk estimates are six times higher than they should be. This significant overestimate of population risk underscores the need to develop a more accurate picture of ambient chromium VI levels before a population estimate can be developed for use in the risk management phase.

It should also be noted that the draft report states that "intake of chromium from ambient air represents by far the most significant exposure route to chromium, especially for chromium (VI)." (Page III-22.) This does not appear to be accurate based on other information provided in the draft report. For example, the report states that "chromium intake from a typical American diet of 43% fat was determined to be

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[1] Langard, S., A. Andersen and B. Gylseth. 1980. Incidence of Cancer Among Ferrochromium and Ferrosilicon Workers. British Journal of Industrial Medicine 114-120.

68 ± 28 ug/day; from a typical American diet of 24% fat, intake of chromium was determined to be 89 ± 56 ug/day." (Page III-21.) Ambient concentrations are approximately 15 ng/m^3 (annual average; Draft Report, Overview, page 4). When the ambient concentrations are multiplied by the amount of air breathed on a daily basis (20 cubic meters/day), the daily exposure to chromium is .3 ug as a result of daily breathing. This is far less than the amounts estimated to occur as a result of diet.

Lastly, more detailed information is needed on emissions of chromium VI from individual point sources. The relative magnitude of chromium VI emissions from sources such as cooling towers needs to be much better defined before it can be determined if a control program is necessary. The draft report estimates that emissions from cooling towers account for between 0.6% to 20% of total chromium emissions from stationary sources. Obviously, this is an imprecise estimate. In addition, WOGA suspects that the effect of chromium VI emissions from cooling towers may be highly localized. Further investigation needs to be undertaken to determine whether chromium VI emissions from cooling towers are carried outside plant boundaries into the ambient air in any appreciable quantities. WOGA offers to participate in such an investigation.

Part B -- Health Effects of Chromium

The epidemiological studies upon which the DHS bases its risk estimates for chromium are not adequate for developing mathematical estimates of risk. Each of the studies relied upon is seriously flawed for one or more reasons. However, these flaws are not adequately discussed by the DHS nor are the risk estimates derived from the studies appropriately qualified.

The limitations in each of the studies used by DHS will be discussed. However, each study is flawed in one of the following general ways:

1. Questionable quantitation and speciation of the exposure estimates. The exposure data is sketchy and is often obtained from a period later than when the cohort was exposed. Therefore, the exposure levels given are probably lower than the actual exposures. From the reports, it is difficult to determine the percentage of chromium VI, even where exposure levels are given or estimated.

2. Exposure to other carcinogens. Confounding factors for lung cancer, principally cigarette smoke or asbestos, were not controlled. The level of "excess risk" supposedly contributed by chromium (unspeciated) is therefore not clear. At the very least, the "unit" risk estimates should be revised to account for these factors or they should be used to qualify the accuracy of the risk estimates.

3. Poor definition of the cohort. In most of the studies, the cohort was loosely defined. For example, there are serious questions as to whether some of the workers studied were exposed to chromium VI at all and the duration of such exposure, if any.

In the paragraphs that follow the major shortcomings of each of the study will be discussed.

1. Pokrovskaya. EPA concludes that "although this study showed a significant increase of lung cancer mortality over the control group, the validity of the data is questionable because the study cohort is not clearly defined." Thus, the study should not be used as a data source for risk estimates. In addition, the study authors reported that workers were exposed to other potentially carcinogenic substances, but no attempts were made to account for these confounding factors.

2. Axelsson. The authors of the study concluded that there was no association between employment in the ferrochromium industry and risk of respiratory cancer. Thus, this study cannot be used in risk estimation. Also, because of the confounding effects of smoking and exposure to asbestos (two of the four cases of respiratory cancer observed were diagnosed as mesotheliomas), no definite conclusions can be drawn from this study about chromium exposure and cancer.

3. Langard. Members of the cohort were also exposed to asbestos. Thus, the author's classification of the observed cases of "lung cancer" is not clear because some of the observed number of cases could have been caused by asbestos instead of chromium and could have included mesotheliomas. In addition, measurements of airborne chromium levels were not taken until 1975 and may seriously underestimate the actual ambient levels to which most of the workers were exposed. EPA's review states that "these concentrations are used in our potency calculations with the understanding that the potency so estimated can only be considered an upper bound estimate." Also, as in the

Pokrovskaya study, the ferrochromium workers may have been exposed to two other carcinogens, asbestos and polycyclic aromatic hydrocarbons.

4. Mancuso. The DHS risk assessment is based primarily on this study, which examined the relationship between exposure to chromium and lung cancer in approximately 300 men employed in a chromate plant between 1931 and 1937. EPA's own review of the study, however, concluded that the observed association between chromium exposure and lung cancer is "based on very small numbers, and thus the finding of a dose-response is probably questionable." The risk associated with exposure to chromium from the application of this study may be overestimated because of the use of 1949 industrial hygiene data and the fact that although lung cancer death was a major outcome of interest, no smoking histories were available for the study cohort.

The 1949 industrial hygiene study mentioned above found the ratio of trivalent chromium to hexavalent chromium to be six. Since only total chromium exposure was measured, and trivalent chromium exposure was assumed to be meaningless, the upper bound of the risk estimate was determined by increasing the "best" estimate by seven fold. On the other hand, EPA felt (and DHS agreed) that using the industrial hygiene data from 1949 may have resulted in overestimating the true exposure levels.[2] Therefore, the "best" estimate was divided by two as part of the procedure to determine the lower bound of risk. The use of such unjustified factors in quantitative risk assessment to produce specific unit risk estimates creates substantial uncertainty.

In addition, the Mancuso study did not include data on exposures that workers may have had to substances in the plant other than chromium or information on substances the workers may have been exposed to at other facilities or in other occupations.

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[2] The DHS states that the authors of the 1949 industrial hygiene study "noted that it was unlikely that the exposure levels experienced by the study cohort were appreciably different from those measured at the time of their exposure assessment study." However, the EPA review cites the authors of the study as stating that there seem to be "little doubt that atmospheric contamination in the past was greater than in 1949."

Because of these deficiencies, the use of the data from any of the studies as the basis for risk assessment results in risk estimates that are of dubious validity. It is misleading to present the risk estimates derived in the draft report as plausible upper bounds. The DHS estimates, if used at all, can only be referred to as "worst-case" estimates.

In this regard, it should be noted that the upper limit determined by DHS implies there is a 93% chance of getting cancer from exposure to one ug/m^3 of chromium. This risk estimate is clearly too high to be considered a reasonable estimate. An effect of this magnitude would have been detected in the epidemiologic studies and was not. Even though DHS concedes that the true risk is unlikely to exceed the upper limit of risk, WOGA believes that using 93% as an upper limit of risk does not provide useful information.

WOGA is also concerned about the potential ramifications of listing a substance as a toxic air contaminant when it is not possible to estimate, with any degree of confidence, the risks posed by exposure to ambient levels of the substance. If risk cannot be quantified, it is not possible to make the cost-benefit analysis required in the risk management phase or to decide whether regulation is necessary at all. For this reason, we suggest that chromium VI be moved from a level 1A compound to a level 2 compound until further information is available to quantify the risk estimates.

In conclusion, while the epidemiological data available may support a purely qualitative decision to list chromium VI as a toxic air contaminant, they cannot be used for quantitative risk estimates or to support the decision to regulate emission sources of chromium VI. In addition, the use of ambient data for total chromium, rather than chromium VI, and the use of EPA's ambient data which is twice the ARB levels, overstates the population risk at ambient levels.

Very truly yours,

Robert N. Harrison/s/

Robert N. Harrison
Assistant General Manager

RHN:wm

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AIR RESOURCES BOARD
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GEORGE DEUKMEJIAN, Governor

June 17, 1985

Mr. Robert N. Harrison
Assistant General Manager
Western Oil and Gas Association
727 West Seventh Street
Los Angeles, CA 90017

Dear Mr. Harrison:

Comments on Draft Chromium Report

Thank you for your comments and suggestions on the Draft Chromium Report. We have referred your comments on Part B to the Department of Health Services for response. Their response, your comments, and this letter will be included in Part C of the Report to the Scientific Review Panel on Chromium. We will send you a copy of that report. I am responding to your comments in the same order as in your letter.

Page 2, paragraph 1: We agree, and have changed the report to reflect the fact that identification of a compound as a toxic air contaminant does not compel the Board to adopt control regulations.

Page 2, paragraph 3 and 4: Several people commented, as you did, that the application of dose-response data for hexavalent chromium to total ambient chromium concentrations provides estimates of excess cancer risk which, because they represent worst case or upper bound estimates, are too high. We have revised the overview to include estimates of excess cancer risk which reflect current knowledge of ambient hexavalent chromium concentrations. The resulting risk estimates are approximately one-third the value of the upper-bound estimates.

Please note that the Department of Health Services has revised the upper-bound dose-response relationship, and that the ranges of excess cancer risk have been changed accordingly.

The ARB is working to better characterize ambient levels of chromium(VI) in California. As more temporally and spatially specific data on chromium(VI) concentrations become available, it will be possible to make a better estimate of the health impact of ambient chromium(VI).

Page 2, paragraph 4: The Langard study used by the Department of Health Services to derive a range of dose-response relationships dealt with the chromium pigment production industry. Because there are no chromium pigment production plants in California, it is unclear how the fraction of hexavalent chromium in chromium in the workplace air (or in emissions) of such plants relates to the fraction of hexavalent chromium in total atmospheric chromium in California.

Page 3, paragraph 3: The draft report states that "the intake of chromium from ambient air represents by far the most significant exposure route to chromium, especially chromium(VI)."

As you point out, larger amounts of chromium are received daily in the average diet than are inhaled. However, dietary chromium occurs in the trivalent state, which according to the Department of Health Services, is poorly absorbed and for which there is only weak evidence of carcinogenicity. In comparison, chromium(VI) has been found by the Department of Health Services to be a human and animal carcinogen with no threshold; the theoretical lifetime cancer risk from a continuous 70-year exposure to atmospheric chromium(VI) ranges from 3 to 85 cases per million people per nanogram per cubic meter, with a best estimate of 12 cases per million people per ng/m^3. Because of this difference in health effects, intake of chromium (particularly chromium(VI)) from ambient air is more important or significant from a health effects standpoint than is chromium(III) intake in the diet.

Page 4, paragraph 2: We agree that an improved emissions inventory will be an important part of any control program for hexavalent chromium. A decision on whether or not to require controls on specific source types will be made during control measure development. We welcome WOGA's offer to participate in investigations of emissions of chromium(VI) from cooling towers, should such investigations be shown to be necessary.

Again, thank you for your comments. If you have any questions, please contact Cliff Popejoy of my staff at (916) 323-8503.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: Peter D. Venturini

DEPARTMENT OF HEALTH SERVICES RESPONSE TO COMMENTS:
CHROMIUM HEALTH EVALUATION DOCUMENT

COMMENT I. The meaning of the exposure parameter in the crude risk assessment model needs to be clarified -- substituting the potency factor into the risk model yields a relationship independent of dose (exposure) which is incorrect. (RN Hazelwood, IT Corporation)

Response: The risk assessment model yields a probability and thus is unitless. Therefore, when evaluating the model at a given exposure level, all exposure units cancel. This is exactly what the commenter has shown! The confusion lies in the notation used to describe the potency factor and the risk estimation model -- the exposure estimate used in deriving the potency factor and the exposure level at which the model is being evaluated are both denoted as "d." Thus, when the commenter substituted the potency factor into the risk model the identically designated exposure parameters algebraically cancelled implying that risk is independent of exposure. More appropriately, substituting the potency factor into the risk model yields a ratio of the two exposure parameters wherein the units of exposure will cancel but the risk is still a function of the exposure.

COMMENT II. The Department of Health Services (DHS) has not acknowledged or has not clearly presented the issues related to the quality of the epidemiologic studies used in the risk assessment. This is important because quantitative risk assessment should be based on the highest

quality epidemiologic studies or, in other words, focus on the most valid data. The studies used have deficiencies or problems related to the quantification and speciation of exposure levels, treatment of (potential) confounding factors, definition of the study cohort, definition of lung cancer, small study populations, and in one instance, a study did not find a statistically significant increase in cancer (and is therefore absurd to use in a quantitative risk assessment); therefore, these studies are not acceptable for use in quantitative risk assessment. (Southern California Edison (SCE); California Council for Environmental and Economic Balance (CCEEB); Diamond Shamrock; Allied Corporation; Chevron).

Response: The epidemiologic studies of the health effects of chromium were not designed for quantitative risk assessment. As such, the staff of DHS agrees with the commenters that the studies have deficiencies and limitations when used for this purpose. The staff of DHS also agrees with the commenters (and EPA) who said that the Mancuso study provided the best data for the carcinogenic risk assessment. Since DHS stated that it was adopting the EPA risk assessment (Part B, p 21) which includes discussions of data quality, the Part B report did not repeat this information in great detail nor does the staff of DHS feel such a discussion is warranted. It should be noted that summaries of the studies' limitations were presented (Part B, pp 22-24). However, specific areas of misunderstanding by some of the commenters will be discussed here.

First, the comment was made that in the Mancuso data based assessment, EPA did not adjust for the fact workers' exposures were less than a complete lifetime. This is incorrect as can be seen on pages 7-84 and 7-93 of the EPA report where the factors 8 working hours/ 24 hour day, 240 working days/year, and proportion of lifetime exposed (1/L) are applied to the occupational exposure level.

Second, in the Langard et al study, EPA used a estimate of the relative risk based on a comparison to a plant internal control group rather than using the general population as a reference group. The staff of DHS concurs with EPA in the choice of this control group since it provides the best controls for potential confounding variables such as smoking and socio-economic status.

Third, the inclusion of the Axelsson data was stated as being absurd because it failed to show a statistically significant increase in lung cancer. The staff of DHS acknowledges that the value of epidemiologic studies which do not demonstrate a "significant" effect is controverial; the interpretation ranges from evidence of a threshold to meaningless. However, the staff of DHS disagrees with this blanket statement made by the commenter; a methodologically sound study of this nature can be used with statistical theory to estimate measures of effect that are compatible with data, for example, the 95% upper confidence limit of risk.

In addition, the staff of DHS disagrees, with those commenters who said that the problems with these studies are of a nature that prohibit the use of the studies in quantitative risk assessment. Indeed, EPA has both invoked assumptions to compensate for the major problems in these studies and provided risk estimates based on the uncertainty in the data; with the exception of the Langard et al study (see Comment IV), the estimates of the potency factors are very similar. The effect of these adjustments is reflected in the upper and lower bounds of the theoretical risks presented in the health evaluation.

The staff of DHS further disagrees with the commenter who stated that quantitative risk assessments should strictly be based on the "highest quality epidemiologic studies" since in many cases these studies still do not provide sufficient data to quantify the dose-response relationship (e.g., no exposure data are given). In these cases, animal studies may provide the best estimate of human risk.

COMMENT III. DHS should more clearly state that the risk assessment applies only to the hexavalent form of chromium (Cr(VI)). (CCEEB; Pacific Gas and Electric Company (PG&E))

Response: The DHS risk assessment is strictly applicable to Cr(VI). The confusion seems to lie not in the body of the report but in the document's summary wherein the discussion of risk estimates does refer to Cr(VI) as

does the graphical display of the dose-response curves but the final sentence does not specifically state "hexavalent" chromium. The staff of DHS agrees that this sentence should be modified.

COMMENT IV. The range of risk provided by DHS is problematic; one commenter stated that the range was too broad because it inappropriately provided separate risk estimates derived from the upper and lower exposure levels while only a single risk estimate, based on the "best estimate," should have been given (SCE). Conversely, a different commenter (CCEEB) felt the range of risks provided was too restrictive, particularly for the lowest estimate; a range of risk of 8.4×10^{-4} cancer cases per ug Cr(VI) per cubic meter ambient air (the lower 95% confidence limit of the Mancuso data) to 1.3×10^{-1} cases/ug/m^3 (the unadjusted risk estimate from the Langard data) is more appropriate than the DHS range of 3.0×10^{-3} to 9.3×10^{-1} cases/ug/m^3. Other commenters (Western Oil and Gas Association; SCE) said that the upper potency factor resulted in risks that were unrealistically high.

Response: The staff of DHS takes exception to the first two statements. With regard to solely presenting the "best estimate," DHS notes that in doing so the assumption is made that there is little or no variability in a worker's exposure, a prospect that would appear very unlikely over an employee's career. Nevertheless, in the absence of complete data for any of

the chromium epidemiologic studies, it is not possible to accurately or precisely state the exposure with great certainty. Hence, the presentation of a single estimate implies that there is a greater degree of certainty with respect to the risk estimate than the data support. On the other hand, the reporting risk estimates based on the range of exposure levels, albeit an estimate of these levels, serves to demonstrate the effect of some of the uncertainty in the data at hand.

The staff of DHS does not agree that the 95% lower confidence limit of a risk estimate should be presented. Such a limit is misleading and attributes a greater certainty to the potential risk than is warranted because the risk is <u>not</u> necessarily bounded by this limit -- it may actually be zero.

The staff of DHS agrees with commenters who suggested that the upper risk level was too high. The upper limit of the potency estimates, $2.7/ug/m^3$, is derived from the Langard et al study. This epidemiologic study applied 1975 exposure data to a cohort of workers comprised of men who were alive as of 1953 and who may have begun working in the plant as early as 1928. In other words, the exposure data probably greatly underestimate the actual exposure which thereby results in an overestimation of the potency and risk. This is supported by the data in Table IV-1 which shows that the risk estimates from the Langard et al study are about 10 times greater than the estimates from the other studies. The EPA health evaluation noted this problem and pointed

out that the potency estimates derived from the Langard study should be interpreted as an upper bound of risk.

The DHS report should have made this explicit. Therefore, the staff of DHS will change Part B to emphasize that the Mancuso data are the focus of its risk assessment and that the other studies are provided for comparative purposes only, that is, because of their deficiencies, they will not be used to calculate the range of risk the staff of DHS recommends to the Air Resources Board.

COMMENT V. The unit risk estimated from the Mancuso study is too high due to the omission of the exposure experience of highly exposed plant maintenance workers, basing exposure levels solely on a 1949 industrial hygiene survey which greatly underestimates the previous 18 year levels and overestimates the subsequent 25 year levels, and fails to include exposure for the period following 1949. This has resulted in a 20-40 fold underestimation of exposure and hence a corresponding overestimation in risk. Animal studies support this overestimation and suggest that the overestimation may be in the range of 42-149 fold. (Allied)

Response: The commenter has raised some valid points but the magnitude of the effect may have been greatly exaggerated as will be shown below. (Since there is incomplete exposure data it is not possible to incontroverably resolve this issue.)

First, with respect to maintenance workers, the commenter has suggested that their omission has resulted in a 2-4 fold underestimate of exposure: ([3 hours of exposure/8 hour day] x [5-10 fold higher exposure levels]). The industrial hygiene survey shows that on the average, maintenance workers' exposures were 1-5 times as great as those of production workers (0.45 - 2.32 ug/m^3 versus 0.42 ug/m^3) with the higher exposures occurring during plant upsets. Since the survey noted that "most" of maintenance workers' time dealt with upsets, the staff of DHS will assume that their average exposure was 5 fold greater than production workers. An overall estimate of a 1.9 fold increase by applying the portion of the day exposed to these levels. The survey also noted that about 30% of the plant work force consisted of maintenance workers. Thus, the overall average exposure for all workers is equal to the weighted average of exposures of the production and maintenance workers or ([.70][X] + [.30][1.9X]) = 1.3X, where X is the exposure of the production workers. To summarize, the staff of DHS estimate that the omission of maintenance workers' exposures from the Mancuso data would maximally underestimate the exposure by a factor of 1.3 and not 2-4 times as the commenter has indicated.

Second, the commenter may have also overestimated the impact of the reliance on the 1949 industrial hygiene survey. As used in the EPA risk assessment, the 1949 data represent an average of the exposure for the time period 1931-74. The commenter believes that the pre-survey exposures were up to 5 times greater than at the time of the survey and though they dropped off

considerably in the following years, the post-survey exposure should not be considered equal to 0 as EPA did in their risk assessment. These factors are seen by the commenter to account for a 10 fold underestimation of exposure. However, weighting the exposures by the time periods they were estimated to be present (1931-1949 and 1950-1974) yields only a 2.1 - 2.7 fold underestimate: ([5X][.42] + [1X][.58]) = 2.7, where X is the 1949 exposure.

Thus, the data used in the Mancuso study are consistent with an overall possible exposure underestimation of 3.5 fold (1.3 x 2.7). Since the upper risk estimate for this data set includes a 2 fold correction for possible underestimation of exposure, the staff of DHS does not feel this unit risk is significantly overestimated.

The commenter also makes a comparison of risks between a rat intratracheal instillation bioassay of chromium with a benzo[a]pyrene control to the risks stated in the EPA report for these substances to support the assertion that the EPA risk estimate is too high. The ratio of benzo[a]pyrene risk to chromuim risk in the rat study ranged from 12 to 42 depending upon which cancers were included in the assessment, however, the EPA report shows chromium as being 3.6 times more potent than benzo[a]pyrene. The commenter then taking the rat study as "truth", that is, benzo[a]pyrene is 12-42 times more potent than chromium, and correcting for the "anomalous" high chromium risk calculated by EPA states that the EPA chromium risk estimate should be reduced by 42-149 times: ([3.6 x 12] to [3.6 x 42]). This analysis is

flawed for several reasons. First, the commenter has included a survival parameter in the risk model. The purpose of the parameter as originally derived is to compensate for the apparent reduced risk when a study is prematurely terminated. Its effect on the risk estimate is inversely related to the survival time. However, the rat study was a lifetime exposure bioassay hence, the survival parameter should not have been used. Recalculating the risk without this factor and using the data the commenter cites yields a benzo[a]pyrene-chromium risk ratio of 0.79, that is, as in the EPA report, chromium is a more potent carcinogen than benzo[a]pyrene. (Differences between the EPA cited potencies and those given by the commenter may be due different study protocols and uncertainties in extrapolating animal data to humans.) Furthermore, using the information provided by the commenter to calculate the survival factor yields average proportion of lifetime survived of 0.498 and 0.998 for benzo[a]pyrene and chromium exposed rats, respectively. However, Table 1 of the bioassay report states the average survival times were about 0.75 and 0.95 for the respective substances. Therefore, it is not clear how the commenter calculated the cited risks.

In summary, the arguments raised by the commenter do not support the assertion that the EPA chromium unit risk is too high.

COMMENT VI. Several comments were directed at the assumptions of the low dose extrapolation model. Specific points were raised concerning

linearity of the dose-response curve at low dose, whether evidence exists to support a dose-response relationship both in general and specifically at ambient levels, the appropriateness of using survival data not dependent on chromium exposure, and the model's inability to adjust for potential confounding factors. (CCEEB; Diamond Shamrock)

Response: While many assumptions were invoked to assess the carcinogenic risk posed by hexavalent chromium, by following the peer reviewed EPA report DHS has taken scientifically accepted positions. Nevertheless, a brief response to the issues raised by the commenters will be given.

First, the assumption of low dose linearity is not amenable to empirical verification in either human or animal species rather, it is an accepted scientific practice particularly when extrapolating from human data. As such, it is possible to estimate health effects at ambient levels from data obtained from higher exposure levels and to use a linear model to do so.

Second, with respect to the demonstration of a dose-reponse relationship, the paucity of worker exposure ("dose") information in epidemiologic studies and the lack of a good animal model for inhalation exposure for other species, even though each of these study groups has clearly demonstrated the carcinogenic potential of Cr(VI), has hampered attempts to show a dose dependent response. The observation that no relationship has been shown for ambient exposure levels is a function of several factors not the least of which is that it has not been looked for! Only one epidemiologic study was

found which addressed lung cancer and ambient chromium exposures. While this ecologic study found no association, several criticisms of this study are noteworthy: exposure data were sparse and did not differentiate between trivalent and hexavalent chromium although it was likely most of the exposure was to Cr(III), migration was considered unimportant when in reality it serves to diminish any association, and statistical power was low. Thus, the staff of DHS does not believe that the absence of evidence is sufficient evidence of the absence of a dose-response relationship.

Third, the meaning of the survival term in the competing risks model (A(s)) has been misinterpreted by the commenter. The probability of surviving to age s is contingent on not having died prior to this age from any cause including exposure to chromium (Cr(VI)). In other words, it implicitly includes the assumption that there has been and continues to be exposure. The risk of dying after age s is then the product of the probability of surviving to s and the risk of dying in this time interval from disease (cancer) related to the chromium exposure. This is what the formulation of the model shows (Part B, p 25).

Fourth, the commenter is correct in noting that the extrapolation models per se cannot directly adjust for covariates. However, that does not preclude indirect adjustment, as the EPA has done, for the effect of smoking in the Mancuso data or by excluding cases of mesotheliomas from the Axelsson data since they probably resulted from asbestos exposure. It is noteworthy that EPA's treatment of potential confounding variables is based on information

presented in peer reviewed scientific literature. In general, the staff of DHS finds it difficult to disregard a risk model which did not rigorously treat potential confounders, such as cigarette smoking and asbestos, even though the studies did not collect any data on these factors.

COMMENT VII. Comments were made regarding the statement that there was not sufficient evidence to demonstrate a carcinogenic threshold for Cr(VI). Several commenters stated that there was substantial evidence in support of this concept stemming from animal studies (which demonstrate site of contact tumors only and observing no (lung) tumors in 80 animals receiving 0.25 mg/kg sodium dichromate 5 days per week for life) and metabolism and/or detoxification studies of chromates (which show Cr(VI) reduced to Cr(III) under physiologic conditions and noting that Cr(III) is non-mutagenic). Further support comes from the existence of occupational threshold limit values (TLVs) and permissible exposure levels (PELs). (Allied; Diamond Shamrock; Ad Hoc Environmental Group (glass manufacturers))

Response: The staff of DHS does not disagree that one interpretation of the animal and metabolic studies cited is consistent with the concept of a carcinogenic threshold but, the information cited by the commenter is not conclusive proof that a threshold exists. Indeed, as one commenter stated, the animal and metabolic evidence "...does not permit quantification of the threshold or description of the dose-response relationship at low doses."

This suggests that even if a threshold exists, current data are insufficient to determine what that level would be. Moreover, the staff of DHS does not accept the argument that the existence of TLVs or PELs for chromium compounds support the threshold concept. The exposures denoted by TLVs and PELs represent acceptable exposure levels for the workplace and not threshold levels; indeed, the question of the existence of a carcinogenic threshold is not usually considered in setting these exposure levels. Also, because TLVs and PELs are developed for occupational settings, these standards allow for higher risks than are, as a rule, permitted for the general population under ambient exposures.

Therefore, in the absence of both the knowledge concerning the mechanism of action and conclusive proof to the contrary, the staff of DHS leans towards the health protective intent of California's Health and Safety Code section 39650 in saying a threshold has not been established for hexavalent chromium.

COMMENT VIII. The report should draw a clearer distinction between various Cr(VI) containing materials especially in terms of chromate pigments where there is evidence showing that not all chromate pigments provide the same hazard. For example, very insoluble lead chromate based pigments conveyed less cancer risk than the more soluble chromate compounds in an animal study. Indeed, one epidemiologic study showed no statistically

significant increase in cancer from the manufacture of lead chromate. (PA Wriede, Heubach Inc.)

Response: The staff of DHS acknowledges that the carcinogenic potency of different Cr(VI) compounds may not be identical, however, current epidemiologic data do not permit distinction among the compounds for purposes of quantitative risk assessment involving airborne exposure. Animal studies present the most suggestive evidence of a compound specific response. However, they are not used for the chromium risk assessment because of difficulties related to determining dose levels to use in the assessment where the route of exposure was implantation (see Part B, p 21 for further discussion of this point). With respect to the epidemiologic studies, few have attempted to distinguish among different compounds and those that have done so tended to be inadequately reported and include only small populations of workers. The International Agency for Research on Cancer (IARC) has concluded, and the staff of DHS concurs, that the current epidemiologic data do not allow an evaluation of the chromium carcinogenic risk based on compounds having different solubilities.

COMMENT IX. There is no human evidence that chromium compounds are associated with teratogenesis. The older animal studies which have reported teratogenic effects should be evaluated relative to dose and maternal toxicity. (Diamond Shamrock)

Response: The two teratogenic studies reported in Part B deal with subcutaneous and intravenous routes of exposure which are not directly applicable to environmental exposure to chromium. They were cited for completeness only. Based on these studies it is possible that Cr(VI) may be teratogenic but this would only occur at levels far exceeding ambient exposures or at doses which are maternally toxic.

COMMENT X. The modifiers "weakly" and "highly" should not be used to describe the mutagenic effects of chromium. The report should provide an indication as to how chromium compared to other mutagens. (Diamond Shamrock)

Response: The terms "weakly" and "highly" were used with reference to the number of test systems in which chromium gave a positive mutagenic response. Although qualitative in nature, since no positive controls were used in the assays, there are no data with which to more precisely describe the mutagenic activity of chromium relative to other mutagens.

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MANAGER OF ENVIRONMENTAL OPERATIONS

TELEPHONE
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September 24, 1985

Mr. Richard Bode
California Air Resources Board
1800 15th Street
P. O. Box 2815
Sacramento, CA 95812

Attention: MEMBERS OF THE SCIENTIFIC REVIEW PANEL

Subject: Report to the Scientific Review Panel on Chromium

Southern California Edison would first like to state that we believe the public was allowed insufficient time to review and prepare comments on this complex and important report. Members of the public had only three (or less) working days to review the revised report and prepare written comments. Although we obtained the report as soon as possible after receiving notice that it was available, it was not possible to submit comments to the ARB in time for them to reach panel members prior to the September 26 meeting. Panel members will now first review and consider public comments at their meeting held to take action on the document. We do not believe that this method of operation is in accord with the intent of AB1807. We recognize the ARB's desire to proceed with these reviews in a timely manner and realize the constraint of time schedules written into state law. We believe, however, that some provision must be made to allow public input to the process when the intent of the law was to do just that.

While we did not have sufficient time to prepare extensive comments, we offer the following general comments on the Report to the Scientific Review Panel on Chromium.

This report concludes that hexavalent chromium should be treated as a substance without a carcinogenic threshold. A recent publication on the metabolism of hexavalent chromium, which we have included as an attachment to these comments, should be considered in this context. Research by Petrilli et. al. (see attachment) indicate that, in addition to already recognized detoxification mechanisms operating outside target cells, specific and inducible chromium-reducing pathways mediating threshold phenomena in chromium carcinogenesis (e.g. mutagenesis) do also occur in the intracellular environment.

We wish to bring this recent data to the attention of the SRP since it can be useful in evaluating the carcinogenic potential of chromium compounds at low doses.

The Overview and Recommendation section of the DHS report states:

> "...the theoretical lifetime cancer risk from a continuous 70 year exposure to atmospheric hexavalent chromium (chromium VI) exposure ranges from 12 to 146 cases per million people per nanogram per cubic meter (ng/m^3)."

We feel this statement is very misleading. The commonly accepted meanings for the word "range" include "the full extent covered by something" or "to vary within specified limits" or "the class of admissable values of a variable". The values presented in this report represent only the mid-to-upper limits of risk. Consideration of factors such as the impact of smoking in the Mancuso study worker population or underestimation of their exposure to hexavalent chromium, factors which would lead to lower estimates of risk, have been systematically excluded in the development of this "range" (Section 8.3.8 - Summary of the Risk Assessment). A more factual estimate of the "range" of risk would extend from the lowest to the highest scientifically reasonable risk estimates. If a more conservative risk range estimate is proposed, the following statement, which currently appears on page 98 of Part B of the report, should be included in the Overview and Recommendation section.

> "The staff of the DHS does not present a lower confidence limit for potency estimates because the true risk may be considerably below even the lower boundary of the 95% confidence interval limit, yet there is no scientific basis for locating this risk."

SCE appreciates this opportunity to provide comments during the development of this important document. It is our hope that more time will be allowed for public input in the development of future reports.

Sincerely,

Edward J. Tosdal

[CANCER RESEARCH 45, 3179-3187, July 1985]

Specificity and Inducibility of the Metabolic Reduction of Chromium(VI) Mutagenicity by Subcellular Fractions of Rat Tissues[1]

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ABSTRACT

The mutagenicity of sodium dichromate in the Ames test was decreased as a consequence of chromium(VI) reduction by tissue postmitochondrial (S-9 or S-12) fractions from untreated rats with the following rank of efficiency: liver; kidney; and lung. The effects of lung preparations were significantly enhanced following the intratracheal administration of high doses (0.25 mg/kg) of dichromate itself, 5 times per week for 4 weeks (*i.e.*, 20 fractionated instillations). No changes were conversely detected following single weekly doses of 1.25 mg/kg for the same period (*i.e.*, four cumulative instillations). The local stimulation of chromium(VI) metabolism was also confirmed by testing the mutagenicity of calcium chromate and chromium trioxide, whereas the metabolism of a number of other activatable or deactivatable mutagens was not significantly affected by intratracheal treatment with chromium(VI). Of three enzyme inducers injected i.p. which modified the spectral properties and/or concentration of cytochromes P-450 in liver and lung microsomes, only Aroclor 1254 proved to stimulate chromium(VI) metabolism in lung cells. In liver cells, Aroclor 1254 and to a lower extent phenobarbital induced chromium(VI) reduction, while 3-methylcholanthrene was ineffective. Pretreatment of rats with these three compounds resulted in a selective induction of the metabolic activation of promutagens [benzo(*a*)pyrene and its *trans*-7,8-diol, 2-aminofluorene, aflatoxin B_1] and of the metabolic deactivation of direct-acting mutagens [2-methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl, epichlorohydrin, 4-nitroquinoline-*N*-oxide] by S-12 and microsomal fractions. These findings indicate that, in addition to already recognized detoxification mechanisms operating outside target cells (26), specific and inducible chromium-reducing pathways, mediating threshold phenomena in chromium carcinogenesis, do also occur in the intracellular environment.

INTRODUCTION

Both epidemiological and experimental data suggest that chromium compounds may possess carcinogenic properties (13, 14). However, an adequate demonstration of carcinogenicity in animals is available only for a limited number of chromium(VI) compounds, and no conclusion can be drawn about the responsibility of specific chromium compounds in inducing lung cancer in occupationally exposed individuals.

Short-term test systems have provided a useful tool for identifying potentially carcinogenic compounds and for elucidating their mechanisms. With very few exceptions, chromium(III) compounds have been reported to be inactive in cellular systems, while chromium(VI) compounds have been consistently found to exert, both *in vivo* and *in vitro*, mutagenic and clastogenic effects in a variety of prokaryotic and eukaryotic cell systems, as well as DNA damage and cell transformation (13, 14, 19, 25). In the Ames reversion test, once solubilized in water or alkali, all the chromium(VI) compounds tested appear to share very similar features, *i.e.*, the same spectrum of sensitivity of *his*⁻ *Salmonella typhimurium* strains, the same order of magnitude of mutagenic potency, as well as the same trend to a decrease of mutagenicity in the presence of metabolic systems (6, 26). These patterns clearly indicate the responsibility of the hexavalent ion in producing genetic effects. However, solubility of chromium compounds, when introduced into an organism under crystalline form, is expected to play an important role *in vivo* by affecting their rate of absorption, distribution, retention, metabolism, and clearance.

The metabolic fate of chromium is of particular concern for predicting and interpreting the *in vivo* effects of this metal. Since the first demonstrations that the direct mutagenicity of chromium(VI) can be decreased by rat liver S-9 fractions (5, 12, 20, 23), many efforts have been devoted to assay the possible interconversion processes between the hexavalent and the trivalent forms. In the past years, we have been investigating the mutagenicity of several chromium compounds in the presence of up to 40 metabolic systems, including body fluids and subcellular fractions from various tissues of humans and other animal species, also under the influence of special diets or treatments, diseases, or drugs. No metabolic activation of chromium(III) could be detected (24), while the mutagenicity of chromium(VI) was markedly decreased by liver preparations from humans, rodents (rat, mouse, hamster, woodchuck), chicken, and fish (Refs. 8 and 26; Footnote 3). Preparations from other tissues and body fluids were also capable, to a variable extent, of reducing chromium(VI) and of lessening its genetic effects.

In a separate paper (9), we are describing the possible biochemical mechanisms responsible for the metabolic reduction of chromium. In this paper, we provide evidence that this metabolic process is specific and that it can be selectively stimulated not only by known enzyme inducers but also, in lung cells, by the repeated i.t.[4] administration of high doses of chromium(VI) itself.

The data herein reported were obtained in 2 consecutive studies. The first one (referred to as Study A) aimed at assessing the decrease of chromium(VI) mutagenicity in the presence of

[1] This work was supported by CNR (Special Project "Oncologia") and by IHF Chromium Chemicals Environmental Health and Safety Committee.

[2] To whom requests for reprints should be addressed.

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[3] F. L. Petrilli, A. Camoirano, C. Bennicelli, P. Zanacchi, M. Astengo, and S. De Flora, unpublished data.

[4] The abbreviations used are: i.t., intratracheal; 2AF, 2-aminofluorene; AFB1, aflatoxin B_1; ANOVA, analysis of variance; AR, Aroclor 1254; BP, benzo(*a*)pyrene; BP 7,8-diol, benzo(*a*)pyrene *trans*-7,8-diol; DMSO, dimethyl sulfoxide; ECH, epichlorohydrin; G6PD, glucose-6-phosphate dehydrogenase; GSH, reduced glutathione; ICR 191, 2-methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine·2HCl; MC, 3-methylcholanthrene; PAH, polycyclic aromatic hydrocarbon; PB, phenobarbital; PCB, polychlorinated biphenyl; 4NQO, 4-nitroquinoline 1-oxide.

lung, liver, and kidney S-9 fractions from rats treated i.t., according to various schedules, with NaCl or sodium dichromate. The second (Study B) aimed at confirming the stimulating effects of i.t. dichromate on chromium(VI) pulmonary metabolism and at comparatively assessing the extent of its reduction by liver and lung S-12 fractions from rats treated i.p. with enzyme inducers. The spectra and concentrations of cytochromes P-450 were determined in the corresponding microsomal fractions. The efficiency and specificity of treatments were also checked by evaluating the ability of subcellular fractions in activating promutagens (BP, BP 7,8-diol, 2AF, AFB1) or in decreasing the mutagenicity of direct-acting compounds (4NQO, ICR 191, ECH) in the Ames test.

MATERIALS AND METHODS

Chemicals. Sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) used for the i.t. treatment of rats was obtained from Riedel-De Haen AG, Merck, Darmstadt, Federal Republic of Germany. It was dissolved, at the concentrations indicated in Table 1, in a 0.9% NaCl solution.

The 3 enzyme inducers, dissolved in corn oil, were PB (E. Merck AG), MC (Fluka AG, Buchs, Switzerland), and the PCB AR (Analabs, Inc., North Haven, CT).

The compounds assayed in the Ames test were sodium dichromate and chromium trioxide (CrO_3) (Merck-Schuchardt, Munich, Federal Republic of Germany), calcium chromate ($CaCrO_4$) (BDH, Poole, England), 2AF and BP (Ega-Chemie KG, Steinheim/Albuch, Federal Republic of Germany), BP 7,8-diol and 4NQO (kind gift of Dr. D. G. Longfellow, National Cancer Institute, Bethesda, MD), AFB1 (Sigma Chemical Co., St. Louis, MO), ECH (Carlo Erba, Milano, Italy), and ICR 191 (Polyscience, Inc., Warrington, PA).

Treatment of Rats. Treatment of 10-week-old male Sprague-Dawley rats was carried out at the Institute of Toxicology of Bayer AG (D-5600 Wuppertal, Federal Republic of Germany) by Dr. D. Steinhoff. The treatment schedule is reported in Table 1.

The i.t. application, consisting of a volume of 1 ml/kg body weight, was performed on rats anaesthetised with ether, as described in more detail by Steinhoff *et al.*[5] The rats were supplied with tap water and Altromin standard diet (Altrogge 4937 Lage) *ad libitum* throughout the period of treatments. During the last 12 h before sacrifice, rats were starved and permitted water.

Preparation of Subcellular Fractions. Irrespective of the treatment schedule, all the rats were sacrificed 24 h after the last i.t. or i.p. administration, with the exception of those receiving AR, which were killed 5 days after its injection. Lungs and liver (Study B) and additionally kidneys (Study A) were aseptically collected from each rat, following anesthesia with ether and killing by decapitation and bleeding. All the subsequent steps were carried out at 0–4°C, using sterile glassware and solutions and operating under aseptic conditions.

Immediately after removal, the organs were washed in flasks containing a 10 mM Tris-0.15 M KCl solution, pH 7.4, transferred into beakers containing 10 ml of the same solution, and finely minced with scissors. Minced organs were wiped on gauze, weighed, and immersed in 3 volumes (*i.e.*, 3 ml/g of wet tissue) of a 50 mM Tris-0.25 M sucrose solution, pH 7.4. Homogenates were prepared using a Potter-Elvehjem apparatus with glass tubes and Teflon pestles (5 strokes).

Homogenates were centrifuged twice for 20 min at 9,000 × *g* (Study A) or 12,000 × *g* (Study B). The supernatants (S-9 or S-12 fractions, respectively) were divided into small aliquots and stored at −80°C.

In Study B, aliquots of liver and lung S-12 fractions from each of the 6 experimental groups were further pooled, gauze filtered, and centrifuged twice for 1 h at 105,000 × *g* using 2 Beckman Spinco L2-65B ultracentrifuges. The microsomal pellet was resuspended, in the proportion of 0.5 ml per g of original tissue, in a 50 mM Tris-0.1 mM EDTA solution, pH 7.4, supplemented with 20% glycerol, divided into small aliquots, and frozen at −80°C.

The protein concentration in S-9, S-12, and microsomal fractions was measured according to the protein-dye method of Bradford (3).

Determination of Cytochromes P-450. The amounts and the spectral properties of cytochromes P-450 in liver microsomes were determined by means of the classic method (22), evaluating CO binding to cytochrome reduced with dithionite. Cytochromes P-450 in pulmonary microsomes were determined according to a specifically designed method (16), involving reduction of methemoglobin with ascorbate and phenazine methosulfate prior to bubbling CO and adding dithionite.

Mutagenicity Assays. The effects of the various subcellular fractions on the mutagenicity of chromium(VI) compounds were investigated in the Ames test, basically following the standard plate incorporation test (21). Since we have recently demonstrated that TA102, a newly developed *S. typhimurium* strain which is efficiently reverted by oxidative mutagens (18), is even more sensitive to chromium(VI) than TA100 (2), both strains were used in the more recent experiments.

Since the decrease of chromium(VI) mutagenicity is more pronounced following liquid preincubation with metabolic systems (9), dichromate (10 to 50 μg/plate in 100 μl of bidistilled water) was preincubated for 1 h at 37°C with subcellular fractions (20 to 200 μl/plate) incorporated in S-9 mix (0.5 ml/plate), prior to application on target cells and embedding in top agar. S-9 mix had the standard composition (21) when combined with S-9 or S-12 fractions, and it was supplemented with 4 IU of yeast G6PD when combined with microsomal fractions.

The other compounds tested were assayed at the concentrations and with the *S. typhimurium* strains indicated under "Results." Mutagens requiring metabolic activation (*i.e.*, 2AF, BP, BP 7,8-diol, and AFB1, all dissolved in DMSO) and a nonmutagenic chromium(III) compound (*i.e.*, chromium acetate, dissolved in water) were directly mixed with metabolic systems, bacteria, and molten top agar according to the standard procedure (21). Mutagens undergoing metabolic deactivation (*i.e.*, calcium chromate, chromium trioxide, ECH, and ICR 191, all dissolved in water, and 4NQO dissolved in DMSO) were preincubated with the metabolic systems as described for dichromate.

All the mutagenicity assays were performed in triplicate plates.

RESULTS

Effect of Treatments on Weight of Organs, on the Protein Concentration in S-9 and S-12 Fractions, and on Cytochromes P-450 in Liver and Lung Microsomes. As shown in Table 1, the i.t. treatments, either with NaCl or with sodium dichromate, had no significant influence, as checked both by ANOVA and by Student's *t* test, on the mean values of weight of organs and on the protein concentration in the corresponding S-9 (Study A) or S-12 (Study B) fractions. Conversely, the i.p. treatment with PB, MC, and AR resulted in a statistically significant increase in liver weight. Such increase was particularly pronounced in the case of AR, which additionally determined an increase in the protein concentration of the corresponding S-12 fractions (significant at the 0.05 level).

Table 1 also shows the wavelength of the peaks of cytochromes P-450 and their concentration in liver and lung microsomes obtained from the 6 experimental groups under scrutiny in Study B. The methods used proved to be very accurate in resolving and discriminating the peaks of cytochromes, as related to treatment of rats. In fact, the peak was consistently at 450 nm for the liver microsomes of untreated rats and of rats treated with NaCl, $Na_2Cr_2O_7$, or PB, while it shifted to 448 to 448.5 nm

[5] D. Steinhoff, S. C. Gad, G. K. Hatfield, and U. Mohr. Carcinogenicity study with sodium dichromate in rats, submitted for publication.

Table 1
Treatment schedule and effects on various parameters

Treatment	No. of rats	Chemical administered	Treatment schedule: Route	Amount/dose (mg/kg)	No. of doses	Frequency and duration	Wt of organs (g): Lungs	Liver	Kidneys	Proteins in S-9 or S-12 fractions (mg/ml): Lungs	Liver	Kidneys	Properties of cytochromes P-450 in microsomal fractions: Liver: Peak (nm)	Liver: Concentration (nmol/mg protein)	Lung: Peak (nm)	Lung: Concentration (nmol/mg protein)
Study A (S-9 fraction)	5	NaCl	i.t.	9	4	1/wk × 4	2.2 ± 0.3[a]	NT[b]	NT	13.6 ± 1.6	NT	NT	NT	NT	NT	NT
	5	$Na_2Cr_2O_7$	i.t.	1.25	4	1/wk × 4	2.5 ± 0.4	NT	NT	13.6 ± 1.6	NT	NT	NT	NT	NT	NT
	5	NaCl	i.t.	9	20	5/wk × 4	2.0 ± 0.3	10.4 ± 1.0	2.5 ± 0.2	14.3 ± 2.6	40.5 ± 4.4	11.0 ± 1.6	NT	NT	NT	NT
	5	$Na_2Cr_2O_7$	i.t.	0.05	20	5/wk × 4	2.2 ± 0.3	10.9 ± 0.8	2.3 ± 0.1	15.2 ± 1.6	36.0 ± 8.7	11.6 ± 1.4	NT	NT	NT	NT
	5	$Na_2Cr_2O_7$	i.t.	0.25	20	5/wk × 4	2.7 ± 0.2	10.9 ± 0.8	2.4 ± 0.1	14.8 ± 2.0	41.7 ± 8.7	12.8 ± 1.0	NT	NT	NT	NT
Study B (S-12 fraction)	10						2.0 ± 0.2	8.9 ± 0.6	NT	16.2 ± 0.5	43.6 ± 8.6	NT	450	0.89 ± 0.13	450–451	0.071 ± 0.014
	10	NaCl	i.t.	9	20	5/wk × 4	2.0 ± 0.1	8.5 ± 0.3	NT	17.2 ± 1.7	43.2 ± 5.4	NT	450	0.93 ± 0.14	450–450.5	0.066 ± 0.013
	10	$Na_2Cr_2O_7$	i.t.	0.25	20	5/wk × 4	2.2 ± 0.1	9.2 ± 0.8	NT	16.1 ± 1.2	40.6 ± 5.7	NT	450	0.84 ± 0.12	450–451	0.079 ± 0.014
	5	PB	i.p.	60	3	1/day × 4	2.0 ± 0.1	10.4 ± 0.6[c]	NT	15.7 ± 1.2	42.0 ± 8.4	NT	450	1.65 ± 0.16[c]	450–451	0.072 ± 0.009
	5	MC	i.p.	80	1	24 h before killing	1.9 ± 0.3	10.0 ± 0.9[d]	NT	16.9 ± 1.5	42.1 ± 4.6	NT	448–448.5	1.36 ± 0.08[c]	448.5–449	0.104 ± 0.020
	5	AR	i.p.	500	1	5 days before killing	2.2 ± 0.2	14.0 ± 0.7[e]	NT	16.6 ± 1.3	53.0 ± 3.0[f]	NT	449–449.5	2.87 ± 0.33[e]	449–450	0.109 ± 0.009[d]

[a] Mean ± SD.
[b] NT, not tested.
[c] Significant at $P < 0.01$ by Student's t test as compared to untreated rats.
[d] Significant at $P < 0.05$ by Student's t test as compared to untreated rats.
[e] Significant at $P < 0.001$ by Student's t test as compared to untreated rats.
[f] Significant at $P = 0.05$ by Student's t test as compared to untreated rats.

in samples from MC-treated rats and to 449 to 449.5 nm in samples from AR-treated rats. The peaks yielded by lung microsomes showed the same or a slightly increased wavelength (0.5 to 1 nm), as compared with liver microsomes.

The concentration of cytochrome P-450 was considerably higher (11- to 24-fold, depending on treatment of rats) in liver than in lung microsomes. The 2 procedures used for liver (22) and lung (16) preparations yielded similar figures, from both qualitative and quantitative standpoints, when comparatively assayed with liver microsomes. The mean increase in cytochrome P-450 levels in hepatic microsomes (based on 3 to 5 assays per sample) was significant in animals treated i.p. with the 3 enzyme inducers and was particularly pronounced in the AR group. Both MC and AR induced a slight increase in P-450 concentration also in pulmonary microsomes, but such increase was statistically significant for the latter inducer only. Neither NaCl nor $Na_2Cr_2O_7$ i.t. affected to a significant extent P-450 levels in liver or lung microsomes.

Decrease of Dichromate Mutagenicity in the Presence of Lung, Liver, and Kidney S-9 Fractions from Rats Treated i.t. with NaCl or with Dichromate Itself (Study A). In the absence of metabolic systems, sodium dichromate induced a dose-related mutagenic response in strain TA100 of *S. typhimurium*, with a narrow range of active concentrations (20 to 40 μg/plate) and occurrence of toxic effects (absence or marked sparing of the background lawn of bacterial growth) at 50 μg/plate. Addition of S-9 mix containing lung, kidney, or liver S-9 fractions from the variously treated rats resulted, to a variable extent, in an evident decrease of mutagenicity and in the conversion of toxic into mutagenic effects at the highest dose tested. An example of results obtained is shown in Chart 1.

In particular, liver preparations (which were examined only in the 3 groups of animals treated 5 times per week) were the most efficient in decreasing dichromate mutagenicity. At 100 μl/plate (Chart 1), their preincubation with dichromate, even at 50 μg/plate, resulted in an almost complete loss of mutagenicity, without any significant difference among the 3 i.t. treatments under scrutiny. Even by lowering the amounts of liver S-9 fractions to 50 or 25 μl/plate (data not shown), in order to obtain an incomplete reversal of mutagenicity, no significant difference could be detected among the 3 groups ($F > 1$, $P > 0.05$).

The kidney S-9 fractions obtained from the same 3 experimental groups were clearly less active than liver S-9 fractions in decreasing dichromate mutagenicity but, despite the slightly lower protein concentration (see Table 1), they were more efficient than the corresponding lung preparations (Chart 1). As for the liver, no significant difference ($F > 1$, $P > 0.05$) could be detected by preincubating varying amounts of chromium(VI) with S-9 fractions pooled within each group (Chart 1), nor in other experiments evaluating the metabolic activity of all the individual kidney preparations with fixed amounts of chromium(VI) (data not shown).

Lung S-9 fractions were prepared from the animals treated i.t. for 4 weeks with NaCl or varying amounts of dichromate, once per week (2 groups) or 5 times per week (3 groups). The ANOVA revealed significant differences, on the whole ($F = 59.62$, $P < 0.001$), in the number of revertants induced by varying amounts of dichromate in the presence of S-9 fractions pooled from the 5 experimental groups. In particular, orthogonal comparisons of the mean values shown in Chart 1 provided evidence that the

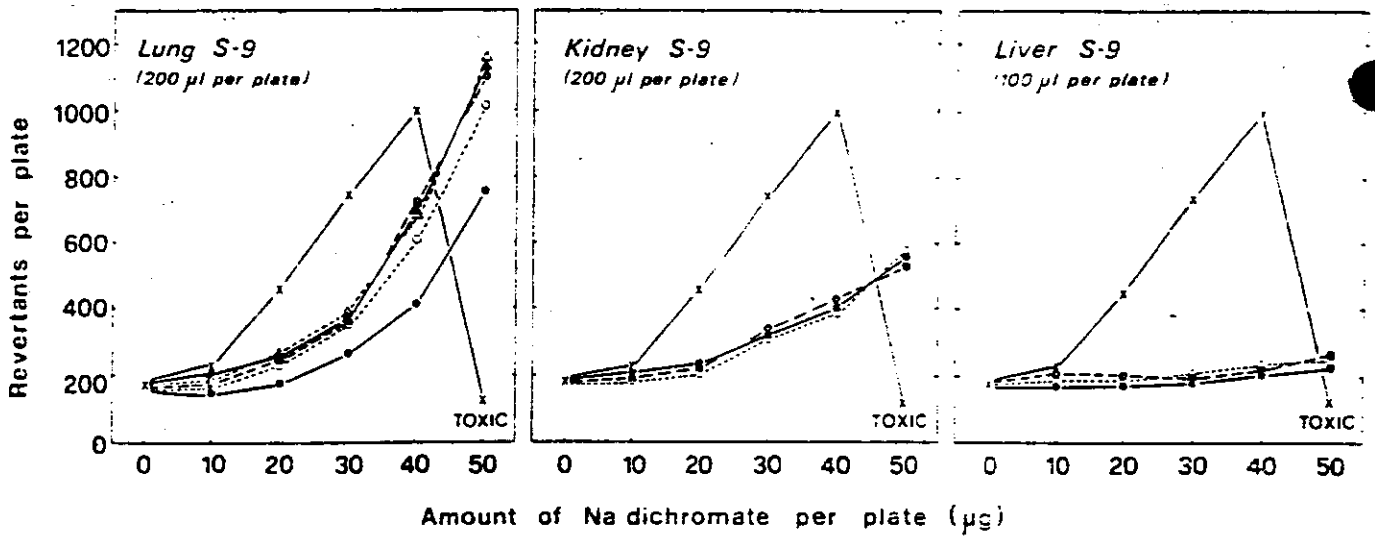

Chart 1. Dose-response curves obtained by testing varying amounts of sodium dichromate (Study A) preincubated for 1 h at 37°C with S-9 mix containing either a 50 mM Tris-0.25 M sucrose solution (controls of dichromate mutagenicity in strain TA100 of *S. typhimurium*, x) or S-9 fractions pooled from rats treated i.t. for 4 weeks as follows. ○—○, NaCl (1 × 9 mg/kg/week). ▲—▲, $Na_2Cr_2O_7$ (1 × 1.25 mg/kg/week). □—□, NaCl (5 × 9 mg/kg/week). ●- - -●, $Na_2Cr_2O_7$ (5 × 0.05 mg/kg/week). ●—● $Na_2Cr_2O_7$ (5 × 0.25 mg/kg/week). Confidence limits are not shown for the sake of visual clarity.

Table 2

ANOVA of 4 experiments aiming at assessing the efficiency of rat lung S-9 fractions in decreasing the mutagenicity of sodium dichromate

Experiments	Amount of dichromate (µg/plate)	T5[a] vs. T3		T3 vs. T4	
		F	*P*	*F*	*P*
1 (Chart 1)	50	26.85	<0.01	3.28	>0.05
1 (Chart 1)	40	21.18	<0.01	14.31	<0.05
1 (Chart 1)	30	19.44	<0.05	<1	>0.05
1 (Chart 1)	20	41.99	<0.01	<1	>0.05
2 (Not shown)	40	9.29	<0.05	<1	>0.05
3 (Not shown)	40	42.10	<0.01	6.61	>0.05
4 (Not shown)	30	4.86	>0.05	1.50	>0.05

[a] T5, rats receiving sodium dichromate (0.25 mg/kg) i.t. 5 times per week for 4 weeks; T3, rats receiving 0.9% NaCl solution i.t. 5 times per week for 4 weeks; T4, rats receiving sodium dichromate (0.05 mg/kg) i.t. 5 times per week for 4 weeks.

decrease of mutagenicity is significantly more pronounced in the group of rats receiving dichromate (0.25 mg/kg) 5 times per week, as compared to the other 4 groups, at all the concentrations of dichromate positive in the Ames test, *i.e.*, 50 µg ($F = 96.66$, $P < 0.001$), 40 µg ($F = 71.94$, $P < 0.001$), 30 µg ($F = 48.85$, $P < 0.001$), and 20 µg ($F = 20.36$, $P < 0.01$) per plate. Although to a lower extent, lung S-9 fractions from rats receiving NaCl 5 times per week showed an increased efficiency, compared to the remaining 3 groups, in reducing dichromate mutagenicity at 50 [illegible] $= 11.77$, $P < 0.01$), 40 µg ($F = 12.64$, $P < 0.01$), and 30 [illegible] $= 6.88$, $P < 0.05$) per plate.

Several other experiments confirmed that, in general, the lung S-9 fractions from rats treated 5 times per week were significantly more active than those from rats treated once per week and that, within the former group, the metabolic activity was the highest in the animals receiving dichromate (0.25 mg/kg).

Table 2 reports the results of a statistical analysis of 4 separate experiments with lung preparations from rats treated 5 times per week. One of these (the one summarized in Chart 1) was carried out by testing the mutagenicity of varying amounts of dichromate in the presence of lung S-9 fractions pooled from the 3 groups, whereas the other 3 (Experiments 2 to 4) were carried out by testing the mutagenicity of a fixed amount of dichromate in the presence of the 15 individual lung S-9 fractions, all of them in triplicate plates. It can be observed that, with the exception of Experiment 4, the i.t. treatment with the higher dose of dichromate (T5) resulted in an increased metabolic efficiency of lung preparations, as compared with administration of its solvent (NaCl) (T3). On the other hand, with the exception of Experiment 1 (at one dose level only), no significant difference was apparent between T3 and T4 (lower dose of dichromate).

Decrease of Dichromate Mutagenicity in the Presence of Lung and Liver S-12 Fractions from Rats Treated i.t. with NaCl or with Dichromate Itself or i.p. with 3 Enzyme Inducers (Study B). As in the previous study, liver preparations were markedly more efficient than lung preparations in decreasing dichromate mutagenicity and were therefore tested in low amounts (20 to 25 µl/plate) in order to point out possible metabolic differences attributable to the various treatments of rats. Again, such a phenomenon was investigated by testing both fixed amounts of dichromate with all the individual S-12 fractions (30 of lung and 30 of liver) and varying amounts of dichromate with S-12 fractions pooled from the 6 experimental groups.

In Study B, neither the repeated i.t. administration of NaCl nor the i.p. injection of MC had any influence on the decrease of chromium(VI) mutagenicity by liver or lung preparations, as compared to untreated controls. Conversely, in all experiments performed, AR induced a highly significant ($P < 0.001$) stimulation in both the liver and, generally with more attenuated effects, the lung. PB, although less efficiently than AR, also enhanced the metabolic effects in the majority of the experiments performed with liver S-12 fractions (once $P < 0.001$, twice $P < 0.01$, twice $P < 0.05$, and once $P > 0.05$). A borderline effect ($P = 0.05$) was observed in the lung of PB-treated rats in only one of 6 experiments. An opposite trend was observed in rats receiving 20 i.t.

doses of dichromate. In fact, no change of chromium(VI) metabolism occurred in the liver, while a stimulation was consistently detected in the lung, in agreement with the results of Study A. Such metabolic enhancement (which quantitatively approached the one afforded by AR in the same tissue) was statistically significant, as compared to lung preparations from untreated or NaCl-treated rats, in all the experiments performed (twice $P < 0.001$, twice $P < 0.01$, and twice $P < 0.05$).

Chart 2 shows an example of dose-response curves obtained with sodium dichromate in the Ames test, in either the absence or the presence of liver and lung S-12 fractions from variously treated rats. For the sake of visual clarity, only the treatments leading to a significant stimulation of chromium(VI) metabolism are reported. As already described, they are: i.p. AR and i.p. PB for the liver; i.p. AR and i.t. dichromate for the lung.

Effect of Lung S-12 Fractions from Rats Treated i.t. with Dichromate on the Mutagenicity of Other Chromium Compounds. Assays with strain TA102 of *S. typhimurium* confirmed

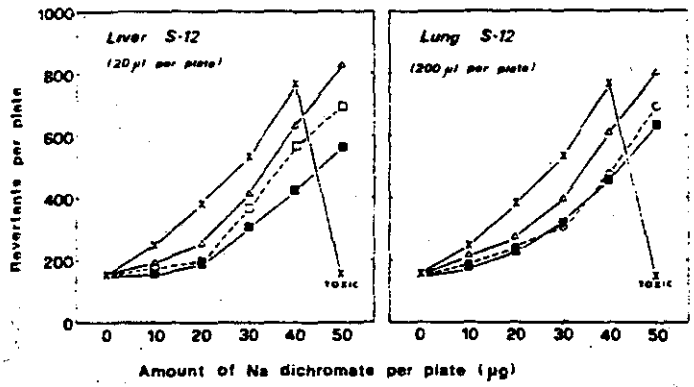

Chart 2. Dose-response curves obtained by testing varying amounts of sodium dichromate (Study B), preincubated for 1 h at 37°C with S-9 mix containing either a 50 mM Tris-0.25 M sucrose solution (controls of dichromate mutagenicity in strain TA100 of *S. typhimurium*; ×) or S-12 fractions pooled from rats treated as follows: △, untreated; ○, $Na_2Cr_2O_7$ i.t. (5 × 0.25 mg/kg/week); □, PB i.p. (3 × 60 mg/kg/day for 3 days); ■, AR i.p. (1 × 500 mg/kg). Confidence limits are not shown for the sake of visual clarity.

the enhanced decrease of dichromate mutagenicity by lung S-12 fractions of rats treated i.t. with dichromate itself and showed a similar behavior also for the 2 other chromium(VI) compounds tested, *i.e.*, calcium chromate and chromium trioxide (Table 3). In terms of revertants per plate, the differences recorded for each compound between lung preparations from NaCl- and dichromate-treated rats were not statistically significant, although they approached the 0.05 significance level. However, the differences were significant ($P = 0.01$ by Student's t test) when the values obtained with the 3 compounds were all analyzed together. Furthermore, similar trends were confirmed in additional experiments. A chromium(III) compound, *i.e.*, chromic acetate, was inactive in both the absence and the presence of lung S-12 fractions, even when tested up to 100-fold-higher doses on a molar basis, compared to chromium(VI) compounds.

Efficiency of Liver and Lung S-12 Fractions from Variously Treated Rats in Activating Promutagens or in Deactivating Direct-acting Mutagens. The same S-12 fractions used for investigating chromium(VI) metabolism were also checked for their efficiency in activating 3 promutagens (2AF, BP, and BP 7,8-diol) and in deactivating 3 direct-acting mutagens (ICR 191, ECH, and 4NQO) in the Ames test.

As shown in Chart 3, each one of the 3 promutagens was tested in the presence of 3 different amounts of S-12 fractions (50, 100, and 200 µl for the lung; 25, 50, and 100 µl for the liver). Lung S-12 fractions failed to activate BP and BP 7,8-diol and were poorly active in converting 2AF into mutagenic metabolites, without any appreciable difference among the 6 experimental groups.

The aromatic amine was activated to a similar extent by 25 and 50 µl of liver S-12 fractions per plate from untreated rats and from rats receiving NaCl, $Na_2Cr_2O_7$, or MC. The efficiency of metabolic activation was further increased following pretreatment of rats with PB or AR. With the latter inducer, the highest mutagenic response was obtained with 25 µl of liver preparations per plate.

The liver S-12 fractions from untreated, NaCl-, or $Na_2Cr_2O_7$-

Table 3

Assay of 3 chromium(VI) and one chromium(III) compounds in the Ames test in the presence of lung S-12 fractions from rats receiving i.t. treatments

Chromium compounds were incubated for 1 h at 37°C with S-9 mix containing either the homogenate buffer or 40% lung S-9 fractions from 2 groups of rats and then plated in triplicate with strain TA102 of *S. typhimurium*, as described in "Materials and Methods."

	Amount/plate		Revertants/plate		
				With lung S-12 fractions	
Compound	Compound (µg)	Chromium (nmol)	Without S-12 fractions	NaCl i.t.[a]	Sodium dichromate i.t.[b]
Distilled water			234 ± 18[c]	282 ± 41	271 ± 12
Sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$)	32.8	50	1702 ± 29	630 ± 66	529 ± 84
Calcium chromate ($CaCrO_4$)	23.6	50	1424 ± 127	593 ± 72	465 ± 24
Chromium trioxide (CrO_3)	9.6	50	1506 ± 91	546 ± 24	457 ± 86
Chromic acetate [$Cr(CH_3COO)_3$]	5044	5000	247 ± 25	269 ± 16	278 ± 36

[a] Pretreatment of rats: 0.9% NaCl solution i.t. 5 times per week for 4 weeks.
[b] Pretreatment of rats: sodium dichromate (0.25 mg/kg) 5 times per week for 4 weeks.
[c] Mean ± SD.

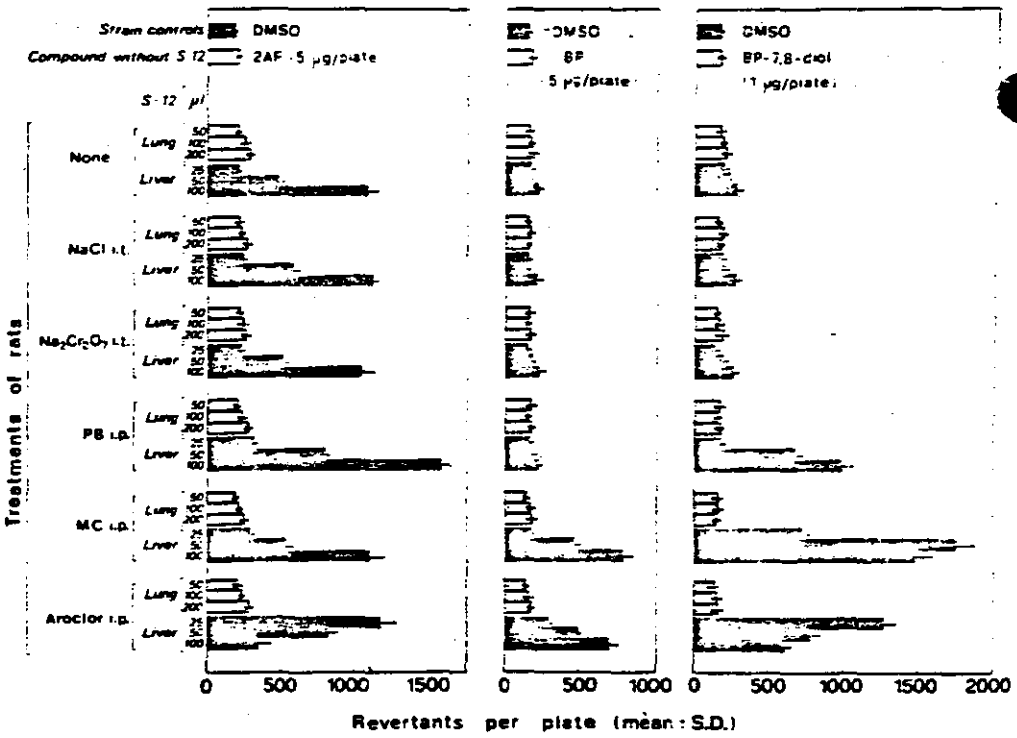

Chart 3. Effect of S-9 mix, containing varying amounts of liver or lung S-12 fractions from variously treated rats, in activating 3 promutagens to mutagenic metabolites in strain TA100 of *S. typhimurium*.

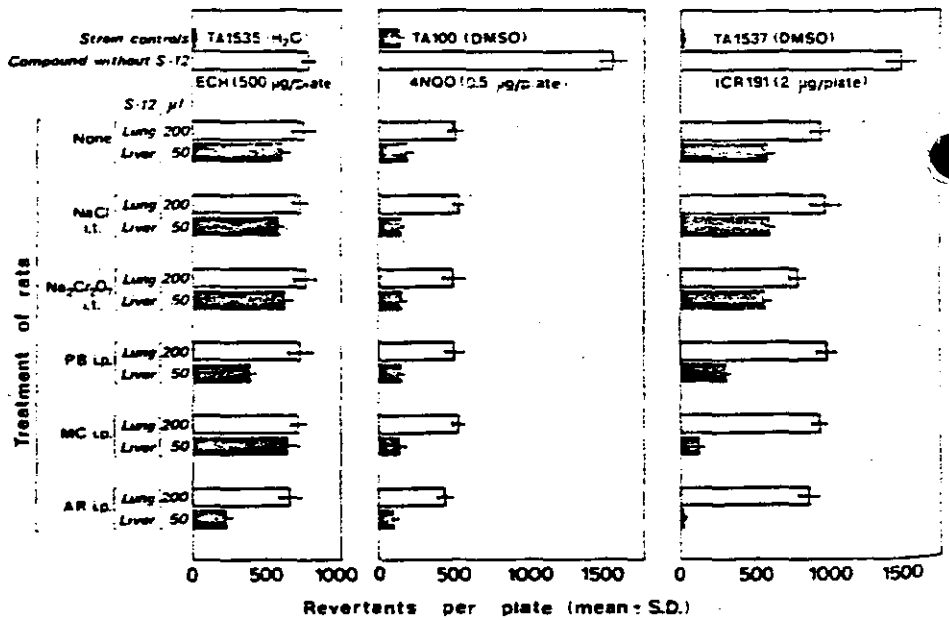

Chart 4. Effect of S-9 mix, containing liver or lung S-12 fractions from variously treated rats, in decreasing the activity of 3 direct-acting mutagens in various strains of *S. typhimurium*.

treated rats showed only a marginal ability in activating the 2 PAHs. Liver preparations from PB-treated rats activated BP 7,8-diol but not BP, whereas AR and MC were highly efficient in stimulating the metabolic activation of both PAHs.

The effects of liver and lung S-12 fractions from the 6 experimental groups on the mutagenicity of 3 direct-acting compounds are shown in Chart 4. The mutagenicity of ECH was only marginally affected by lung preparations, with some more evident consequences following AR treatment. Conversely, all the liver preparations decreased the mutagenicity of this epoxide, and such an effect was more pronounced following PB and especially AR treatment. 4NQO was deactivated by both liver and, to a lower extent, lung preparations, without any appreciable difference among the 6 groups excepting, again, some further stimulation by AR. All 3 enzyme inducers stimulated ICR 191 deactivation by liver S-12 fractions, with the following rank of efficiency: AR (which completely reverted its mutagenicity); MC; and PB. The most interesting finding in this series of assays was that some stimulation of ICR 191 deactivation by lung S-12 fractions was afforded by not only AR but also (and even to a larger extent) the i.t. pretreatment of rats with dichromate. The difference recorded between NaCl- and dichromate-treated ra*

Table 4

Effect of liver microsomes from variously treated rats on the activity of various mutagens

Mutagenic compounds were assayed in triplicate in the Ames test in the presence of S-9 mix (supplemented with G6PD), without or with liver microsomes (recovered from 25 mg of wet tissue) from rats receiving enzyme inducers i.p., as specified in Table 1.

Compound	Amount/plate (μg)	*S. typhimurium* strain	No. of spontaneous revertants	No. of induced revertants				
				Without microsomes	With rat liver microsomes			
					Untreated	PB	MC	AR
Sodium dichromate	30	TA100	134 ± 6[a]	837 ± 27	347 ± 26	268 ± 23[b]	326 ± 31	204 ± 9[c]
4NQO	0.5	TA100	134 ± 6	1218 ± 33	316 ± 8	253 ± 15[d]	256 ± 21[b]	138 ± 12[c]
ICR 191	2.5	TA1537	8 ± 3	1930 ± 47	622 ± 30	248 ± 11[c]	56 ± 6[c]	19 ± 5[c]
2AF	5	TA98	35 ± 4	47 ± 6	396 ± 21	670 ± 17[c]	465 ± 11[d]	561 ± 21[c]
BP	5	TA100	134 ± 6	139 ± 10	146 ± 16	155 ± 6	339 ± 17[c]	447 ± 13[c]
AFB1	1	TA100	134 ± 6	154 ± 9	149 ± 13	547 ± 21[c]	155 ± 8	542 ± 41[c]

[a] Mean ± SD.
[b] Significant at $P < 0.05$ by Student's t test as compared to untreated rats.
[c] Significant at $P < 0.001$ by Student's t test as compared to untreated rats.
[d] Significant at $P < 0.01$ by Student's t test as compared to untreated rats.

was not significant, although it was very close to the 0.05 significance level, as evaluated by Student's t test.

Ability of Liver Microsomes from Variously Treated Rats in Metabolizing Mutagens in the Ames Test. The effects of the i.p. treatment of rats with the 3 enzyme inducers were also investigated by checking the ability of liver microsomes in affecting the mutagenicity of both promutagens and direct-acting mutagens (including dichromate) in the Ames test (Table 4).

The direct mutagenicity of sodium dichromate was decreased to the same extent by liver microsomes from untreated and from MC-treated rats. In agreement with the trends observed with liver S-12 fractions, the activity of liver microsomes was further amplified by PB and especially by AR treatment.

The mutagenicity of 4NQO was also decreased in the presence of liver microsomes, a process which was slightly enhanced by PB and MC and, more efficiently, by AR. All 3 inducers stimulated the metabolic deactivation of ICR 191, with the following rank of efficiency: AR > MC > PB.

Of the 3 procarcinogens tested, BP and AFB1 could not be activated by liver microsomes from untreated rats. Activation to mutagenic metabolites required induction with AR (both BP and AFB1), MC (BP only), or PB (AFB1 only). 2AF showed inducibility patterns similar to those of AFB1, but an evident activation was also afforded by microsomes from untreated and MC-treated rats.

DISCUSSION

All the metabolic systems tested led to reduction of the mutagenicity of sodium dichromate in the Ames test. As also confirmed in this study with calcium chromate and chromium trioxide, a similar trend is shared by a number of chromium(VI) compounds (2, 6, 7, 25, 26), and therefore, it appears to be a common property attributable to the hexavalent ionic species of this element. The observed efficiency of liver, kidney, and lung preparations is also consistent with the already reported rank of ability of S-9 fractions from rat tissues in lowering chromium(VI) mutagenicity, *i.e.*, liver > adrenals > kidney > testis > stomach > lung, preparations from striated muscle, spleen, bladder, and colon being inactive (7, 25, 26).

The 2 studies reported in this paper agreed in demonstrating that the i.t. treatment of rats with high doses of dichromate (0.25 mg/kg) 5 times per week for 4 weeks, is capable of specifically enhancing the efficiency of lung preparations in decreasing the mutagenicity of the same compound. In contrast, such treatment did not modify the reducing ability of liver S-12 fractions, presumably because, during transfer from the respiratory tract to other tissues, chromium(VI) is accumulated and reduced in erythrocytes (11, 23). Interestingly, the local stimulation that we have observed *in vivo* is in agreement with the reported increased tolerance of human cultured cells to potassium dichromate, following repeated *in vitro* exposures to the same salt (29).

Administration of 3 enzyme inducers; *i.e.*, PB, MC, and AR, resulted in the expected changes (1, 4) in the concentrations and spectral properties of cytochromes P-450 in hepatic and pulmonary microsomes. Additionally, liver and lung S-12 fractions, as well as liver microsomal fractions, were found to selectively induce the metabolic activation or deactivation of known mutagens in the *S. typhimurium* test system. AR was the only one of these inducers which succeeded in stimulating reduction of chromium in the lung, although less effectively than in the liver. Chromium metabolism in hepatic microsomes was also induced by PB, which is in agreement with the conclusions of a study on the reduction of chromium(VI) by rat liver microsomal preparations (10). Our biochemical findings (9) provide evidence that an important role in chromium(VI) intracellular reduction is played by not only microsomal but also cytosolic components, including electron donors (*e.g.*, GSH) and chiefly inducible enzyme activities. In particular, several lines of evidence support the view that DT-diaphorase, acting via a 2-electron transfer from reduced pyridine nucleotides (NADPH and NADH), may represent a key mechanism in the intracellular reduction of chromium(VI).

The interpretation of the results obtained in the present study and their possible relevance to the *in vivo* situation deserve some comments. Outside target cells, reduction of chromium(VI) is undoubtedly a beneficial mechanism, because chromium(III) is not capable of permeating mammalian cell membranes (17, 19) and is recognized to be inactive in cellular test systems (13, 14, 19, 26) and to be devoid of carcinogenic activity (13). On this ground, penetration of chromium(VI) entering the blood stream into erythrocytes and its subsequent reduction in these cells (11, 23) are consistent with the known lack of carcinogenicity of chromium at a distance from implant sites (13). Moreover, the daily reducing capacity of several mg of chromium(VI) by human saliva and gastric juice (26) is expected to constitute a very efficient barrier against the oral toxicity and carcinogenicity of this element.

It has been speculated that, after penetrating the cells as chromium(VI), a reduced form of it, such as chromium(V) (15) or chromium(III) (17, 19), might interact with DNA. In any case, irrespective of the form of chromium bound to DNA, the site of reduction inside the cell should represent a limiting factor for its availability to the genetic target (19). In particular, reduction in the cytoplasm (which can be mimicked *in vitro* by using various subcellular preparations, *e.g.*, S-9 and S-12, cytosolic, and microsomal fractions) is likely to represent a detoxification phenomenon, due to trapping of the reduced species outside the cell nucleus. It is well known, for instance, that chromium(III) binds avidly a variety of cellular components (27). Such interpretation is consistent with the evidence that the ability of subcellular fractions from various tissues in reducing chromium(VI) is inversely related to the susceptibility of the same tissues as targets of chromium carcinogenicity. For instance, S-9 fractions from rat striated muscle, where experimentally injected chromium(VI) is carcinogenic (13), have no detectable reducing ability (23).

An intermediate situation can be postulated for the lung, which in humans is the only accepted target of chromium carcinogenicity (13, 14), yet with a broad variability of epidemiological and experimental data, which might reflect a variability in exposure levels as related to pulmonary defense mechanisms. In this respect, of particular interest are the results of an i.t. carcinogenicity assay with sodium dichromate,[5] which was carried out in the same laboratory where the rats used in the present study were treated. Excepting for duration of treatments (30 months instead of 4 weeks), the treatment technique and schedule were identical in the 2 studies, and the same rat strain was used. In the carcinogenicity assay, tumor induction was only observed in the lungs, and dichromate was weakly carcinogenic only when administered once per week at 1.25 mg/kg. On the other hand, no cancer was induced in rats treated with the same frequency but at lower doses (0.25 or 0.05 mg/kg), nor in rats treated 5 times per week with equivalent total weekly doses (*i.e.*, 0.25, 0.05, and 0.01 mg/kg).

These patterns suggest that fractionated instillations of chromium(VI), even close to the maximum tolerated dose for a lifetime carcinogenicity study, can be detoxified more readily than a single massive dose, which may exceed lung defense mechanisms. The specific enhancement of chromium(VI)-reducing ability, observed in the present study using lung preparations from rats receiving 0.25 mg of dichromate per kg i.t. 5 times per week (but not in rats receiving 1.25 mg per kg once per week), is likely to represent a further defense mechanism against repeated exposures to chromium(VI) by the respiratory route. It may have also contributed to prevent carcinogenic effects in rats treated 5 times per week.

Therefore, also in the lung, the capability of chromium to interact with DNA and, presumably, to initiate cancer seems to depend on a quantitative balance between chromium(VI) entering the cell and its cytoplasmic reducing capacity. Under the experimental conditions of this paper and of its biochemical counterpart (9), it can be calculated that the post-mitochondrial components of the lungs of a rat would be capable, on the whole, of reducing hundreds of μg of chromium(VI) in 1 h. One should be very cautious in relating these figures, inferred from the *in vitro* efficiency of subcellular preparations, to the *in vivo* situation. However, it may be more than a coincidence that, in the carcinogenicity study,[5] induction of tumors was observed only in a small proportion of rats receiving i.t. doses of 250 to 500 μg of dichromate (*i.e.*, the single weekly administrations of 1.25 mg/kg) and that no induction was observed in those receiving doses of 50 to 120 μg (*i.e.*, the daily administrations of 0.25 mg/kg). Note that, as demonstrated in experiments with radiolabeled sodium dichromate, the i.t. administration of solutions of this salt results in a uniform distribution throughout the whole lung (28).

Several factors (some of which were identified in this study) can affect the magnitude of the observed detoxification processes, which renders questionable any attempt of extrapolating quantitative data to humans. Nevertheless, also considering that the capability of human lung S-9 fractions (from both cancer and noncancer patients) in reducing the mutagenicity of chromium(VI) is similar to the one observed with rat preparations (8), there seems to be sufficient evidence to support the conclusion that threshold phenomena, regulated by specific and inducible metabolic factors operating in pulmonary cells, are involved in the initiation of lung cancer by chromium. Additionally, the preliminary findings of a study that we have now in progress show that further inducible defense mechanisms against inhaled chromium are highly efficient in pulmonary alveolar macrophages.

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Diamond Shamrock
Chemicals Company

Technical Center

October 29, 1985

Dr. Emil M. Mrak
Chancellor Emeritus
University House
University of California
Davis, California 95616 (#0004)

Dear Dr. Mrak:

I am writing on two counts:

1. To cry "foul" with regards to the scheduling of the September 26, 1985 Scientific Review Panel Meeting to discuss the ARB report on Chromium prior to our having received the revised document.

2. To point out that the Petrilli/DeFlora articles published in the journal Cancer Research should not have been considered a "bombshell" since I alerted you to their publication in my August 9, 1985 communication to you. As you may recall, you promised to forward my letter and attachments to ARB/DHS.

As to the first point, our group did not receive copies of SRP Public Meeting Notice or the Chromium draft report until the day of the meeting. In addition, a copy of the draft that I requested through ARB on September 18 did not arrive until October 4. I should also mention that in my telephone conversation with ARB personnel on the 18th, no mention was made of the September 26 SRP meeting.

In the way of further comment, I would like address specific responses as contained in Part C of the Draft Report that DHS made in reference to public comments it received on the Chromium Health Evaluation Document.

1) Comment V discusses the idea that the unit risk estimated from the Mancuso study is too high due to the omission of the exposure experience of highly exposed plant maintenance workers. DHS in its response applied its own estimates of maintenance worker exposure to recalculate the risk.

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1) (Continued)

I would suggest that Allied, who made the original comments, would have a better feel for what a reasonable exposure level for maintenance workers employed in the chromate industry would be since they, like Diamond Shamrock Chemicals Company, were a producer of chromium chemicals at that time. Regardless, if DHS acknowledges the likelihood of a 3.5 fold underestimation of unit risk from the Mancuso data based on its own estimates of exposure, I believe that the unit risk should be adjusted accordingly. I would also point out that Allied's estimate of maintenance worker exposure levels indicated an exposure at 5-10 times that of the operators. The 3.5 fold DHS estimate utilized the low side of that exposure estimate; thus an additional correction is still appropriate to allow for underestimation of exposure.

2) Comment VII addressed the fact that several organizations submitting comments (Diamond Shamrock Chemicals Company among them) felt that data from a recent animal study and metabolism and/or detoxification studies along with the existence of published TLV's were supportive of a carcinogenic threshold for Cr(VI). The staff of DHS agreed that one interpretation of this information is consistent with the concept of a carcinogenic threshold. However, DHS, in its response, does not present other interpretations even though it implies there are. It also concludes that the information is not conclusive proof that a threshold exists.

In light of the recent work by Petrilli and DeFlora I feel that a case for a Cr(VI) carcinogenic threshold is stronger than ever. Conclusive proof in support of a carcinogenic threshold is unlikely, if not impossible, in that we are testing a hypothesis by demonstrating that a response (cancer) does not occur. Likewise, there is no conclusive proof to correlate exposure to hexavalent chromium at current ambient air levels with an increased cancer incidence rate either in man or animals.

Finally, to put things into a proper perspective the U.S. EPA, Office of Air and Radiation, Office of Policy, Planning and Evaluation in their July 1984 report "The Magnitude and Nature of the Air Toxics Problem in the United States" states that in 1983 there were 440,000 estimated cancer deaths (1900/million) based on 850,000 estimated incidences (3700/million).

Of these, 154,000 (670/million) were attributed to diet; 132,000 (570/million) to smoking; and 8,800 (38/million) to environmental pollution (about 2% of the total estimated cases). In addition, the report indicated that 3,000 to 14,000 cancer cases (13-61 incidences per million) were attributable to "passive smoking"; i.e. being around smokers. Contrasting these figures, the EPA report also estimated the cancer incidence rate for ambient level chromium based on three different studies to be 0.11, 0.29, and 1.05 incidences per million respectively.

It is questionable in my mind whether or not further regulation of chromium is justified. If, due to further restrictive regulation, the use of chromium in various application areas is displaced by inferior chromium substitutes, I could see the potential for loss of life associated with this action as being greater than the estimated incidence rate associated with that of cancer. For example, if the lead chromate pigment used in traffic paint and known for its brilliance, stability and hiding power were displaced with an inferior pigment, one could reasonably speculate that the loss of life due to increased highway traffic fatalities associated with this one change might equal the 3 to 25 cases of cancer per year which the EPA would estimate occur as a result of chromium exposure in the State of California. Similar arguments can be made for the other end use areas of chromium; i.e. production of alloys, use in refractories, metal finishing, wood treating, leather tanning, corrosion control, etc.

As always, thank you for the opportunity to express my personal views as well as the views of Diamond Shamrock Chemicals Company.

Sincerely,

Russell J. Morgan

Russell J. Morgan
Research & Development
Chromium Chemicals

kjv

CC: Messrs. Cliff Popejoy & William V. Loscutoff
Air Resources Board

STATE OF CALIFORNIA
AIR RESOURCES BOARD
1102 O STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

GEORGE DEUKMEJIAN, Governor

November 14, 1985

Mr. Russell J. Morgan
Diamond-Shamrock Chemicals Co.
P.O. Box 191
Painesville, OH 44077

Dear Mr. Morgan:

Your October 29 Letter to Dr. Mrak

Thank you for providing me with a copy of your comments on the revised health effects document on chromium. I have forwarded your letter to the Department of Health Services.

Regarding your receipt of the SRP Public Meeting Notice, we will send future notices regarding chromium to you directly. SRP Public Meeting Notices were sent on September 16, 1985 to Ms. Jill S. Barson of Diamond-Shamrock Corporation in Pasadena, Texas, and to Dr. J.B. Worthington of Diamond Shamrock Corporation in Dallas, Texas. Ms. Barson and Dr. Worthington will remain on our mailing list.

Your concern about regulation of chromium is understandable. Please recognize, however, that the identification of a substance as a toxic air contaminant is not in itself a restriction on the use of that substance. If a substance is identified by the Air Resources Board as a toxic air contaminant, a report on the need and appropriate degree of regulation for that substance will be prepared by the ARB staff, with the participation of Air Pollution Control (or Management) Districts and in consultation with affected sources and the interested public. The issues which the regulatory needs report shall address are described in Section 39665 of the California Health and Safety Code. I have enclosed a copy of the Chapter of the Code which includes that section. The issue of substitution of other materials for chromium, and any resulting potential impacts, will be addressed in the needs report, as described in Section 39665:

"(b) The report shall address all of the following issues, to the extent data can reasonably be made available: ...

(6) The availability, suitability, and relative efficacy of substitute compounds of a less hazardous nature.

(7) The potential adverse health, safety, or environmental impacts that may occur as a result of implementation of an airborne toxic control measure."

If hexavalent chromium is identified by the Board as a toxic air contaminant, we will welcome your participation in preparation of the regulatory needs report.

If you have questions concerning our regulatory program, or would like to discuss any of the issues you raised in your letter, please contact me at (916) 322-6023.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

Attachment

cc: Dr. Emil M. Mrak
Peter D. Venturini
John Holmes