CRITERIA DOCUMENT UPDATE

Occupational Exposure to

Hexavalent Chromium

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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External Review Draft

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FOREWORD

When the U.S. Congress passed the Occupational Safety and Health Act of 1970 (Public Law 91-596), it established the National Institute for Occupational Safety and Health (NIOSH). Through the Act, Congress charged NIOSH with recommending occupational safety and health standards and describing exposure levels that are safe for various periods of employment, including but not limited to the exposures at which no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience. By means of criteria documents, NIOSH communicates these recommended standards to regulatory agencies (including the Occupational Safety and Health Administration [OSHA]), health professionals in academic institutions, industry, organized labor, public interest groups, and others in the occupational safety and health community. Criteria documents contain a critical review of the scientific and technical information about the prevalence of hazards, the existence of safety and health risks, and the adequacy of control methods. This criteria document is derived from reviews of information from human, animal, and experimental studies of the toxicity of hexavalent chromium (Cr(VI)) compounds and is intended to describe the potential health effects of occupational exposure to this group of chemical compounds.

Cr(VI) compounds include a large group of chemicals with varying chemical properties, uses, and workplace exposures. The major chromium-containing materials in the marketplace are chromite ore, chromium chemicals, ferroalloys, and metal. The United States is a major world producer of chromium metal, chromium chemicals, and stainless steel. Sodium dichromate is the most common chromium chemical from which other Cr(VI) compounds may be produced. Cr(VI) compounds commonly manufactured include sodium dichromate, sodium chromate, potassium dichromate, potassium chromate, ammonium dichromate, and Cr(VI) oxide. Other Cr(VI)-containing materials commonly manufactured include various paint and primer pigments, graphic art supplies, fungicides, corrosion inhibitors, and wood preservatives.

Currently more than 558,000 U.S. workers are exposed to airborne Cr(VI) compounds in the

workplace. Some of the industries in which the largest numbers of workers are exposed to high concentrations of Cr(VI) compounds include electroplating, welding, and painting. It is expected that these workers' exposures to Cr(VI) will continue until substitutes acceptable to these industries have been developed and adopted. Approximately 1,045,500 workers are exposed to Cr(VI) in cement.

This Criteria Document Update describes the most recent NIOSH scientific evaluation of occupational exposure to Cr(VI) compounds, including the justification for a revised Recommended Exposure Limit (REL) derived using current quantitative risk assessment methodology on human health effects data. The policies and recommendations in this document are consistent with those of the January 2005 NIOSH testimony on the OSHA Proposed Rule on Occupational Exposure to Hexavalent Chromium and the corresponding NIOSH Post-Hearing Comments. NIOSH recommends that airborne exposure to all Cr(VI) compounds be limited to a concentration of 0.2 µg Cr(VI)/m^3 for an 8-hr TWA exposure, during a 40-hr workweek. The available scientific evidence supports the inclusion of all Cr(VI) compounds into this recommendation. Due to the residual risk of lung cancer at the REL, NIOSH further recommends that all reasonable efforts be made to reduce exposures to Cr(VI) compounds below the REL through the use of engineering controls and work practices. The REL is intended to reduce workers' risk of death from lung cancer associated with occupational exposure to Cr(VI) compounds over a 45-year working lifetime. It is expected that reducing airborne workplace exposures of Cr(VI) will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa.

In addition to limiting airborne concentrations of Cr(VI) compounds, NIOSH recommends that dermal exposure to Cr(VI) be prevented in the workplace to reduce the risk of adverse dermal health effects including irritation, ulcers, skin sensitization, and allergic contact dermatitis. Skin notations of SK-DIR(COR) (causing corrosion by direct skin contact) and SK-SEN (causing allergic contact dermatitis or other allergic effects due to dermal exposure) are recommended for

all Cr(VI) compounds[†].

Engineering controls, appropriate respiratory protection programs, and other preventive measures should be implemented to minimize workers' exposures to Cr(VI) compounds. NIOSH urges employers to disseminate this information to workers and customers. NIOSH also requests that professional and trade associations and labor organizations inform their members about the hazards of workplace exposure to Cr(VI) compounds.

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[†] The draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals,* is in the NIOSH review and clearance process. The skin notations are included here for review with the expectation that the revised dermal policy will be approved prior to final publication of this Cr(VI) criteria document.

CONTENTS

To be finalized upon completion of the review process.

ABBREVIATIONS

ACD	allergic contact dermatitis
ACGIH	American Conference of Governmental Industrial Hygienists
ACS	American Cancer Society
AlM	alveolar macrophage
AL	action level
AM	arithmetic mean
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
BEI	Biological Exposure Index
BMC	benchmark concentration
CCA	chromated copper arsenate
CI	confidence interval
CPC	chemical protective clothing
Cr	chromium
Cr(0)	metallic or elemental chromium
Cr(III)	trivalent chromium
Cr(VI)	hexavalent chromium
CrO_3	chromic acid or chromium trioxide
d	day
DECOS	Dutch Expert Committee on Occupational Standards
DNA	deoxyribonucleic acid
EID	Education and Information Division
EPA	U.S. Environmental Protection Agency
FEF_{25-75}	forced expiratory flow (liter/second) between 25% and 75% of the forced vital capacity
FEV_1	forced expiratory volume in one second
FEV_1/FVC	ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC)
FVC	forced vital capacity
G2/M	gap 2/mitosis
GM	geometric mean
GSD	geometric standard deviation
hr	hour
H_2O_2	hydrogen peroxide
HIF-1	hypoxia-induced factor 1
HHE	Health Hazard Evaluation
Ig	immunoglobulin
i.t.	intratracheal
IARC	International Agency for Research on Cancer
ICDA	International Chromium Development Association

IDLH	Immediately Dangerous to Life and Health
ILO	International Labour Organization
IMIS	Integrated Management Information System
ISO	International Organization for Standardization
IU	International Unit
l	liter
LCL	lower confidence limit
LDH	lactate dehydrogenase
LD_{50}	lethal dose resulting in 50% mortality
LH	luteinizing hormone
LHC	lymphatohematopoietic cancer
LOAEL	lowest observed adverse effect level
LOD	limit of detection
M	molar
mg/m^3	milligrams per cubic meter of air
MIG	metal inert gas (welding)
MLE	maximum likelihood estimate
mM	millimolar
MMA	manual metal arc (welding)
MMD	mass median diameter
MMAD	mass median aerodynamic diameter
MRL	minimum risk level
MSDS	Material Safety Data Sheet
MSHA	Mine Safety and Health Administration
n	number (sample size)
NAG	N-acetyl-β-D-glucosaminidase
nd	not detectable
ng	nanogram
nmol	nanomoles
Ni	nickel
NADPH	nicotinamide adenine dinucleotide phosphate
NAICS	North American Industrial Classification System
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NOES	National Occupational Exposure Survey
NTP	National Toxicology Program
OD	Office of the Director
OEL	Occupational Exposure Limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
p	probability

PBZ	personal breathing zone
PCMR	proportionate cancer mortality ratio
PEL	Permissible Exposure Limit
PFT	pulmonary function test
PPE	personal protective equipment
ppm	parts per million
PVC	polyvinyl chloride
RBC	red blood cell(s)
redox	reduction-oxidation
REL	Recommended Exposure Limit
RfC	reference concentration
ROM	reactive oxygen metabolite
ROS	reactive oxygen species
SD	standard deviation
SIC	Standard Industrial Classification
SK-DIR(COR)	skin notation denoting substance that results in corrosion by direct skin contact
SK-SEN	skin notation denoting substance that causes allergic contact dermatitis, or sensitization of skin, mucous membranes, or airways due to dermal exposure
SMR	standardized mortality ratio
SOD	superoxide dismutase
SPF	specific pathogen free
T	tons
TLV	Threshold Limit Value
TWA	time-weighted average
µg	microgram(s)
µg/g	microgram(s) per gram
µg/l	microgram(s) per liter
$\mu g/m^3$	microgram(s) per cubic meter of air
µM	micromolar
UCL	upper confidence limit
UICC	Union Internationale Contre le Cancer
U.K.	United Kingdom
U.S.	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell(s)
WHO	World Health Organization
wk	week
yr	year(s)

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CHAPTER ONE: INTRODUCTION

1.1 PURPOSE AND SCOPE

This Criteria Document Update describes the most recent NIOSH scientific evaluation of occupational exposure to Cr(VI) compounds, including the justification for a revised REL derived using current quantitative risk assessment methodology on human health effects data. This Criteria Document Update focuses on literature published since the NIOSH [1975] Cr(VI) criteria document through February 2006. The policies and recommendations in this document are consistent with those of the January 2005 NIOSH testimony on the OSHA Proposed Rule on Occupational Exposure to Hexavalent Chromium and the corresponding NIOSH Post-Hearing Comments (Appendices A and B, respectively).

1.2 HISTORY OF THE NIOSH REL FOR Cr(VI) COMPOUNDS

In the 1973 *Criteria for a Recommended Standard: Occupational Exposure to Chromic Acid*, NIOSH recommended that the Federal standard for chromic acid, 0.1 mg/m^3 as a 15-minute ceiling concentration, be retained due to reports of nasal ulceration occurring at concentrations only slightly above this concentration [NIOSH 1973]. In addition, NIOSH recommended supplementing this ceiling limit with a time-weighted average of 0.05 mg/m^3 for an 8-hour work day to protect against possible chronic effects, including lung cancer and liver damage.

In the 1975 *Criteria for a Recommended Standard for Occupational Exposure to Chromium(VI)*, NIOSH supported two distinct recommended standards for Cr(VI) compounds [NIOSH 1975]. Some Cr(VI) compounds were considered to be noncarcinogenic at that time, including the chromates and bichromates of hydrogen, lithium, sodium, potassium, rubidium, cesium, and ammonium, and chromic acid anhydride. These Cr(VI) compounds are relatively soluble in water. It was recommended that a 10-hr TWA limit of 25 µg Cr(VI)/m^3 and a 15-minute ceiling limit of 50 µg Cr(VI)/m^3 be applied to these Cr(VI) compounds.

All other Cr(VI) compounds were considered carcinogenic [NIOSH 1975]. These Cr(VI) compounds are relatively insoluble in water. At that time NIOSH subscribed to a carcinogen policy which called for "no detectable exposure levels for proven carcinogenic substances" [Fairchild 1976]. Thus the basis for the REL for carcinogenic Cr(VI) compounds, 1 μg Cr(VI)/m^3 TWA, was the quantitative limitation of the analytical method available for measuring workplace exposures to Cr(VI) at that time.

NIOSH revised its policy on Cr(VI) compounds in its 1988 testimony to OSHA on the Proposed Rule on Air Contaminants [NIOSH 1988b]. NIOSH testified that while insoluble Cr(VI) compounds had previously been demonstrated to be carcinogenic, there was now sufficient evidence that soluble Cr(VI) compounds were also carcinogenic. NIOSH recommended that all Cr(VI) compounds, whether soluble or insoluble in water, be classified as potential occupational carcinogens based on the OSHA carcinogen policy. The adoption of the most protective of the available standards, the NIOSH RELs, was recommended. Consequently the REL of 1 μg Cr(VI)/m^3 TWA was adopted by NIOSH for all Cr(VI) compounds.

NIOSH reaffirmed its policy that all Cr(VI) compounds be classified as occupational carcinogens in its response to the 2002 OSHA Request for Information on Occupational Exposure to Hexavalent Chromium and in its testimony on the OSHA Proposed Rule on Occupational Exposure to Hexavalent Chromium [NIOSH 2002, 2005a] (see Appendix A).

1.3 THE REVISED REL FOR Cr(VI) COMPOUNDS

NIOSH recommends that airborne exposure to all Cr(VI) compounds be limited to a concentration of 0.2 μg Cr(VI)/m^3 for an 8-hr TWA exposure, during a 40-hr workweek. The use of NIOSH Methods 7605 or 7703 (or validated equivalents) is recommended for Cr(VI) determination in the laboratory and field, respectively. The REL represents the

upper limit of exposure for each worker during each work shift. Due to the residual risk of lung cancer at the REL, NIOSH further recommends that all reasonable efforts be made to reduce exposures to Cr(VI) compounds below the REL through the use of engineering controls and work practices. The available scientific evidence supports the inclusion of all Cr(VI) compounds into this recommendation. The REL is intended to reduce workers' risk of death from lung cancer associated with occupational exposure to Cr(VI) compounds over a 45-year working lifetime. Although the quantitative analysis is based on lung cancer mortality data, it is expected that reducing airborne workplace exposures will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa.

In addition to limiting airborne concentrations of Cr(VI) compounds, NIOSH recommends that dermal exposure to Cr(VI) be prevented in the workplace to reduce the risk of adverse dermal health effects including irritation, ulcers, skin sensitization, and allergic contact dermatitis. Based on the draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals*[†], skin notations of SK-DIR(COR) (causing corrosion by direct skin contact) and SK-SEN (causing skin sensitization or allergic contact dermatitis) are recommended for all Cr(VI) compounds [NIOSH 2008 draft]. The SK-DIR notation identifies Cr(VI) compounds as substances known to cause direct damage to the skin. The sub-category (COR) identifies Cr(VI) compounds as corrosive. The SK-SEN identifies Cr(VI) compounds as substances that cause skin sensitization or allergic contact dermatitis.

[†] The draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals,* is in the NIOSH review and clearance process. The skin notations are included here for review with the expectation that the revised dermal policy will be approved prior to final publication of this Cr(VI) criteria document update.

CHAPTER TWO: PROPERTIES, PRODUCTION, AND POTENTIAL FOR EXPOSURE

2.1. PHYSICAL AND CHEMICAL PROPERTIES

Chromium (Cr) is a metallic element that may occur in several valence states, including Cr^{-4} and Cr^{-2} through Cr^{+6}. In nature chromium exists almost exclusively in the trivalent (Cr(III)) and hexavalent (Cr(VI)) oxidation states. In industry the oxidation states most commonly found are Cr(0) (metallic or elemental chromium), Cr(II), Cr(III), and Cr(VI).

Select chemical and physical properties of select Cr(VI) compounds are listed in Table 2–1. The chemical and physical properties of Cr(VI) compounds relevant to workplace sampling and analysis are discussed further in Chapter Three: Measurement of Exposure.

Table 2–1. Chemical and physical properties of select hexavalent chromium compounds

Compound	Molecular Weight	Boiling point (°C)	Melting point (°C)	Solubility: Cold water g/100 cc	Solubility: Cold water °C	Solubility: Other
Ammonium chromate	152.07	——	Decomposes at 180	40.5	30	Insoluble in alcohol; slightly soluble in NH_3, acetone
Ammonium dichromate	252.06	——	Decomposes at 170	30.8	15	Soluble in alcohol; insoluble in acetone
Barium chromate	253.32	——	——	0.00034	160	Soluble in mineral acid
Calcium chromate (dehydrate)	156.07	——	$-2H_2O$, 200	16.3	20	Soluble in acid, alcohol
Chromium (VI) oxide	99.99	Decomposes	196	67.45	100	Soluble in alcohol, ether, sulfuric acid, nitric acid
Lead chromate	323.19	Decomposes	844	0.0000058	25	Soluble in acid, alkali; insoluble in acetic acid
Lead chromate oxide	546.39	——	——	Insoluble	——	Soluble in acid, alkali
Potassium chromate	194.19	——	968.3 975	62.9 36	20 20	Insoluble in alcohol
Potassium dichromate	294.18	Decomposes at 500	Triclinic becomes monoclinic at 241.6; Melting point is 398	4.9 102	0 100	Insoluble in alcohol
Silver chromate	331.73	——	Decomposes	0.0014	——	Soluble in NH_4OH, KCN

(Continued)

Table 2–1 (Continued). Chemical and physical properties of select hexavalent chromium compounds

Compound	Formula weight	Boiling point (°C)	Melting point (°C)	Solubility: Cold water g/100 cc	Solubility: Cold water °C	Solubility: Other
Sodium chromate	161.97	——	19.92	87.3	30	Slightly soluble in alcohol; soluble in MeOH
Sodium dichromate	261.97	Decomposes At 400 (anhydrous)	——	238 (anhydrous) 180	0 20	Insoluble in alcohol
Strontium chromate	203.61	——	——	0.12	15	Soluble in HCl, HNO_3, acetic acid, NH_4 salts
Zinc chromate	181.36	——	——	Insoluble	Insoluble	Soluble in acid, liquid NH_3; insoluble in acetone

Source: The Merck Index [2006].

2.2. PRODUCTION AND USE IN THE UNITED STATES

The major chromium-containing materials in the marketplace are chromite ore, chromium chemicals, ferroalloys, and metal. The United States is a major world producer of chromium metal, chromium chemicals and stainless steel [USGS 2004]. No chromite ore has been mined in the United States since 1961. From 2001 to 2004, chromite ore was imported into the United States primarily from South Africa (53%) and Kazakhstan (29%) [USGS 2006]. Table 2–2 lists select statistics of chromium use in the United States.

Sodium dichromate is the primary chemical from which other Cr(VI) compounds are produced. Currently the United States has only one sodium dichromate production facility. Although production processes may vary, the following is a general description of Cr(VI) compound production. The process begins by roasting chromite ore with soda ash and varying amounts of lime at very high temperatures to form sodium chromate. Impurities are removed through a series of pH adjustments and filtrations. The sodium chromate is acidified with sulfuric acid to form sodium dichromate. Chromic acid may be produced by reacting concentrated sodium dichromate liquor with sulfuric acid. Other Cr(VI) compounds may be produced from sodium dichromate by adjusting the pH and adding other compounds. Solutions of Cr(VI) compounds thus formed may then be crystallized, purified, packaged, and sold. Cr(VI) compounds commonly manufactured include sodium dichromate, sodium chromate, potassium dichromate, potassium chromate, ammonium dichromate, and Cr(VI) oxide. Other Cr(VI)-containing materials commonly manufactured include various paint and primer pigments, graphic art supplies, fungicides, corrosion inhibitors, and wood preservatives.

Table 2–2. Selected chromium statistics, United States, 2001–2005

[In thousands of metric tons, gross weight]

Statistic	2001	2002	2003	2004	2005*
Production, from scrap	141	174	180	168	170
Imports for consumption	239	263	317	326	330
Exports	43	29	46	35	40

Source: USGS [2006].
* Estimated

2.3 POTENTIAL SOURCES OF OCCUPATIONAL EXPOSURE

Workers have potential exposures to airborne Cr(VI) compounds in many industries including chromium metal and chromium metal alloy production and use, electroplating, welding, and the production and use of Cr(VI)-containing compounds. Primary industries with the majority of occupational exposures to airborne Cr(VI) compounds include: welding, painting, electroplating, steel mills, iron and steel foundries, wood preserving, paint and coatings production, chromium catalyst production, plastic colorant producers and users, production of chromates and related chemicals from chromite ore, plating mixture production, printing ink producers, chromium metal production, chromate pigment production, and chromated copper arsenate producers [Shaw Environmental 2006]. Operations and industries with limited potential for occupational exposure to Cr(VI) compounds include: producers of chromium dioxide, chromium dye, and chromium sulfate; chemical distributors, textile dyeing, glass production, printing, leather tanning, chromium catalyst users, refractory brick producers, woodworking, solid waste incineration, oil and gas well drilling, Portland cement producers, non-ferrous superalloy producers and users, construction, and concrete products [Shaw Environmental 2006].

Workers have potential dermal exposure to Cr(VI) compounds in any industry or task in which there is the potential for splashing, spilling, or other skin contact with Cr(VI)-containing material.

Construction workers and others who work with Portland cement are exposed to the Cr(VI) that occurs naturally in the cement.

2.4 NUMBER OF U.S. WORKERS POTENTIALLY EXPOSED

The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 2.5 million workers were potentially exposed to chromium and its compounds [NIOSH 1974]. It was estimated that 175,000 workers were potentially exposed to Cr(VI) compounds. The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated that 196,725 workers were potentially exposed to Cr(VI) compounds [NIOSH 1983a].

In 1981, Centaur Research, Inc. estimated that 391,400 workers were exposed to Cr(VI) in U.S. workplaces, with 243,700 workers exposed to Cr(VI) only and an additional 147,700 workers exposed to a mixture of Cr(VI) and other forms of chromium [Centaur 1981].

In 1994, Meridian Research, Inc. estimated that the total number of production workers in U.S. industries with potential exposure to Cr(VI) was 808,177 [Meridian 1994]. Industries included in the analysis included electroplating, welding, painting, chromate producers, chromate pigment producers, CCA producers, chromium catalyst producers, paint and coatings producers, printing ink producers, plastic colorant producers, plating mixture producers, wood preserving, ferrochromium producers, iron and steel producers, and iron and steel foundries. More than 98 percent of the potentially exposed workforce was found in six industries: electroplating, welding, painting, paint and coatings production, iron and steel production, and iron and steel foundries.

In 2006, OSHA estimated that more than 558,000 workers are exposed to Cr(VI) compounds [71 Fed. Reg. 10099 (2006)*; Shaw Environmental 2006]. The largest number of workers potentially exposed to Cr(VI) were in the following application groups: carbon steel welding (>141,000), stainless steel welding (>127,000), painting (>82,000), electroplating (>66,000), steel mills (>39,000), iron and steel foundries (>30,000), and textile dyeing (>25,000) [71 Fed. Reg. 10099

* *Federal Register*. See Fed. Reg. in references.

(2006); Shaw Environmental 2006]. Within the welding application group (stainless steel and carbon steel combined) the largest numbers of exposed workers were reported in the construction (>140,000) and general industries (>105,000). Within the painting application group the largest number of exposed workers were reported in the general (>37,000) and construction industries (>33,000). Table 2–3 summarizes the estimated number of workers exposed by application group [71 Fed. Reg. 10099 (2006)].

In addition to those workers exposed to airborne Cr(VI) compounds, there are 1,045,500 workers potentially exposed to Cr(VI) in cement [Shaw Environmental 2006]. Most of these workers are exposed to wet cement.

Table 2–3. Number of Cr(VI)-Exposed Workers by Application Group (Adapted from 71 Fed. Reg. 10099, Table VIII-3 [2006]).

Application Group	Number of Exposed Workers
Welding (stainless steel and carbon steel)	269,379
Painting	82,253
Electroplating	66,859
Steel mills	39,720
Iron and steel foundries	30,222
Textile dyeing	25,341
Woodworking	14,780
Printing	6,600
Glass producers	5,384
Construction Other*	4,069
Chemical distributors	3,572
Paint and coatings producers	2,569
Solid waste incineration	2,391
Non-ferrous metallurgical uses	2,164
Chromium catalyst users	949
Plastic colorant producers and users	492
Chromium catalyst producers	313
Chromate production	150
Plating mixture producers	118
Printing ink producers	112
Chromium dye producers	104
Refractory brick producers	90
Ferrochromium producers	63
Chromate pigment producers	52
Chromated copper arsenate producers	27
Chromium sulfate producers	11
Total	558,431

* Does not include welding, painting, and woodworking; does include government construction

2.5 MEASURED EXPOSURE IN THE WORKPLACE

2.5.1 Blade et al. 2007

From 1999 through 2001, NIOSH conducted a Cr(VI) field research study consisting of industrial-hygiene and engineering surveys at 21 selected sites representing a variety of industrial sectors, operations, and processes [Blade et al. 2007]. This study characterized workers' exposures to Cr(VI)-containing airborne particulate and evaluated existing technologies for controlling these exposures. Evaluation methods included the collection of full work shift, personal breathing-zone (PBZ) air samples for Cr(VI), measurement of ventilation system parameters, and documentation of processes and work practices. Operations and facilities evaluated included: chromium electroplating; painting and coating; welding in construction; metal cutting operations on chromium-containing materials in ship breaking; chromate-paint removal with abrasive blasting; atomized alloy-spray coating; foundry operations; printing; and the manufacture of refractory brick, colored glass, prefabricated concrete products, and treated wood products. The field surveys represent a series of case studies rather than a statistically representative characterization of U.S. occupational exposures to Cr(VI).

The industrial processes and operations were classified into one of four categories based on a qualitative assessment of the potential relative difficulty of controlling worker Cr(VI) exposures to the approximate magnitude of the existing REL of 1 $\mu g/m^3$ using the exposure and exposure-control information collected at each site. Specifically, the measured exposures were compared with the REL, and in cases of exposures exceeding that level, the extent to which it was exceeded was considered along with a qualitative assessment of effectiveness of the existing controls, and a qualitative determination based on professional judgement then was made as to the likely relative difficulty of improving control effectiveness to an adequate degree to achieve the REL. The four categories into which the processes or operations were categorized are as follows: (1) those with minimal worker exposures to Cr(VI) in air; (2) those with workers' exposures to Cr(VI) in air easier to control to existing NIOSH REL than categories (3) and (4); (3) those with workers' exposures to Cr(VI) in air moderately difficult to control to the existing NIOSH REL; and (4) those most difficult

to control workers' airborne Cr(VI) exposures to approximate magnitude of the existing NIOSH REL.

The results of the field surveys are summarized in Tables 2–4 through 2–7. The results characterize the potential exposures as affected by engineering controls and other environmental factors but not by the use or disuse of PPE as the PBZ air samples were collected outside any respiratory protection worn by the workers. A wide variety of processes and operations were classified as those with minimal worker exposures to Cr(VI) in air or where workers' exposures to airborne Cr(VI) would be easier to control to the existing REL. Most of the processes and operations where controlling workers' Cr(VI) exposures to the existing REL would be moderately difficult involved joining and cutting metals when the chromium content of the materials involved was relatively high. All of the processes and operations where it would be most difficult to control workers' airborne Cr(VI) exposures to the existing REL involved the application of coatings and finishes. The classification of these processes based on the potential relative difficulty of controlling occupational exposures to Cr(VI) in air without reliance on respiratory protection devices represents qualitative assessments based on the professional judgment of the authors of this paper. Recommendations for reducing workers' exposures to Cr(VI) at these sites are discussed in Blade et al. [2007] and in Chapter Eight.

Table 2–4. Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 1 Processes and Operations (Minimal Worker Exposures to Cr[VI] in Air).

Operation(s)	SIC Code	(NIOSH Site No.) Site Description	Key Job(s) Exposed				Other Jobs Exposed, Full-Shift PBZ Cr(VI) Exposures in Air[A] ($\mu g/m^3$)	Process Details, Engineering Exposure-Control Measures, Other Comments
			Job Title(s)	Full-shift PBZ Cr(VI) Exposures in Air[A]		Tasks, Comments		
				Range, $\mu g/m^3$ (N = no. of values)	Geometric Mean, $\mu g/m^3$ (Geometric Std. Dev.)			
"Bright" chromium electroplating (mfg.)	3471	(1) Chromium electroplating and coating processes (mfg.)	Production worker	~0.09 – 0.28 (N=6)	0.15 (1.6)	Place and remove parts to be plated, tend tanks.	None.	No local exhaust ventilation.
Chromium coating processes (non-electroplating) (mfg.)	3471	(1) Chromium electroplating and coating processes (mfg.)	Production worker	0.27 (N=1, "still zinc"). 0.25 (N=1, "cad line")	N/A	Place and remove parts to be coated, tend tanks.	"Strip line" operator 0.25 $\mu g/m^3$ (N=1). "Dye line" operator ~0.10 $\mu g/m^3$ (N=1)	No local exhaust ventilation. One tank on "cad line" covered with tarp.
TIG, fusion, dual-shield welding; submerged-arc plasma cutting	3494	(14) Welding and cutting on stainless and mild steels (mfg.)	TIG Welder	<0.06 – <0.08 (N=6, all "not detected")	N/A	TIG welding on stainless steel	Fusion, dual-shield weld, submerged-arc plasma cut (all on mild steel); all "not detected," <0.2 (N=15)	"Welding fume extractor" local exhaust ventilation on welding stations, but contaminant capture poor; none on plasma cutting.
Foundry – casting operations – stainless steel, other ferrous alloys (mfg.)	3324	(19) Foundry – stainless steel and other ferrous alloys (mfg.)	All casting operations workers	0.008 – 0.19 (N=13)	0.032 (2.4)	Melt alloy, pour. Alloy Cr content <0.25% – 26%	None.	"Good" local exhaust ventilation in "old facility" (N=3 exposure measurements, all ≤0.02), but none yet in "new facility."
Stick, MIG welding on steel, galvanized piping and sheet metal (construction)	1711	(20) Welding on piping and sheet metal (construction)	Welder	<0.04 – 0.42 (N=7) (N=4, "not detected")	N/A	Welding (mainly "stick") and grinding, indoors	Welding outdoors, <0.04 – 0.053 (N=8) (N=6, "not detected")	One indoor area had effective local exhaust ventilation. Other work areas in the open, partially enclosed, or passive ventilation.

Manufacturing of pre-cast concrete products	3272	(10) Manufacture of pre-cast concrete products	Mixer operator	0.22, 0.36 (N=2)	N/A	Mixes batches	All other jobs, <0.02 – 0.25 (N=32) (N=9, "not detected")	Cr(VI) is natural constituent of portland cement. Minimal exposure-control measures, no engineering exposure controls.
Table 2–4 (continued). Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 1 Processes and Operations (Minimal Worker Exposures to Cr[VI] in Air).								
Foundry – ductile iron (mfg.)	3321	(15) Foundry – ductile iron (mfg.)	All jobs	<0.04 – 0.04 (N=27) (N=26, "not detected")	N/A	All foundry tasks	None.	Little to no exposure. Local exhaust ventilation in furnace area, but ineffective capture. Elsewhere, general ventilation.
Crushing and recycling of concrete from demolition	1795	(12) Crushing and recycling of concrete from demolition	All jobs	<0.02 – 0.03 (N=4) (N=3, "not detected")	N/A	All tasks	None.	Cr(VI) is natural constituent of portland cement. Little to no exposure. Outdoor operations, water-spray dust suppression.
Manufacturing of colored glass products, using chromate pigments	3229	(6) Manufacture of colored glass products	All jobs	<0.02 – 0.02 (N=9) (N=8, "not detected")	N/A	All tasks	None.	Local exhaust ventilation at pigment weighing, and batch weighing and mixing; spray-mist dust suppression at cullet station.
Screen printing (mfg.) with inks containing chromate pigments	2759	(8) Screen printing (mfg.). Also, electronic-component mfg.	All jobs	<0.02 (N=4, all "not detected")	N/A	Ink mixing, screen printing	None.	No detectable exposure. Local exhaust ventilation for ink-mixing, general ventilation with HEPA-filtered supply for screen-printing.
Chromate-conversion treatment process (mfg.) for electronic-component boards	3679	(8) Screen printing (mfg.). Also, electronic-component mfg.	All jobs	<0.02 (N=2, both "not detected")	N/A	Operate chromic-acid tank ("chromate conversion")	None.	No detectable exposure. Local exhaust ventilation for chromic acid tanks, general ventilation for adjacent shipping dept.

Source: Blade et al. [2007].

A concentration value preceded by a "less-than" symbol ("<") indicates that the Cr(VI) level in the sampled air was less than the minimum detectable concentration (i.e., the mass of Cr[VI] collected in the sample was less than the analytical limit of detection [LOD]). A concentration value preceded by an "approximately" symbol ("~") indicates that Cr(VI) was detectable in the sampled air, but at a level less than the minimum quantifiable concentration (i.e., the mass of Cr[VI] collected in the sample was between the analytical LOD and limit of quantification [LOQ]). These concentration values are less precise than fully quantifiable values.

Table 2–5. Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 2 Processes and Operations (Worker Exposures to Cr(VI) in Air Easier to Control to 1 µg/m^3 or Below than Those in Higher-Category Processes).

Operation(s)	SIC Code	(NIOSH Site No.) Site Description	Key Job(s) Exposed				Other Jobs Exposed, Full-Shift PBZ Cr(VI) Exposures in Air[A] (µg/m^3)	Process Details, Engineering Exposure-Control Measures, Other Comments
			Job Title(s)	Full-shift PBZ Cr(VI) Exposures in Air: Range, µg/m^3 (N = no. of values)	Full-shift PBZ Cr(VI) Exposures in Air: Geometric Mean, µg/m^3 (Geometric Std. Dev.)	Tasks, Comments		
Alodyne/anodize chromium-coating processes (mfg.)	3471	(2) Painting and coating processes (mfg.)	Chem Line operator	0.55, 1.1 (N=2)	N/A	Tending chromic-acid dip tanks (non-electroplating)	Chemist (lab and waste treatment) 0.82 and 1.2 µg/m^3	No local exhaust ventilation. Dip tanks covered with tarps.
TIG welding on stainless steel in sheet-metal fabrication (mfg.)	3444	(9) Welding and cutting in sheet-metal fabrication (mfg.)	TIG Welder	0.65 (N=1)	N/A	TIG welding on stainless steel	None. (Welder's exposure inside welding helmet = 0.67 µg/m^3)	Local exhaust ventilation for welding, but poor capture.
Manufacturing of refractory brick using chromic oxide	3297	(5) Manufacture of refractory brick (non-clay)	Salvage operator	0.04, 1.8 (N=2)	N/A	Exposure higher when cleaned yellow chromate matl.	All other jobs: 0.012 – 0.74 (N=20), geom. mean = 0.052, geom. std. dev. = 3.4	No local exhaust ventilation on the salvage-material cleaning operation. Local ventilation, and other controls, in other areas.
Manufacturing of chromium sulfate from sodium dichromate	2819	(4) Manufacture of chromium sulfate	Reactor operator	0.22, 1.4 (N=2)	N/A	Transfer materials, collect process QC samples	Railcar operator. Transfers sodium dichromate solution. 0.12, 0.22 (N=2)	Reactors equipped with local exhaust ventilation, and anti-frothing surfactant. Railcar unloading is closed process.
Remove chromate-containing paint by abrasive blasting (construction)	1721	(17) Remove paint (by abrasive blast) and reapply (construction)	Painter	0.10 – 1.3 (N=8)	0.43 (2.3)	"Spot" abrasive blasting on steel bridge	Exposures during "blowdown" and non-chromate repainting tasks, 0.077 – 0.29 (N=7)	Work inside containment area for environmental contaminants. Natural ventilation only. Low production job, "spot" blasting only.

Table 2–5 (continued). Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 2 Processes and Operations (Worker Exposures to Cr(VI) in Air Easier to Control to 1 µg/m^3 or Below than Those in Higher-Category Processes).

SMAW, FCAW, dual-shield, TIG, MIG welding on stainless, other steels (shipyd.)	3731	(16) Welding in shipyard operations	Welder	0.19 – 0.96 (N=3)	0.36 (2.4)	SMAW, TIG welding in tight below-deck spaces	TIG, MIG, stick welding in relatively open areas, <0.04 – 0.22 (N=15)	Local exhaust ventilation was provided to varying degrees in the tight below-deck spaces by moving flex ducts to work space.
Manufacturing of products from wood treated with Cr-Copper-Arsenate	2452	(11) Manufacture of products from treated wood	Fabricator	Limited evaluation, no full-shift measurements	N/A	Sawing, drilling	None. (Two short-term samples collected outdoors; no Cr[VI] detected.)	No engineering exposure-control measures used, even indoors. Thus, indoor operations may result in detectable exposures.

Source: Blade et al. [2007].
A concentration value preceded by a "less-than" symbol ("<") indicates that the Cr(VI) level in the sampled air was less than the minimum detectable concentration (i.e., the mass of Cr[VI] collected in the sample was less than the analytical limit of detection [LOD]).

Table 2–6. Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 3 Processes and Operations (Worker Exposures to Cr(VI) in Air Moderately Difficult to Control to Approximately 1 µg/m^3)

Operation(s)	SIC Code	(NIOSH Site No.) Site Description	Key Job(s) Exposed				Other Jobs Exposed, Full-Shift PBZ Cr(VI) Exposures in Air[A] (µg/m^3)	Process Details, Engineering Exposure-Control Measures, Other Comments
			Job Title(s)	Full-Shift PBZ Cr(VI) Exposures in Air[A]		Tasks, Comments		
				Range, µg/m^3 (N = no. of values)	Geometric Mean, µg/m^3 (Geometric Std. Dev.)			
Manufacturing of screen-printing inks containing chromate pigments	2893	(3) Manufacture of screen-printing inks	Ink-batch weigher	<0.08 – 3.0 (N=4) (N=1 "not detected")	0.9 (6.2)	Add pigment (powder), other ingredients, then Mix ink batch	Other jobs in process: <0.08 – 0.4 µg/m^3 (N=6) (N=4 "not detectable")	Local exhaust ventilation ("fair") for batch weighing/mixing, and certain other operations. Others only general ventilation.
MIG welding on stainless steel in sheet-metal fabrication (mfg.)	3444	(9) Welding and cutting in sheet-metal fabrication (mfg.)	MIG Welder	2.8, 5.2 (N=2)	N/A	MIG welding on stainless steel	None. (Welder's exposures inside welding helmet = 2.6, 1.0, respectively)	Local exhaust ventilation for welding, but poor capture.
MIG, TIG welding, plasma-arc cutting, on stainless-steel sheet metal (mfg.)	3444	(9) Welding and cutting in sheet-metal fabrication (mfg.)	Welding Supervisor	2.0, 3.7 (N=2)	N/A	MIG, TIG weld, plasma-arc cut, grind, metal forming	None. (Supervisor's exposures inside welding helmet = 8.5, 3.2, respectively)	Local exhaust ventilation for welding, but poor capture. Only general ventilation for plasma-arc cutting, no local ventilation.
MIG welding on stainless steel (mfg.)	3494	(14) Welding and cutting on stainless and mild steels (mfg.)	MIG Welder	0.20 – 5.5 (N=4) (N=1, >1.0)	0.84 (4.0)	MIG welding (non-automated) on stainless steel	Automated MIG-welder operator (stainless steel) <0.07, <0.08 µg/m^3 (N=2)	"Welding fume extractor" local exhaust ventilation on welding stations, but contaminant capture poor. Also general ventilation.
Metal cutting (torch and carbon-arc) in ship demolition (shipyard)	4499	(13) Metal cutting in ship demolition (shipyard)	Burner	<0.07 – 27. (N=14) (N=2, >1.0)	0.35 (5.4)	Carbon-arc and torch cutting on steel (some with chromate paint)	Firewatch (assist burner) <0.04 – 1.0 (N=10) Supervisor <0.07 (N=2)	Most work performed outdoors, including a partly-enclosed area. Some work indoors, only general ventilation provided there.

Table 2–6 (continued). Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 3 Processes and Operations (Worker Exposures to Cr(VI) in Air Moderately Difficult to Control to Approximately 1 µg/m^3)

Repair welding and cutting on alloy and stainless-steel castings (mfg.)	3324	(19) Foundry – stainless steel and other ferrous alloys (mfg.)	Welder	0.37 – 22. (N=4) (N=1, <12)	6.6 (7.0)	MIG, TIG, SMAW weld, carbon-arc gouge (cut)	None.	Welding work load 2- to 3-times normal, on various Cr-content steels and alloys. Cutting on 25% Cr alloy. No local ventilation.

Source: Blade et al. [2007].

A concentration value preceded by a "less-than" symbol ("<") indicates that the Cr(VI) level in the sampled air was less than the minimum detectable concentration (i.e., the mass of Cr[VI] collected in the sample was less than the analytical limit of detection [LOD]). For some other samples in these sets, Cr(VI) was detectable in the sampled air but at a level less than the minimum quantifiable concentration (i.e., the mass of Cr[VI] collected in the sample was between the analytical LOD and limit of quantification [LOQ]). These concentration values are less precise than fully quantifiable values.

Table 2–7. Summary of Results for NIOSH Personal Breathing-Zone, Full-Work Shift Air Sampling for Cr(VI), 1999 Through 2001, for Category 4 Processes and Operations (Control of Worker Airborne-Cr(VI) Exposures to Approximately 1 µg/m^{3}Considered Most Difficult).

Operation(s)	SIC Code	(NIOSH Site No.) Site Description	Key Job(s) Exposed				Other jobs Exposed, Full-Shift PBZ Cr(VI) Exposures in Air[A] (µg/m^3), etc.	Process Details, Engineering Exposure-Control Measures, Other Comments, etc.
			Job Title(s)	Full-shift PBZ Cr(VI) Exposures in Air[A]		Tasks, Comment		
				Range, µg/m^3 (N = no. of values)	Geometric Mean, µg/m^3 (Geometric Std. Dev.)			
Spray application and re-sanding of chromate-containing paints (mfg.)	3479	(2) Painting and coating processes (mfg.)	Painter	3.8 – 55. (N=5)	16. (3.4)	Spray/sand/ clean-up. Paints: 1–30% chromates	Painter's helpers (same work areas) 2.4 – 22 µg/m^3 (N=4)	Painting in fully and partially enclosed paint booths — effectiveness judged as "fair."
Spray application and re-sanding of chromate-containing paints (mfg.)	3728	(7) Painting and associated re-sanding (mfg.)	Painter	<0.02 – 4.3 (N=13)	0.23 (6.3)	Spraying paint, some sanding. Paints: 1–30% chromates	Assemblers using rotary-disc sanders 0.27 – 2.1 µg/m^3 (N=4)	Fully-enclosed paint booths. Vacuum-attached disc sanders. Both judged as "fair." Other workers' exposures were lower.
"Hard" chromium electroplating (mfg.)	3471	(1) Chromium electroplating and coating processes (mfg.)	Plater	3.0 – 16. (N=4)	7.9 (2.0)	Place and remove parts to be plated, tend tanks.	Lab tech 9.0 µg/m^3 when add CrO_3 flake. Otherwise, lab workers 0.22, 0.27 µg/m^3 (N=3).	Mist suppressant, push-pull local exhaust ventilation, tarps used on tanks. Lab workers work at tanks along with lab duties.
"Hard" and "bright" chromium electroplating (mfg.)	3471	(18) Chromium electroplating (mfg.)	Plater	0.22 – 8.3 (N=12)	2.5 (2.6)	Place and remove parts to be plated, tend tanks.	None.	Platers work throughout plant, various plating tanks. Local exhaust ventilation on all tanks, new mist suppressant on one.
Atomized Cr-alloy spray-coating operation (industr. maintenance)	1799	(21) Cr-alloy "metalization" coating operation (industr. maint.)	Production worker	≥820, ≥1900 (N=2)	N/A	Prep surfaces by abrasive blasting. Then spray coating.	Supervisor, entered enclosed work area: 330 Other supervisors 44, 47 Abrasive-pot tender: 7.0	Work area inside large boiler, resurfacing heat-exchange tubes. Electric arc melts alloy, then compressed air propels to surface.

Source: Blade et al. [2007].

A concentration value preceded by a "less-than" symbol ("<") indicates that the Cr(VI) concentration in the sampled air was less than the minimum detectable concentration (i.e., the

mass of Cr[VI] collected in the sample was less than the analytical limit of detection [LOD]). For some other samples in these sets, Cr(VI) was detectable in the sampled air, but at a level less than the minimum quantifiable concentration (i.e., the mass of Cr[VI] collected in the sample was between the analytical LOD and limit of quantification [LOQ]). These concentration values are less precise than fully quantifiable values. Additionally, a concentration value preceded by a "greater-than-or-equal-to" symbol ("≥") indicates that the reported value is an estimate, and the "true" concentration likely is greater, because of air-sampling pump failure before the end of the intended sampling period.

2.5.2 Shaw Environmental Report [2006]

The full-shift exposure data from OSHA and NIOSH site visits, NIOSH industrial hygiene surveys, NIOSH health hazard evaluations (HHEs), OSHA Integrated Management Information System (IMIS) data, U.S. Navy and other government and private sources were compiled to demonstrate the distribution of full-shift personal exposures to Cr(VI) compounds in various industries [Shaw Environmental 2006]. Those industries identified as having the majority of occupational exposures include: electroplating, welding, painting, producers of chromates and related chemicals from chromite ore, chromate pigment production, chromated copper arsenate producers, chromium catalyst production, paint and coatings production, printing ink producers, plastic colorant producers and users, plating mixture production, wood preserving, chromium metal production, steel mills, and iron and steel foundries. An estimate of the number of workers exposed to various Cr(VI) exposure levels in each primary industry sector is summarized in Table 2—5 [adapted from Shaw Environmental 2006]. Industry sectors with the greatest number of workers exposed above the revised REL include welding, painting, electroplating, steel mills, and iron and steel foundries. These industries also have the greatest number of workers exposed to Cr(VI) compounds.

Industries that were identified with a lesser potential for airborne Cr(VI) exposure include: chromium dioxide producers, chromium dye producers, chromium sulfate producers, chemical distributors, textile dyeing, colored glass producers, printing, leather tanning, chromium catalyst users, refractory brick producers, woodworking, solid waste incineration, oil and gas well drilling, Portland cement producers, non-ferrous superalloy producers and users, construction, and concrete products [Shaw Environmental 2006].

Table 2–8. Full-Shift 8-Hour TWA Personal Cr(VI) Exposures in Primary Industry Sectors (Adapted from Shaw Environmental [2006] Table ES-2)

Industry	Total No. Exposed Workers	Below LOD	LOD to 0.25 µg/m^3	0.25 to 0.5 µg/m^3	0.5 to 1 µg/m^3	≥1 µg/m^3
Welding	247,269	47,361	12,588	50,709	75,722	77,307
Painting	82,254	11,283	20,120	17,766	12,876	20,209
Electroplating	66,857	0	21,410	27,470	2,028	16,149
Steel mills	39,720	10,038	9,390	6,417	8,456	5,419
Iron and steel foundries	30,222	4,184	11,875	3,481	4,578	6,104
Paint and coating production	2569	400	1443	38	38	650
Plastic colorant producers; users	492	37	15	15	0	425
Chromium catalyst production	313	0	127	25	31	130
Chromate chemical production	150	1	89	24	24	12
Plating mixture producers	118	0	16	80	0	22
Printing ink production	112	27	4	3	17	61
Chromium metal producers	63	16	8	9	17	13
Chromate pigment production	52	0	0	0	1	51
CCA production	27	0	12	0	5	10

Abbreviations: CCA= chromated copper arsenate; LOD=limit of detection; TWA=time-weighted average.

2.6 EXISTING OCCUPATIONAL EXPOSURE LIMITS

The revised NIOSH REL for all Cr(VI) compounds is 0.2 µg Cr(VI)/m^3 8-hr TWA. Values for other U.S. occupational exposure limits (OELs) are also listed in Table 2–9. Values for OELs from various other countries are presented in Table 2–10.

Table 2–9. U.S. occupational exposure limits for Cr(VI) compounds*

Agency	OEL	Cr(VI) compound(s)	8-hr TWA µg Cr(VI)/m^3
NIOSH	REL	All	0.2
	IDLH		15,000
OSHA	PEL		5
ACGIH	TLV	Water-soluble	50
		Insoluble	10
		Chromite ore processing	50
		Calcium chromate	1
		Lead chromate	12
		Strontium chromate	0.5
		Zinc chromate	10

Source: ACGIH [2005a]; OSHA [2007].
*Measured as Cr unless noted otherwise.

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Table 2–10. Occupational exposure limits for Cr(VI) compounds in various countries*

Country	Insoluble Cr(VI) TWA (µg/m^3)	Soluble Cr(VI) TWA (µg/m^3)	STEL (µg/m^3)
Australia	50	50	
Canada – Alberta	10	50	150
- Quebec	50	50	
Hong Kong	10	50	
Ireland	50	50	
Japan	10	10	
Mexico	10	50	
Netherlands	10	25	Soluble 50
Poland	25	25	Soluble 500; Insoluble 50
Sweden	20	20	
United Kingdom	50	50	

Source: ACGIH [2005b].
* Specific Cr(VI) compounds such as calcium, lead, strontium, and zinc chromate may have distinct OELs.

7

8 **2.7 SUMMARY**

9 Industries with the greatest number of workers exposed to Cr(VI) compounds, and the
10 largest number of workers exposed to Cr(VI) compounds above the revised REL include
11 welding, painting, electroplating, steel mills, and iron and steel foundries [Shaw
12 Environmental 2006; 71 Fed. Reg. 10099 (2006)]. There are some industries, including
13 electroplating, welding, and aerospace painting which reportedly have not found
14 satisfactory substitutes for Cr(VI) compounds. It is expected that worker exposures to
15 Cr(VI) compounds will continue in these industries until acceptable substitutes have been
16 developed and adopted. It is also expected that the removal of lead chromate paints will
17 continue to be a risk of Cr(VI) exposure to workers for many years [71 Fed. Reg. 10099
18 (2006)].

19

20 Some industries such as wood working, printing ink manufacturing, and printing have
21 decreased their use of Cr(VI) compounds [71 Fed. Reg. 10099 (2006)]. However, many

of these workplaces have only a small number of employees or low exposure levels.

Since the 1970s the majority of lumber used in U.S. residential settings for external structures (e.g. decks, fences, and playsets) has been chromated copper arsenate(CCA)-treated wood. Workers at highest risk of exposure to Cr(VI) in this application are those working in CCA treatment plants and carpenters working with CCA-treated wood. In February 2002 the U.S. EPA announced a voluntary decision by industry to move consumer use of treated lumber products away from CCA lumber after December 30, 2003 [EPA 2002]. CCA is a restricted use product, for use only by certified pesticide applicators [EPA 2006]. CCA applicators are under the jurisdiction of the U.S. EPA [71 Fed. Reg. 10099 (2006)].

CHAPTER THREE: MEASUREMENT OF EXPOSURE

Recently developed analytical methods provide an improved ability to determine Cr(VI) concentrations in workplace air. These methods and sampling considerations for Cr(VI) compounds have been reviewed [Ashley et al. 2003]. New NIOSH methods have been developed and evaluated. NIOSH Methods 7605 and 7703 for Cr(VI) determination in the laboratory and in the field, respectively, are published in the "NIOSH Manual of Analytical Methods" (www.cdc.gov/niosh/nmam) [NIOSH 1994c]. These methods provide improved Cr(VI) measurement by allowing for the detection of Cr(VI) (versus total chromium), quantification of Cr(VI) at trace levels, and measurement of Cr(VI) in soluble and insoluble chromate compounds.

3.1 SAMPLING CONSIDERATIONS

Important sampling considerations when determining Cr(VI) levels in workplace air have been reviewed [Ashley et al. 2003]. One of the most important considerations is the reduction of Cr(VI) to Cr(III) during sampling and sample preparation. Another concern is the possibility of oxidation of Cr(III) to Cr(VI) during sample preparation. Factors which affect the reduction of Cr(VI) or oxidation of Cr(III) include the presence of other compounds in the sampled workplace air which may affect reduction or oxidation (notably iron, especially Fe(II)), the ratio of Cr(VI) to Cr(III) concentrations in the sample, and solution pH [Ashley et al. 2003]. The pH of a solution is an important factor since in acidic conditions the reduction of Cr(VI) is favorable, while in basic conditions Cr(VI) is stabilized. The sampling and analytical methods developed recently for the determination of Cr(VI) in the workplace attempt to minimize the influence of these redox reactions in order to obtain accurate Cr(VI) measurements.

Selection of a filter material that does not react with Cr(VI) is important. All filters to be used for sampling should be tested prior to use, but ordinarily polyvinyl chloride (PVC) filters are recommended (NIOSH Method 7605; OSHA Method ID-215). Other suitable filter materials which are generally acceptable for airborne Cr(VI) sampling include polyvinyl fluoride (PVF), polytetrafluoroethylene (PTFE), PVC- and PVF-acrylic

copolymers, and quartz fiber filters [Ashley et al. 2003]. Cr(VI) can also be reduced to Cr(III) due to reaction with other substances in the workplace air, notably Fe(II). Using NIOSH Method 7703 in the field is one option to minimize the reduction that may occur during sample transport and storage [Marlow et al. 2000; Wang et al. 1999].

3.2 SAMPLING AND ANALYTICAL METHODS

3.2.1 Cr(VI) Detection in Workplace Air

There are several methods developed by NIOSH and others to quantify Cr(VI) levels in workplace air. NIOSH Method 7605 describes the determination of Cr(VI) levels in workplace air by ion chromatography [NIOSH 2003b]. This method is a modification of NIOSH Methods 7604 and 7600, employing the hot plate extraction and ion chromatographic separation method of the former and the spectrophotometric detection technique of the latter. NIOSH Method 7605 also includes ultrasonic extraction as an optional sample preparation method for Cr(VI) [Wang et al. 1999]. The limits of detection (LODs) for NIOSH Methods 7605, 7604, and 7600 are 0.02 μg, 3.5 μg, and 0.05 μg per sample, respectively. OSHA Method ID-215 also uses ion chromatography to separate Cr(VI); its stated LOD is 0.01 μg per sample [OSHA 1998]. The OSHA method employs a precipitation reagent to prevent Cr(III) oxidation to Cr(VI) during sample preparation while NIOSH Method 7605 relies on sonication and/or a nitrogen atmosphere to achieve the same end.

NIOSH Method 7703 measures Cr(VI) levels by field-portable spectrophotometry [NIOSH 2003a]. This method is designed to be used in the field with portable laboratory equipment but can also be used in the fixed-site laboratory. It is a relatively simple, fast, and sensitive method for Cr(VI) determination [Wang et al. 1999; Marlow et al. 2000]. The method uses ultrasonic extraction instead of hotplate extraction, and solid-phase extraction instead of ion chromatography to isolate Cr(VI). Its estimated LOD is 0.08 μg per sample. The method has been modified to enable the determination of insoluble Cr(VI) compounds [Hazelwood et al. 2004].

Boiano et al. [2000] conducted a field study to compare results of airborne Cr(VI) determination obtained using NIOSH Methods 7605 and 7703 and OSHA Method ID-215. All three of these methods use extraction of the PVC filter in alkaline buffer solution, chemical isolation of Cr(VI), complexation of Cr(VI) with 1,5-diphenylcarbazide, and spectrometric measurement. However, there are specific differences regarding sample handling in each method (Table 3–1, adapted from Boiano et al. [2000]). Three sets of twenty side-by-side air samples (ten at each facility on each of three sampling media) were collected at a chromic acid electroplating operation and a spray paint operation, and were then analyzed using the three methods. No statistically significant differences were found between the mean Cr(VI) values obtained using the three methods ($p<0.05$). Results obtained using NIOSH Method 7703 were slightly higher (statistically significant) than those obtained using OSHA ID-215.

International standards for the determination of Cr(VI) in workplace air samples have been published. American Society for Testing and Materials (ASTM) Method D6832-02, "Standard Test Method for the Determination of Hexavalent Chromium in Workplace Air by Ion Chromatography and Spectrophotometric Measurement Using 1,5-diphenylcarbazide," allows for the determination of airborne Cr(VI) [ASTM 2002]. International Organization for Standardization (ISO) 16740, "Workplace Air – Determination of Hexavalent Chromium in Airborne Particulate Matter – Method by Ion Chromatography and Spectrophotometric Measurement using Diphenylcarbazide," provides a method to extract Cr(VI) compounds of different solubilities [ISO 2005]. Sulfate buffers are suitable for extraction of Cr(VI) from soluble and sparingly soluble compounds, while carbonate buffers are required for the dissolution of Cr(VI) from insoluble chromate compounds [Hazelwood et al. 2004]. Several other validated procedures for the sampling and analysis of Cr(VI) in occupational settings have been published in the United Kingdom, France, and Germany [Ashley et al. 2003].

3.2.2 Wipe Sampling Methods

NIOSH, OSHA, and ASTM have developed methods that can be used for the detection of

Cr(VI) by using wipe samples. OSHA Method W-4001 is a wipe method specific for Cr(VI) sampling [OSHA 2001]. NIOSH Method 9102, "Elements on Wipes," is a simultaneous elemental analysis which is not compound specific [NIOSH 2003d]. ASTM D6966, "Standard Practice for the Collection of Dust Samples using Wipe Sampling Methods for Subsequent Determination of Metals" [ASTM 2003] applies to metals determination, so the same sampling procedure may be applicable to the collection of Cr(VI) in surface dust. Sample preparation and analysis procedures using this method for Cr(VI) determination would be similar to those for the airborne Cr(VI) methods in section 3.2.1. However, media and matrix effects could be problematic for the reasons already discussed (i.e., biases in Cr(VI) measurement due to redox reactions with the sampling media and/or the co-sampled matrix).

NIOSH Method 9101, "Hexavalent Chromium in Settled Dust Samples", allows for screening of soluble Cr(VI) in settled dust [NIOSH 1996a]. Estimation of Cr(VI) in dust may be obtained by laboratory analysis for Cr(VI) using NIOSH Method 7605 or equivalent methods. Analytical results from wipe sampling and analysis should be viewed as qualitative or semi-quantitative.

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Table 3–1. Comparison of NIOSH and OSHA analytical methods for airborne hexavalent chromium determination (adapted from Boiano et al. [2000])

Parameter	NIOSH 7605	OSHA ID-215	NIOSH 7703
Sample collection, handling and storage:			
Media	PVC 37 mm; 5.0 µm Cellulose backup pad	PVC 37 mm; 5.0 µm Cellulose backup pad	PVE, MCE, or PTFE 37 mm; 5.0, 0.8, 1.0 µm Cellulose backup pad
Equipment	Personal sampling pump	Personal sampling pump	Personal sampling pump
Flow rate	1-4 L min^{-1}	2 L min^{-1}	1-4 L min^{-1}
Sample preparation for shipment to laboratory	Using Teflon®-coated tweezers, transfer filter to 20 mL glass vial with Teflon® cap liner	Using Teflon®-coated tweezers, transfer filter to 20 mL glass vial with Teflon® cap liner	Not applicable if analyzed on-site. Same sample handling as NIOSH 7605 and OSHA ID-215 if analyzed off-site.
Sample refrigeration	Optional	4ºC	None required
Sample preparation and analysis:			
Extraction solution	2% NaOH/3% Na_2CO_3 or 0.05 M $(NH_4)_2SO_4$/0.05 M $(NH_4OH$ (pH 8)	10% Na_2CO_3/2% $NaHCO_3$/phosphate buffer/Mg II (as $MgSO_4$) (pH 8)	0.05 M $(NH_4)_2SO_4$/0.05 M NH_40H (pH 8)
Extraction equipment	Hot plate	Hot plate	Ultrasonic bath
Cr^{VI} isolation	Ion chromatography	Ion chromatography	Strong anion exchange solid phase extraction
Eluent	0.25 M $(NH_4)_2SO_4$/ 0.1M NH_4OH	0.25 M $(NH_4)_2SO_4$/ 0.1M NH_4OH	0.5M $(NH_4)_2SO_4$/ 0.1M NH_4OH
Post-column reagent (derivatization)	2 mM 1,5 diphenyl-carbazide/10% methanol/1 M H_2SO_4	2 mM 1,5 diphenyl-carbazide /10% methanol/1 M H_2SO_4	1,5 diphenylcarbazide/ acetonitrile solution added to eluent acidified with 1 M HCl
Analyte	Cr-DPC complex	Cr-DPC complex	Cr-DPC complex
Detection	UV-Vis: 540 nm	UV-Vis: 540 nm	UV-Vis: 540 nm
LOD/LOQ/µg	0.02/0.06	0.01/0.03	0.09/0.27
Accuracy	±16.5%	±12.9%	±16.8%

Abbreviations: DPC=diphenylcarbazide/diphenylcarbazone; LOD/LOQ=limit of detection/limit of quantitation; MCE=mixed cellulose ester; PTFE=polytetrafluoroethylene; PVC=polyvinylchloride; UV-Vis=ultraviolet-visible.

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3.3 BIOLOGICAL MARKERS

Biomarkers may serve several purposes where there is epidemiological evidence that exposure causes a particular disease: answering questions of intensity and timing of exposure; testing the effectiveness of controls; assessing subgroups within a worker population; and functioning as an indicator of early disease [Schulte 1995]. Research is ongoing to identify reliable quantifiable biomarkers of Cr(VI) occupational exposure that can indicate exposure levels, effects of exposure, or early disease conditions. The biological markers of Cr(VI) exposure and effect have been reviewed [ATSDR 2000]. Biomarkers should be evaluated carefully as variables including diet, Cr(VI)-reducing capacity, type of occupational exposure, sensitivity of the analytical method used, and other factors affect results. Biomarkers for Cr(VI) compounds are currently of uncertain value as early indicators of potential Cr(VI)-related health effects (see Appendix A, [NIOSH 2005a]).

An important consideration in biological testing for Cr(VI) is the reduction of Cr(VI) to Cr(III) throughout the body. Some biological markers distinguish Cr(VI) levels while others assess only total chromium levels due to the varying distribution of Cr(III) and Cr(VI) within body compartments. Inhalation is the primary route of concern for occupational Cr(VI) exposure. Inhaled Cr(VI) enters the respiratory system where it may remain, be reduced or enter the bloodstream. Cr(VI) may be reduced to Cr(III) in the lungs or plasma and excreted as Cr(III) in the urine. Cr(VI) that is not reduced in the plasma may enter erythrocytes and lymphocytes. This distribution of absorbed Cr(VI) permits the biological monitoring of Cr in urine, whole blood, plasma, and blood cells in Cr(VI)-exposed workers [Miksche and Lewalter 1997].

Urinary chromium levels have been extensively studied. They are a measure of total chromium exposure as Cr(VI) is reduced within the body to Cr(III). Blood Cr levels are lower than urinary levels. Biological monitoring of blood chromium requires careful techniques and equipment to avoid contamination of the samples and a sensitive method of analytical detection. Measurement of erythrocyte Cr levels is a measure of Cr(VI)

exposure as Cr(VI) passes through the cell membranes while Cr(III) does not [Gray and Sterling 1950].

3.3.1 Biological markers of exposure

3.3.1.1 Measurement of chromium in urine

Urinary chromium levels are a measure of total chromium exposure as Cr(VI) is reduced within the body to Cr(III). ACGIH [2005a] has recommended BEIs of 10 μg/g creatinine and 30 μg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. These BEIs are applicable to manual metal arc (MMA) stainless steel welding and apply only to workers with a history of chronic Cr(VI) exposure.

Gylseth et al. [1977] reported a significant correlation ($p<0.001$) between workplace Cr exposure and urinary Cr concentration after work in five alloyed steel welders. It was assumed that most of their exposure was to soluble Cr(VI). A urinary Cr concentration of 40–50 μg Cr per liter of urine corresponded to an approximate workplace exposure of 50 μg Cr/m^3.

Lindberg and Vesterberg [1983] measured the Cr(VI) exposures of eight chromeplaters with personal air samplers and monitored their urinary Cr concentrations. The urinary Cr levels increased from Monday morning until Tuesday afternoon and then remained constant throughout the workweek. The Monday and Thursday preshift and postshift urinary Cr level and exposure were also monitored on a larger group of 90 chromeplaters. Exposure correlated with Thursday postshift urinary Cr levels with exposures of approximately 2 μg/m^3 correlating with ≤ 100nmol Cr/l urine.

Angerer et al. [1987] measured Cr concentrations in the erythrocytes, plasma and urine of 103 MMA welding and/or metal inert gas (MIG) welders. Personal air monitoring was also conducted; chromium trioxide exposures ranged from <1 to 50 μg/m^3. The urinary chromium concentrations ranged from 5.40 to 229.4 μg/l; approximately five and 200

times higher than the level of non-exposed people. Erythrocyte, plasma, and urine chromium levels were highly correlated ($p<0.0001$). The authors reported that plasma chromium levels of approximately 10 μg/l and urine chromium levels of 40 μg/l corresponded to an external exposure of 100 μg CrO_3/m^3 while erythrocyte chromium concentrations greater than 0.60 μg/l indicated exposures greater than 100 μg CrO_3/m^3.

Minoai and Cavalleri [1988] measured urinary Cr levels in dichromate production workers exposed predominantly to Cr(VI) or Cr(III). A correlation was found between Cr(VI) exposure as measured by personal air sampling and postshift urinary levels. Cr(VI) was not detected in the urine samples indicating the in vivo reduction of Cr(VI) to Cr(III).

Liu et al. [1998] reported a correlation between air and urinary chromium concentrations in hard-chrome platers, nickel-chrome electroplaters, and aluminum anode-oxidation plant workers. Hard-chrome plating workers had the highest air and urinary chromium concentrations with geometric means of 4.2 μg Cr/m^3 TWA and 2.44 μg/g creatinine, respectively.

Individual differences in the ability to reduce Cr(VI) have been demonstrated [Miksche and Lewalter 1997]. Individuals with a weaker Cr(VI)-reducing capacity have lower urine Cr levels in comparison to individuals with a stronger Cr(VI)-reducing capacity. Therefore, analyzing only urinary Cr(VI) levels may not provide an accurate analysis of occupational exposure and health hazard.

3.3.1.2 Measurement of chromium in blood, plasma and blood cells

Plasma or whole blood chromium levels are indicative of total chromium exposure as Cr(VI) may be reduced to Cr(III) in the plasma. Intracellular chromium levels are indicative of Cr(VI) exposure as Cr(VI) passes through cell membranes while Cr(III) does not [Gray and Sterling 1950]. The chromium concentration inside erythrocytes indicates exposure to Cr(VI) sometime during the approximate 120 day lifespan of the

cells. There are two advantages to the monitoring of chromium levels in red blood cells versus urine: the sampling time may be relatively independent of the time of exposure, and it permits the determination of Cr(VI), rather than only total chromium, absorption [Wiegand et al. 1988].

Wiegand et al. [1985] investigated the kinetics of $^{51}Cr(VI)$ uptake into human erythrocytes in vitro. Two different first order processes, with half-life times of 22.7 seconds and 10.4 minutes, were observed when erythrocytes were incubated with sodium dichromate concentrations ranging from 10μM to 50 mM. Approximately 15 percent of the administered dose of Cr(VI) remained in the plasma after a two hour incubation. The maximal capacity for Cr(VI) uptake into erythrocytes was $3.1x10^8$ chromate ions per cell per minute.

There are many variables that may affect chromium levels in the blood including diet, individual Cr(VI)-reducing capacity, and type of occupational exposure. Corbett et al. [1998] reported an enhanced in vitro Cr(VI)-reducing ability in the plasma from an individual who had recently eaten in comparison to a fasted individual. A concentration-dependent distribution of Cr between the RBCs and plasma was reported. A higher Cr(VI) concentration was associated with a higher Cr(VI) concentration in erythrocytes resulting in a lower plasma to erythrocyte ratio of total chromium.

Individual differences in the ability to reduce Cr(VI) have been demonstrated [Miksche and Lewalter 1997]. Individuals with a weaker plasma Cr(VI)-reducing capacity have elevated plasma Cr(VI) levels in comparison to individuals with a stronger Cr(VI)-reducing capacity. Therefore elevated blood plasma levels may be indicative of high chromium exposures and/or a low plasma Cr(VI)-reducing ability.

Cr(VI) uptake into erythrocytes may also be dependent on the Cr(VI) particle size [Miksche and Lewalter 1997]. Smaller particles, as in welding fume exposure (<0.5 μm), may be more efficiently reduced in the lungs than larger particles, such as those of

chromate dust exposure (>10 μm).

Minoai and Cavalleri [1988] measured serum and erythrocyte Cr levels in dichromate production workers exposed predominantly to Cr(VI) compounds (chromic trioxide or potassium dichromate) or Cr(III) (basic chromium sulphate) compounds. Workers exposed predominantly to Cr(VI) compounds had lower serum and higher erythrocyte Cr levels in comparison to predominantly Cr(III)-exposed workers, providing evidence of an enhanced ability of Cr(VI) to enter erythrocytes in comparison to Cr(III).

Angerer et al. [1987] measured Cr concentrations in the erythrocytes, plasma and urine of 103 MMA welding and/or metal inert gas (MIG) welders. Personal air monitoring was also conducted. Airborne chromium trioxide concentrations for MMA welders ranged from <1 to 50 μg/m^3 with 50% <4 μg/m^3. Airborne chromium trioxide concentrations for MIG welders ranged from <1 to 80 μg/m^3 with a median of 10 μg/m^3. More than half (54%) of measured erythrocyte Cr levels were below the limit of detection of 0.6 μg/l. Erythrocyte Cr concentration was recommended for its specificity but limited by its low sensitivity. Chromium was detected in the plasma of all welders, ranging from 2.2 to 68.5 μg/l; approximately two to 50 times higher than the level of non-exposed people. Plasma Cr concentration was recommended as a sensitive parameter limited by its lack of specificity. Erythrocyte, plasma, and urine chromium levels were highly correlated with each other ($p<0.0001$).

3.3.2 Biological markers of effect

3.3.2.1 Renal biomarkers

The concentration levels of certain proteins and enzymes in the urine of workers may indicate early effects of Cr(VI) exposure. Liu et al. [1998] measured urinary *N*-acetyl-ß-glucosaminidase (NAG), $ß_2$-microglobulin ($ß_2$M), total protein, and microalbumin levels in 34 hard-chrome plating workers, 98 nickel-chrome electroplating workers, and 46 aluminum anode-oxidation workers who had no metal exposure and served as the reference group. Hard-chrome platers were exposed to the highest airborne chromium

concentrations (geometric mean 4.20 μg Cr/m^3 TWA) and had the highest urinary NAG concentrations (geometric mean of 4.9 IU/g creatinine). NAG levels were significantly higher among hard-chromeplating workers while the other biological markers measured were not. NAG levels were significantly associated with age ($p<0.05$) and gender ($p<0.01$) and not associated with employment duration.

3.3.2.2 Genotoxic biomarkers

Genotoxic biomarkers may indicate exposure to mutagenic carcinogens. More information about the genotoxic effects of Cr(VI) compounds is presented in Chapter Five, Section 5.2.

DNA strand breaks in lymphocytes and 8-hydroxy-deoxyguanosine (8-OHdG) excretion in urine can be induced by Cr(VI) exposure in vitro [Aiyar et al. 1991; Gao et al. 1992].

Gao et al. [1994] investigated DNA damage in the lymphocytes of Cr(VI)-exposed workers. No significant increases in DNA strand breaks or 8-OHdG levels were found in the lymphocytes of exposed workers in comparison to controls. The exposure level for the exposed group was reported to be approximately 0.01 mg Cr(VI)/m^3.

Gambelunghe et al. [2003] evaluated DNA strand breaks and apoptosis in the peripheral lymphocytes of chrome-plating workers. Previous air monitoring at this plant indicated total chromium levels from 0.4 to 4.5 μg/m^3. Cr(VI)-exposed workers had higher levels of chromium in their urine, erythrocyte and lymphocytes than unexposed controls. The comet assay demonstrated an increase in DNA strand breaks in Cr(VI)-exposed workers. The percentage of apoptotic nuclei did not differ between exposed workers and controls. Urinary chromium concentrations correlated with erythrocyte chromium concentrations while lymphocyte chromium concentrations correlated with comet tail moment, an indicator of DNA damage.

Kuo et al. [2003] reported positive correlations between urinary 8-OHdG concentrations

and both urinary Cr concentration ($p<0.01$) and airborne Cr concentration ($p<0.1$) in a study of 50 electroplating workers.

3.3.2.3 Other biomarkers of effect

Li et al. [2001] reported that sperm count and sperm motility were significantly lower ($p<0.05$) in the semen of Cr(VI)-exposed workers in comparison to unexposed control workers. The seminal volume and liquefaction time of the semen from the two groups was not significantly different. Cr(VI)-exposed workers had significantly ($p<0.05$) increased serum follicle stimulating hormone levels compared to controls; LH and Cr levels were not significantly different between groups. The seminal fluid of exposed workers contained significantly ($p<0.05$) lower levels of lactate dehydrogenase (LDH), lactate dehydrogenase C4 isoenzyme (LDH-x), and zinc; Cr levels were not different.

CHAPTER 4: HUMAN HEALTH EFFECTS

Most of the health effects associated with occupational Cr(VI) exposure are well-known and have been widely reviewed (see citations in Section 4.1.1, Lung Cancer). The following discussion will focus on quantitative exposure-response studies of those effects and new information not previously reviewed by NIOSH [1975, 1980].

4.1 Cancer

4.1.1 Lung Cancer

Hexavalent chromium is a well-established occupational carcinogen associated with lung cancer and nasal and sinus cancer. In 1989, the International Agency for Research on Cancer (IARC) critically evaluated the published epidemiologic studies of chromium compounds including Cr(VI), and concluded that "there is sufficient evidence in humans for the carcinogenicity of chromium[VI] compounds as encountered in the chromate production, chromate pigment production and chromium plating industries" (i.e., IARC category "Group 1" carcinogen) [IARC 1990]. The IARC-reviewed studies of workers in those industries and the ferrochromium industry are presented in Tables 4-1—4-4. Additional details and reviews of those studies are available in the IARC monograph and elsewhere [IARC 1990; NIOSH 1975, 1980; WHO 1988; ATSDR 2000; EPA 1998; Dutch Expert Committee on Occupational Standards 1998; Government of Canada et al. 1994; Hughes et al. 1994; Cross et al. 1997; Cohen et al. 1993; Lees 1991; Langård 1983, 1990, 1993; Hayes 1980, 1988, 1997; Gibb et al. 1986; Committee on Biologic Effects of Atmospheric Pollutants 1974]. Although these studies established an association between occupational exposure to chromium and lung cancer, the specific form of chromium responsible for the excess risk of cancer was usually not identified nor were the effects of tobacco smoking always taken into account. However, the observed excesses of respiratory cancer (i.e., two- to more than 50-fold in chromium production workers) were likely too high to be due solely to smoking.

4.1.1.1 Epidemiologic Exposure-Response Analyses of Lung Cancer

Sections 4.1.1.1.1—4.1.1.1.4 focus on epidemiologic studies published after the IARC

review that investigated exposure-response relationships for hexavalent chromium and lung cancer using cumulative quantitative Cr(VI) exposure data. Exposure-response models based on cumulative exposure data can predict disease risk for a particular Cr(VI) exposure over a period of time. Epidemiologic studies that provided evidence of an exposure-response relationship based on other kinds of exposure data (e.g., duration of exposure) have been reviewed by the authors cited above and others [CRIOS 2003; K.S. Crump Division 1995]. Reanalyses of data from published epidemiologic studies (i.e., quantitative risk assessments) are described in Chapter Six, Assessment of Risk.

4.1.1.1.1 U.S. Chromate Production Workers, North Carolina (Pastides et al. [1994a])

A retrospective cohort study of 398 current and former workers employed for at least one year between 1971 and 1989 was conducted in a large chromate production facility in Castle Hayne, North Carolina. The plant opened in 1971 and was designed to reduce the high level of chromium exposure found at the company's former production facilities in Ohio and New Jersey. The study was performed to determine if there was early evidence for an increased risk of cancer incidence or mortality and to determine whether any increase was related to the level or duration of exposure to Cr(VI). More than 5,000 personal breathing zone samples collected from 1974 to 1989 were available from company records for 352 of the 398 employees. Concentrations of Cr(VI) ranged from below the limit of detection to 289 $\mu g/m^3$ (8-hour TWA), with >99% of the samples less than 50 $\mu g/m^3$. Area samples were used to estimate personal monitoring concentrations for 1971—1972. (Further description of the exposure data is available in Pastides et al. [1994b]). Forty-two of the forty-five workers with previous occupational exposure to chromium had transferred from the older Painesville, Ohio plant to Castle Hayne. Estimated airborne chromium concentrations at the Ohio plant ranged from 0.05 mg/m^3–1.45 mg/m^3 of total chromium for production workers to a maximum of 5.67 mg/m^3 for maintenance workers.

Mortality of the 311 white male Castle Hayne workers from all causes of death (n=16),

cancer (all sites) (n=6), or lung cancer (n=2) did not differ significantly from the mortality experience of eight surrounding North Carolina counties or the United States white male population. Internal comparisons were used to address an apparent "healthy worker" effect in the cohort. Workers with "high" cumulative Cr(VI) exposure (i.e., ≥10 "µg-years" of Cr(VI)) were compared to workers with "low" exposure (i.e., <10 "µg-years" Cr(VI)). No significant differences in cancer risk were found between the two groups after considering the effects of age, previous chromium exposure, and smoking. There was a significantly increased risk of mortality and cancer, including lung cancer, among a subgroup of employees (11% of the cohort) that transferred from older facilities (odds ratio (OR)=1.27 for each three years of previous exposure; 90% CI=1.07—1.51; cancer OR=1.22 for each three years of previous exposure; 90% CI=1.03—1.45, controlling for age, years of previous exposure, and smoking status and including malignances among living and deceased subjects). (Regression analyses that excluded transferred employees were not reported). The results of this study are limited by a small number of deaths and cases and a short followup period and the authors stated "only a large and early-acting cancer risk would have been identifiable" [Pastides et al. 1994a]. The average total years between first employment in any chromate production facility and death was 15.2 years; the maximum was 35.3 years [Pastides et al. 1994a].

4.1.1.1.2 U.S. Chromate Production Workers, Maryland (Hayes et al. [1979]; Gibb et al. [2000a])

Gibb et al. [2000a] conducted a retrospective analysis of lung cancer mortality in a cohort of Maryland chromate production workers first studied by Hayes et al. [1979]. The cohort studied by Hayes et al. [1979] consisted of 2,101 male salaried and hourly workers (restricted to 1,803 hourly workers) employed for at least 90 days between January 1, 1945 and December 31, 1974 who had worked in new and/or old production sites (Table 1). Gibb et al. [2000a] identified a study cohort of 2,357 male workers first employed between 1950 and 1974. Workers who started employment before August 1, 1950 were excluded because a new plant was completed on that date and extensive exposure information began to be collected. Workers starting after that date, but with short-term

employment (i.e., <90 days) were included in the study group to increase the size of the low exposure group. The Hayes et al. [1979] study identified deaths through July 1977. Gibb et al [2000a] extended the followup period until the end of 1992, and included a detailed retrospective assessment of Cr(VI) exposure and information about most workers' smoking habits (see Chapter Six, Assessment of Risk for further description of the exposure and smoking data). The mean length of employment was 3.3 years for white workers (n=1,205), 3.7 years for nonwhite workers (n=848), 0.6 years for workers of unknown race (n=304), and 3.1 years for the total cohort (n=2,357). The mean followup time ranged from 26 years to 32 years. The mean cumulative exposures to hexavalent chromium were 0.18 mg/m^3-years and 0.13 mg/m^3-years for nonwhite (n=848) and white employees (n=1,205), respectively.

Lung cancer mortality ratios increased with increasing cumulative exposure (i.e., mg CrO_3/m^3-years)—from 0.96 in the lowest quartile to 1.57 (95% CI 1.07—2.20; five-year exposure lag) and 2.24 (95% CI 1.60—3.03; five-year exposure lag) in the two highest quartiles. The number of expected lung cancer deaths was based on age-, race-, and calendar year-specific rates for Maryland. Proportional hazards models that controlled for the effects of smoking predicted increasing lung cancer risk with increasing hexavalent chromium cumulative exposure (relative risks: 1.83, 2.48, and 3.32 for second, third, and fourth exposure quartiles, respectively, compared with first quartile of cumulative exposure; confidence intervals not reported; five-year exposure lag) [Gibb et al. 2000a].

In an analysis by industry consultants of simulated cohort data, lung cancer mortality ratios remained statistically significant for white workers and the total cohort regardless of whether city, county, or state reference populations were used [Exponent 2002]. The simulated data were based on descriptive statistics for the entire cohort provided in Gibb et al. [2000a], mainly Table 2.

4.1.1.1.3 U.S. Chromate Production Workers, Ohio (Luippold et al. [2003])

Luippold et al. [2003] conducted a retrospective cohort study of lung cancer mortality in 493 chromate production workers employed ≥ one year between 1940 and 1972 in a Painesville, Ohio plant studied earlier by Mancuso et al. [1975; 1997]. The current study identified a more recent cohort that did not overlap with the Mancuso et al. cohorts. These workers had not been employed in any of the company's other facilities that used or produced Cr(VI). (However, workers who later worked at the North Carolina plant that had available quantitative estimates of Cr(VI) were included in this study without consideration of their subsequent exposure at the North Carolina plant). Their mortality was followed from 1941 to the end of 1997 and compared with U.S. and Ohio rates. More than 800 area samples of airborne Cr(VI) from 21 industrial hygiene surveys were available for formation of a job-exposure matrix. The surveys were conducted in 1943, 1945, 1948, and every year between 1955 and 1971. Samples were collected in impingers and analyzed colorimetrically for Cr(VI). Details about the exposure data are given by Proctor et al. [2003]. The effects of smoking could not be assessed because of insufficient data.

Cumulative Cr(VI) exposure was divided into five categories: 0.00—0.19, 0.20—0.48, 0.49—1.04, 1.05—2.69, and 2.70—23.0 mg/m^3-years. (A rationale for selection of these categories was not described). Person-years in each category ranged from 2,369 to 3,220 and the number of deaths from trachea, bronchus, or lung cancer ranged from three in the lowest exposure category to 20 in the highest (n=51). The standardized mortality ratios (SMRs) were statistically significant in the two highest cumulative exposure categories (3.65 (95% CI 2.08—5.92) and 4.63 (2.83—7.16), respectively). SMRs were also significantly increased for year of hire before 1960, ≥20 years of employment, and ≥20 years since first exposure. The tests for trend across increasing categories of cumulative exposure, year of hire, and duration of employment were statistically significant ($p \leq 0.005$). A test for departure of the data from linearity was not statistically significant (χ^2 goodness of fit of linear model; p=0.23).

4.1.1.1.4 European welders (Simonato et al. [1991])

IARC researchers conducted a large study of lung cancer in 11,092 male welders (164,077 person-years) from 135 companies in nine European countries. Stainless steel welders are exposed to welding fumes that can contain hexavalent chromium and other carcinogens such as nickel. Mortality and incidence were analyzed by cause, time since first exposure, duration of employment, and estimated cumulative exposure to total fumes, chromium (Cr), Cr(VI), and nickel (Ni). The observation period and criteria for inclusion of welders varied from country to country. Data about subjects' smoking habits were not available for the entire cohort so no adjustment could be made. While mortality from all causes of death was significantly lower than national rates, the number of deaths from lung cancer (116 observed; 86.81 expected; SMR 1.34 (95% CI 1.10-1.60)), and malignant neoplasms of the bladder (15 observed; 7.86 expected; SMR 1.91 (95% CI 1.07-3.15)) were significantly higher. Lung cancer SMRs tended to increase with years since first exposure for stainless steel welders and mild steel welders; the trend was statistically significant for the stainless steel welders ($p<0.05$). The SMRs for subgroups of stainless steel welders with at least five years of employment and 20 years since first exposure and high cumulative exposure to either Cr(VI) or Ni (i.e., $\geq$0.5 mg-years/m^3) were not significantly higher than SMRs for the low cumulative exposure subgroup (i.e., <0.5 mg-years/m^3) [Simonato et al. 1991].

IARC classifies welding fumes and gases as Group2B carcinogens—limited evidence of carcinogenicity in humans [IARC 1990] and NIOSH recommends that "exposures to all welding emissions be reduced to the lowest feasible concentrations using state-of-the-art engineering controls and work practices" [NIOSH 1988a].

4.1.2 Nasal and Sinus Cancer

Cases or deaths from sinonasal cancers were reported in five IARC-reviewed studies of chromium production workers in the United States, United Kingdom, and Japan, chromate pigment production workers in Norway, and chromium platers in the United Kingdom (see Tables 4-1—4-3). IARC concluded that the findings represented a "pattern of excess risk" for these rare cancers [IARC 1990].

Subsequent mortality studies of chromium or chromate production workers employed in New Jersey between 1937 and 1971 and in the United Kingdom between 1950 and 1976 reported significant excesses of deaths from nasal and sinus cancer (proportionate cancer mortality ratio (PCMR)=5.18 for white males, $p<0.05$, six deaths observed and no deaths observed in black males [Rosenman and Stanbury 1996]; SMR adjusted for social class and area=1,538, $p<0.05$, four deaths observed [Davies et al. 1991]). Cr(VI) exposure concentrations were not reported. However, an earlier survey of three chromate production facilities in the UK found that average air concentrations of Cr(VI) in various phases of the process ranged from 0.002 to 0.88 mg/m^3 [Buckell and Harvey 1951; ATSDR 2000].

Four cases of carcinoma of the nasal region were described in male workers with 19 to 32 years of employment in a Japanese chromate factory [Satoh et al. 1994]. No exposure concentrations were reported.

Although increased or statistically significant numbers of cases of nasal or sinonasal cancer have been reported in case-control or incidence studies of leather workers (e.g., boot and shoe production) or leather tanning workers in Sweden and Italy [Comba et al. 1992; Battista et al. 1995; Mikoczy and Hagmar [2005], a U.S. mortality study did not find an excess number of deaths from cancer of the nasal cavity [Stern et al. 2003]. The studies did not report quantitative exposure concentrations of Cr(VI) and a causative agent could not be determined. Leather tanning workers may be exposed to several other potential occupational carcinogens, including formaldehyde.

4.1.3 Nonrespiratory Cancers

Statistically significant excesses of cancer of the oral region, liver, esophagus, and all cancer sites combined were reported in a few studies reviewed by IARC (Tables 4-1—4-4). IARC [1990] concluded that "for cancers other than of the lung and sinonasal cavity, no consistent pattern of cancer risk has been shown among workers exposed to

chromium compounds." More recent reviews by other groups also did not find a consistent pattern of nonrespiratory cancer risk in workers exposed to inhaled hexavalent chromium [ATSDR 2000; Proctor et al. 2002; Chromate Toxicity Review 2001; EPA 1998; Government of Canada 1994; Cross et al. 1997; CRIOS 2003; Criteria group for occupational standards 2000].

4.1.4 Cancer Meta-analyses

Meta-analysis and other systematic literature review methods are useful tools for summarizing exposure risk estimates from multiple studies. Meta-analyses or summary reviews of epidemiologic studies have been conducted to investigate cancer risk in chromium-exposed workers.

Steenland et al. [1996] reported overall relative risks for specific occupational lung carcinogens, including chromium. Ten epidemiologic studies were selected by the authors as the largest and best-designed studies of chromium production workers, chromate pigment production workers, and chromium platers (i.e., Enterline 1974; Hayes et al. 1979; Alderson et al. 1981; Satoh et al. 1981; Korallus et al. 1982; Frentzel-Beyme 1983; Davies 1984; Sorahan et al. 1987; Hayes et al. 1989; Takahashi and Okubo 1990). The summary relative risk for the ten studies was 2.78 (95% confidence interval 2.47—3.52; random effects model), which was the second highest relative risk among eight carcinogens summarized.

Cole and Rodu [2005] conducted meta-analyses of epidemiologic studies published in 1950 or later to test for an association of chromium exposure with all causes of death and death from malignant diseases (i.e., all cancers combined, lung cancer, stomach cancer, cancer of the central nervous system (CNS), kidney cancer, prostate gland cancer, leukemia, Hodgkin's disease, and other lymphatohematopoietic cancers (OLHC)). Available papers (n=114) were evaluated independently by both authors on eight criteria that addressed study quality. In addition, papers with data on lung or stomach cancer were assessed for control of cigarette smoking effects or economic status, respectively.

Lung or stomach cancer papers that were negative or "essentially negative" regarding chrome exposure were included with papers that controlled for smoking or economic status. Forty-nine epidemiologic studies based on 84 papers published since 1950 were used in the meta-analyses. The number of studies in each meta-analysis ranged from 9 for Hodgkin's disease to 47 for lung cancer. Most studies investigated occupational exposure to chromium. Association was measured by an author-defined "SMR" which included odds ratios, proportionate mortality ratios, and most often, standardized mortality ratios. Confidence intervals (i.e., 95%) were calculated by the authors. Mortality risks were not significantly increased for most causes of death (i.e., all causes, prostate gland cancer, kidney cancer, CNS cancer, leukemia, Hodgkin's disease, or OLHC). However, SMRs were significantly increased in all lung cancer meta-analyses (smoking controlled: 26 studies; 1,325 deaths; SMR=118; 95% CI 112-125) (smoking not controlled: 21 studies; 1,129 deaths; SMR=181; 95% CI 171-192) (lung cancer—all: 47 studies; 2,454 deaths; SMR=141; 95% CI 135-147). Stomach cancer mortality risk was significantly increased only in meta-analyses of studies that did not control for effects of economic status (economic status not controlled: 18 studies; 324 deaths; SMR=137; 95% 123-153). The authors stated that statistically significant SMRs for "all cancer" mortality were due mainly to lung cancer (all cancer: 40 studies; 6,011 deaths; SMR=112; 95% CI 109-115). Many of the studies contributing to the meta-analyses did not address bias from the healthy worker effect and thus the results are likely underestimates of the cancer mortality risks. Other limitations of these meta-analyses include lack of (1) exposure characterization of populations such as the route of exposure (i.e., airborne versus ingestion) and (2) detail of criteria used to exclude studies based on "no or little chrome exposure" or "no usable data".

Paddle [1997] conducted a meta-analysis of four studies of chromate production workers in plants in the United States (i.e., Hayes et al. 1979; Pastides et al 1994a), United Kingdom (i.e., Davies et al. 1991), and Germany (i.e., Korallus et al. 1993) that had undergone modifications to reduce chromium exposure. Most of the modifications occurred around 1960. This meta-analysis of lung cancer "postmodification" did not find

a statistically significant excess of lung cancer (30 deaths observed; 27.2 expected; risk measure and confidence interval not reported). The author surmised that none of the individual studies in the meta-analysis or the meta-analysis itself had sufficient statistical power to detect a lung cancer risk of moderate size because of the need to exclude employees who worked before plant modifications and the need to incorporate a latency period, thus leading to very small observed and expected numbers. Meta-analyses of gastrointestinal cancer, laryngeal cancer, or any other nonlung cancer were considered inappropriate by the author because of reporting bias and inconsistent descriptions of the cancer sites [Paddle 1997].

Sjögren et al. authored a brief report of their meta-analysis of five lung cancer studies of Canadian and European welders exposed to stainless steel welding fumes. The meta-analysis found an estimated relative risk of 1.94 (95% CI 1.28—2.93) and accounted for the effects of smoking and asbestos exposure [Sjögren et al. 1994]. (Details of each study's exposure assessment and concentrations were not included).

4.1.5 Summary of Cancer and Cr(VI) Exposure

Occupational exposure to Cr(VI) has long been associated with nasal and sinus cancer and cancers of the lung, trachea, and bronchus. No consistent pattern of nonrespiratory cancer risk has been identified.

Few studies of Cr(VI) workers had sufficient data to determine the quantitative relationship between cumulative hexavalent chromium exposure and lung cancer risk while controlling for the effects of other lung carcinogens, such as tobacco smoke. One such study found a significant relationship between cumulative Cr(VI) exposure (measured as CrO_3) and lung cancer mortality (e.g., Gibb et al. [2000a]); the data were reanalyzed by NIOSH to further investigate the exposure-response relationship (see Chapter Six, Assessment of Risk).

The three meta-analyses and summary reviews of epidemiologic studies with sufficient

statistical power found significantly increased lung cancer risks with chromium exposure.

4.2 Nonmalignant Effects

Cr(VI) exposure is associated with contact dermatitis, skin ulcers, irritation and ulceration of the nasal mucosa, and perforation of the nasal septum [NIOSH 1975]. Reports of kidney damage, liver damage, pulmonary congestion and edema, epigastric pain, erosion and discoloration of the teeth, and perforated ear drums were found in the literature and NIOSH concluded that "sufficient contact with any chromium(VI) material could cause these effects" [NIOSH 1975]. Later studies that provided quantitative Cr(VI) information about the occurrence of those effects is discussed here. (Studies of nonmalignant health effects and total chromium concentrations (i.e., non-speciated) are included in reviews by the Criteria group for occupational standards [2000] and ATSDR [2000]).

4.2.1 Respiratory Effects

The ATSDR [2000] review found many reports and studies published from 1939—1991 of workers exposed to Cr(VI) compounds for intermediate (i.e., 15 days to 364 days) to chronic durations that noted these respiratory effects: epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulcerations of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia.

Five recent epidemiologic studies of three cohorts analyzed quantitative information about occupational exposures to Cr(VI) and respiratory effects. The three worksite surveys described below provide information about workplace Cr(VI) concentrations and health effects at a particular point in time only and do not include statistical analysis of the quantitative relationship between specific work exposures and reported health symptoms; thus contributing little to evaluation of the exposure-response association. (Studies and surveys previously reviewed by NIOSH [1975, 1980] are not included).

4.2.1.1 Work Site Surveys

A NIOSH Health Hazard Evaluation (HHE) of eleven male employees in an Ohio electroplating facility reported that most men had worked in the "hard-chrome" area for the majority of their employment (average duration: 7.5 years; range: 3—16 years). Four of the 11 workers had a perforated nasal septum. Nine of the 11 men had hand scars resulting from past chrome ulcerations. Other effects found during the investigation included nose bleeds, "runny nose", and nasal ulcerations. A total of 17 air samples for hexavalent chromium were collected with a vacuum pump in two days during two- to four-hour periods(14 personal; 3 area). The mean Cr(VI) concentration was 0.004 mg/m^3 (range: <0.001 mg/m^3—0.02 mg/m^3) [Lucas and Kramkowski 1975]. This survey focused on chromic acid exposure; other potential exposures were not noted in the report. Possible limitations of this study include (1) lack of a comparison or unexposed "control" group, (2) inclusion of only current workers, and (3) a small and possibly unrepresentative study group. Other NIOSH HHEs that noted nasal sores or other respiratory effects in chromium-exposed workers had similar limitations and are not discussed here. In addition, some surveys were conducted in workplaces with air concentrations of chromium and other metals, dusts, and chemicals (e.g., nickel, copper, zinc, particulates, ammonia [Zey and Lucas 1985a,b], sulfur dioxide, welding fume, aluminum, carbon monoxide, nitrogen dioxide [Burkhart and Knutti 1994]) that could have contributed to observed and reported effects.

An HHE at a small chrome plating shop with six workers (including four platers) found no nasal ulcerations, nasal septal perforations, or lesions on the hands among the workers. However, information was obtained by interview, observation, and questionnaire and no medical examinations were performed. Four personal breathing zone samples with durations of 491 to 505 minutes were analyzed and found to contain low air concentrations of Cr(VI) and total chromium (0.003—0.006 mg/m^3 and 0.009—0.011 mg/m^3, respectively). The HHE was requested because of reported overexposure to chemicals used in chrome plating, poor ventilation, and cardiovascular disorders among employees. NIOSH determined that (1) overexposures to plating chemicals did not exist, (2) local exhaust systems were operating "below recommended levels", and (3) no

occupational factors contributing to heart disease were identified. Recommendations were made for ventilation, housekeeping, and personal protective equipment (PPE) [Ahrenholz and Anderson 1981].

Eleven cases of nasal septum perforation were found in 2,869 shipyard welders in Korea [Lee et al. 2002]. The workers had no history of trauma, surgery, diseases, or medication use that could account for the perforations. Blood and urine chrome concentrations of the cases were below the limit of detection. The cases ranged in age from 37 to 51 years and had welded 12—25 years. Personal air samples for hexavalent chromium were collected from 31 workers in a stainless steel welding shop (shop "F") and the five work locations (i.e., CO_2 welding shops "A--E") where the eleven cases were last employed. ("Most" of the cases had not recently worked in shop "F"). Mean, maximum, and minimum Cr(VI) concentrations, and number of cases were reported for each shop (shops A,B, D, and E had two cases; shop "C" had three). The total number of other workers (non-cases) per shop was not reported. The mean concentrations of Cr(VI) in the welding fume ranged from 0.0012 mg/m^3 (shop "B") to 0.22 mg/m^3 (8-hour time-weighted average) in shop "F". The highest maximum (0.34 mg/m^3) and minimum (0.044 mg/m^3) Cr(VI) concentrations were also measured in shop "F". The mean Cr(VI) concentrations in shops "A", "C", "D" and "E" ranged from 0.0014 (shop "C") to 0.0028 mg/m^3 (shop "E")(maximums for "A"—"E": 0.0013 mg/m^3—0.0050 mg/m^3). Annual industrial hygiene surveys for air concentrations of metals conducted from 1991—2000 found that mean total "chrome" (i.e., Cr) concentrations ranged from 0.002—0.025 mg/m^3 and the maximum concentrations were 0.010—0.509 mg/m^3. The authors judged that pre-1990 concentrations were higher. The authors could not obtain annual total Cr or Cr(VI) concentrations for the stainless steel welding workplace. Use of a comparison group was not reported. The authors assumed that the nasal septal perforations were caused by "long-term exposure to the low-levels of hexavalent chromium during welding" [Lee et al. 2002].

4.2.1.2 Epidemiologic studies

Lindberg and Hedenstierna [1983]

A cross-sectional study of respiratory symptoms, changes in nasal mucosa, and lung function was conducted in chrome plating workers in Swedish factories (n=43: 16 male nonsmokers; 21 male smokers; 3 female nonsmokers; 3 female smokers) [Lindberg and Hedenstierna 1983]. Five chrome baths in three factories were studied for a total of 19 work days. Office employees (n=19: 13 males; 14 nonsmokers) and auto mechanics (n=119 males; 52 nonsmokers) were used as comparison groups for nose and throat effects, and lung function, respectively. For analysis of subjective symptoms and nasal conditions, the 43 exposed workers were divided into two groups: "low" exposure (eight-hour mean $\leq$1.9 $\mu g/m^3$ chromic acid; 19 workers) and "high" mean exposure (2—20 $\mu g/m^3$ chromic acid; 24 workers). Mean daily Cr(VI) exposures ranged from $\leq$1.9—20 $\mu g/m^3$. Their median duration of employment was 2.5 years (range: 0.2—23.6 years). Exposure concentrations were measured with personal air samplers and stationary equipment placed near the chromic acid baths. A statistically significant difference was found in the low exposure group when compared with controls for the effect of "smeary and crusty septal mucosa" (11/19 workers versus 5/19 controls; $p<0.05$). There were no perforations or ulcerations in the low exposure group. Frequency of nasal atrophy was significantly greater in the high exposure group compared with the controls (8/24 workers versus 0/19 controls; $p<0.05$). The high exposure group also had higher frequency of nasal mucosal ulcerations and/or septal perforations (8 workers with ulcerations—2 of those also had perforations; 5 workers with perforations—2 of those also had ulcerations; $p<0.01$; number of controls not reported). Fourteen workers were temporarily exposed to peak concentrations of 20—46 $\mu g/m^3$ when working near the baths; ten of those workers had nasal mucosal ulcerations with or without perforation or perforation only. Workers with low exposure had no significant changes in lung function during the survey. Workers in the high exposure group had slight transient decreases in forced vital capacity (FVC), forced expired volume in one second (FEV_1) and forced mid-expiratory flow during the work week.

The results of that study were used by ATSDR to determine an inhalation minimum risk

level (MRL) of 0.000005 mg/m^3 (0.005 µg/m^3) for intermediate-duration exposure (15 to 364 days) to Cr(VI) as chromium trioxide mist and other dissolved hexavalent chromium aerosols and mists. (An intermediate-duration inhalation MRL of 0.001 mg Cr(VI)/m^3 for exposure to chromium (VI) particulates was derived from studies of rats). ATSDR concluded in its public health statement that "breathing in high levels (greater than 2 µg/m^3) chromium (VI), such as in a compound known as chromic acid or chromium(VI) trioxide, can cause irritation to the nose, such as runny nose, sneezing, itching nosebleeds, ulcers, and holes in the nasal septum".

Huvinen et al. [1996; 2002a,b]

No increased prevalences of respiratory symptoms, lung function deficits, or signs of pneumoconiosis (i.e., small radiographic opacities) were found in a 1993 cross-sectional study of stainless steel production workers [Huvinen et al. 1996]. The median personal Cr(VI) concentration measured in the steel smelting shop in 1987 was 0.5 µg/m^3 (i.e., 0.0005 mg/m^3). (Duration of sample collection and median Cr(VI) concentrations for other work areas were not reported). The study group consisted of 221 production workers with at least eight years of employment in the same department and a control group of 95 workers from the cold rolling mill and other areas where chromium or dust exposure was minimal or non-existent. The chromium-exposed workers were divided into three groups: Cr(VI)-exposed (n=109), Cr(III) exposed (n=76), and chromite-exposed (n=36). Questionnaires regarding health symptoms were completed by 37 former workers; none of those workers reported leaving the company because of a disease. One person reported having chronic bronchitis and two reported having bronchial asthma and no former workers reported other pulmonary diseases, allergic rhinitis, or cancer. Controls and Cr(VI)-exposed workers had similar mean durations of employment (exposed: 16.0 years; controls: 14.4 years), smoking habits, and other characteristics. Logistic regression analyses adjusted for effects of confounding factors and found no significant differences between Cr(VI) exposed workers and controls in reported symptom prevalences, prevalence of impaired lung function (with the exception of impaired peak expiratory flow which was significantly more prevalent in the control

group ($p<0.05$)), or occurrence of small opacities.

A similar cross-sectional study of the same cohort five years later yielded similar results [Huvinen et al. 2002a]. The median Cr(VI) personal concentration (duration of sample collection time not reported) measured in the steel smelting shop in 1999 had decreased to 0.0003 mg/m^3 (maximum: 0.0007 mg/m^3), which the authors attributed to technological improvements in production processes. (Exposure concentrations reported in the text and tables differed; table values are reported here). Cr(VI)-exposed workers (n=104; mean duration of employment: 21.0 years) and controls (n=81; mean employment: 19.4 years)) did not differ significantly in prevalence of respiratory symptoms or lung function deficits. The profusion of small opacities had progressed in three workers (ILO category $\geq$1/0), including one exposed to Cr(VI). Based on the findings in both studies, the authors concluded that exposure to chromium compounds at the measured concentrations does not produce pulmonary fibrosis. Clinical examinations of 29 CrVI-exposed workers from the steel smelting shop found no nasal tumors, chronic ulcerations, or septal perforations (mean duration of employment: 21.4 years) [Huvinen et al. 2002b].

Gibb et al. [2000b]

A retrospective study of 2,357 males first employed between 1950 and 1974 at a chromate production plant included a review of clinic and first aid records for physician findings of nasal irritation, ulceration, perforation, and bleeding, skin irritation and ulceration, dermatitis, burns, conjunctivitis, and perforated eardrum [Gibb et al. 2000b]. The mean and median annual airborne Cr(VI) concentrations (measured as CrO_3) for the job title where the clinical finding first occurred and cohort percentages with various clinical findings, from start of employment to occurrence of the first finding, were determined. (See Chapter Six for further description of the exposure data). About forty percent of the cohort (n=990) worked less than 90 days. These short-term workers were included to increase the low exposure group. Medical records were available for 2,307 men (97.9% of total cohort). The record review found that more than 60% of the cohort

had irritated nasal septum (68.1%) or ulcerated nasal septum (62.9%). Median Cr(VI) exposure (measured as CrO_3) at the time of first diagnosis of these findings and all others (i.e., perforated nasal septum, bleeding nasal septum, irritated skin, ulcerated skin, dermatitis, burn, conjunctivitis, and perforated eardrum) was 0.020—0.028 mg/m^3 (20—28 μg/m^3). The median time from date first employed to date of first diagnosis was less than one month for three conditions: irritated nasal septum (20 days), ulcerated nasal septum (22 days), and perforated eardrum (10 days). (The mean time from date first employed to date of first diagnosis for each of these conditions was 89, 86, and 235 days, respectively). The relationship between Cr(VI) exposure and first occurrence of each clinical finding was evaluated with a proportional hazards model. The model predicted that ambient Cr(VI) exposure was significantly associated with occurrence of ulcerated nasal septum (p=0.0001), ulcerated skin (p=0.004), and perforated eardrum (p=0.03). Relative risks per 0.1 mg/m^3 increase in CrO_3 were 1.20, 1.11, and 1.35 for ulcerated nasal septum, ulcerated skin, and "perforated ear", respectively. Calendar year of hire was associated with each finding except conjunctivitis and irritated skin; the risk decreased as year of hire became more recent. The authors suggested that the reduction could possibly be due to decreases in ambient Cr(VI) exposure from 1950—1985 or changes in plant conditions, such as use of respirators and personal hygiene measures [Gibb et al. 2000b]. The authors also suggested that the proportional hazards model did not find significant associations with all symptoms because the Cr(VI) concentrations were based on annual averages rather than on shorter, more recent average exposures which may have been a more relevant choice.

4.2.1.3 Summary of respiratory effects studies and surveys

A few workplace surveys measured Cr(VI) air concentrations and conducted medical evaluations of workers. These short-term surveys did not include comparison groups or exposure-response analyses. Two surveys found U.S. electroplaters and Korean welders with nasal perforations or other respiratory effects; the lowest mean Cr(VI) concentrations at the worksites were 0.004 mg/m^3 and 0.0012 mg/m^3, respectively [Lucas and Kramkowski 1975; Lee et al. 2002].

Cross-sectional epidemiologic studies of chrome plating workers [Lindberg and Hedenstierna 1983] and stainless steel production workers [Huvinen et al. 1996; 2002a, b] found no nasal perforations at average chromic acid concentrations <2 $\mu g/m^3$. The platers experienced nasal ulcerations and/or septal perforations and transient reductions in lung function at mean concentrations ranging from 2 $\mu g/m^3$ to 20 $\mu g/m^3$. Nasal mucosal ulcerations and/or septal perforations occurred in plating workers exposed to peak concentrations of 20—46 $\mu g/m^3$.

The best exposure-response information to date is from the only epidemiologic study with sufficient health and exposure data to estimate the risks of ulcerated nasal septum, ulcerated skin, perforated nasal septum, and perforated eardrum over time [i.e., Gibb et al. 2000b]. This retrospective study reviewed medical records of more than 2,000 male workers and analyzed thousands of airborne Cr(VI) measurements collected from 1950—1985. More than 60% of the cohort had experienced an irritated nasal septum (68.1%) or ulcerated nasal septum (62.9%) at some time during their employment. The median Cr(VI) exposure (measured as CrO_3) at the time of first diagnosis of these findings and all others (i.e., perforated nasal septum, bleeding nasal septum, irritated skin, ulcerated skin, dermatitis, burn, conjunctivitis, perforated eardrum) was 0.020 mg/m^3—0.028 mg/m^3 (20 $\mu g/m^3$—28 $\mu g/m^3$). Of particular concern is the finding of nasal and ear effects occurring in less than one month: the median time from date first employed to date of first diagnosis was less than one month for irritated nasal septum (20 days), ulcerated nasal septum (22 days), and perforated eardrum (10 days). A proportional hazards model predicted relative risks of 1.20, 1.11, and 1.35 for ulcerated nasal septum, ulcerated skin, and "perforated ear", respectively, for each 0.1 mg/m^3 increase in ambient CrO_3. The authors noted that the chrome platers studied by Lindberg and Hedenstierna [1983] were exposed to chromic acid which may be more irritative than the chromate chemicals occurring with chromate production [Gibb et al. 2000b].

4.2.1.4 Asthma

Occupational asthma due to chromium exposure occurs infrequently compared with allergic contact dermatitis [Leroyer et al. 1998]. The exposure concentration below which no cases of occupational asthma would occur, including cases induced by chromium compounds, is not known [Chan-Yeung 1995]. Furthermore, that concentration is likely to be lower than the concentration that initially led to the employee's sensitization [Chan-Yeung 1995]. Although there have been case series reports of asthma in UK electroplaters [Bright et al. 1997], Finnish stainless steel welders [Keskinen et al. 1980], Russian alumina industry workers [Budanova 1980], and Korean metal plating, construction, and cement manufacturing workers [Park et al. 1994] and a cross-sectional study of UK electroplaters [Burges et al. 1994], there are no quantitative exposure-response assessments of Cr(VI)-related asthma in occupational cohorts and further research is needed.

4.2.2 Dermatologic Effects

Cr(VI) compounds can cause skin irritation, skin ulcers, skin sensitization, and allergic contact dermatitis. In 1975 NIOSH recommended protective clothing and other measures to prevent occupational exposure [NIOSH 1975]. Because of those health hazards, potential eye contact, or other nonrespiratory hazards, protective measures and appropriate work practices are recommended "regardless of the airborne concentration of chromium(VI)" [NIOSH 1975]. Current recommendations for prevention of dermal exposure to Cr(VI) compounds are presented in Chapter Eight, Risk Management.

There are many occupational sources of chromium compounds. Dermatologic effects (i.e., mainly allergic contact dermatitis (ACD)) have been reported from exposure to cement and cement hardening agents, cleaning, washing, and bleaching materials, textiles and furs, leather and artificial leather tanned with chromium, chrome baths, chromium ore, chrome colors and dyes, pigments in soaps, primer paints, anti-corrosion agents, cutting fluids, machine oils, lubricating oils and greases, glues, resin hardeners, wood preservatives, boiler linings, foundry sand, matches, welding fumes, and other sources [Burrows et al. 1999; Burrows 1983, 1987; Handley and Burrows 1994; Haines and

Nieboer 1988; Polak 1983].

No occupational studies have examined the quantitative exposure-response relationship between Cr(VI) exposure and a specific dermatologic effect, such as ACD; thus, an exposure-response relationship has not been clearly established.

Gibb et al. [2000b] evaluated mean Cr(VI) exposure and mean and median time from first employment to diagnosis of several skin or membrane irritations: irritated skin, ulcerated skin, dermatitis, burn, and conjunctivitis (see sections 3.4.2.1 and 3.4.2.1.1). Ulcerated skin and burns were reported in more than 30% of the cohort. The mean Cr(VI) concentration (measured as CrO_3) ranged from 0.049 mg/m^3—0.058 mg/m^3 at the time of first diagnosis of those five effects. The mean days on the job until first diagnosis ranged from 373 to 719 days (median 110—221 days).

Other assessments evaluated the occurrence of ACD from contact with Cr(VI) in soil [e.g., Proctor et al. 1998; Paustenbach et al. 1992; Bagdon and Hazen 1991; Stern et al. 1993; Nethercott et al. 1994, 1995].

4.2.3 Reproductive Effects

The six available studies of pregnancy occurrence, course, or outcome reported little or no information about total Cr or Cr(VI) concentrations at the workplaces of female chromium production workers [Shmitova 1978; 1980] or male welders that were also spouses [Bonde et al. 1992; Hjollund et al. 1995, 1998, 2000]. The lack of consistent findings and exposure-response analysis precludes formation of conclusions about occupational Cr(VI) exposure and adverse effects on pregnancy and childbirth. Further research is needed.

4.2.4 Other Health Effects

4.2.4.1 Mortality studies

More than 30 studies examined numerous noncancer causes of death in jobs with

potential chromium exposure, such as chromate production, chromate pigment production, chromium plating, ferrochromium production, leather tanning, welding, metal polishing, cement finishing, stainless steel grinding or production, gas generation utility work, and paint production or spraying. (Studies previously cited by NIOSH [1975, 1980] are not included).

Most studies found no statistically significant increases (i.e., $p<0.05$) in deaths from nonmalignant respiratory diseases, cardiovascular diseases, circulatory diseases, accidents, or any other noncancer cause of death that was included [i.e., Hayes et al. 1979, 1989; Korallus et al. 1993; Satoh et al. 1981; Sheffet et al. 1982; Royle 1975a; Franchini et al. 1983; Sorahan and Harrington 2000; Axelsson et al. 1980; Becker et al. 1985; Becker 1999; Blair 1980; Dalager et al. 1980; Järvholm et al. 1982; Silverstein et al. 1981; Sjögren et al. 1987; Svensson et al. 1989; Bertazzi et al. 1981; Blot et al. 2000; Montanaro et al. 1997; Milatou-Smith et al. 1997; Moulin et al. 2000; Pastides et al. 1994a; Simonato et al. 1991; Takahashi and Okubo 1990; Luippold et al. 2005]. However, these studies did not include further investigation of the nonsignificant outcomes and therefore do not confirm the absence of an association.

Some studies did identify significant increases in deaths from various causes [i.e., Davies et al. 1991; Alderson et al. 1981; Sorahan et al. 1987; Deschamps et al. 1995; Itoh et al. 1996; Rafnsson and Jóhannesdóttir 1986; Gibb et al. 2000a; Kano et al. 1993; Luippold 2003; Moulin et al. 1993; Rosenman and Stanbury 1996; Stern et al. 1987; Stern 2003]. However, the findings were not consistent: no noncancer cause of death was found to be significantly increased in at least five studies. Furthermore, exposure-response relationships were not examined for those outcomes. Therefore, the results of these studies do not support a causal association between occupational Cr(VI) exposure and a nonmalignant cause of death.

4.2.4.2 Other Health Effects

NIOSH [1975] concluded that Cr(VI) exposure could cause other health effects such as

"kidney damage", "liver damage", pulmonary congestion and edema, epigastric pain, and erosion and discoloration of the teeth. Other effects of exposure to chromic acid and chromates not discussed elsewhere in this section include eye injury, leukocytosis, leukopenia, and eosinophilia [NIOSH 2003c; Johansen et al. 1994]. Acute renal failure and acute chromium intoxication occurred in a male worker following a burn with concentrated chromic acid solution to 1% of his body [Stoner et al. 1988].

There has been little post-1975 research of those effects in occupational cohorts. Furthermore, there is insufficient evidence to conclude that occupational exposure to respirable Cr(VI) is related to other health effects infrequently reported in the literature after the NIOSH [1975] review. These effects included cerebral arachnoiditis in 47 chromium industry workers [Slyusar' and Yakovlev 1981] and cases of gastric disturbances (e.g., chronic gastritis, polyps, ulcers, and mucous membrane erosion) in chromium salt workers [Sterekhova et al. 1978]. Neither study analyzed the relationship of air Cr(VI) concentrations and health effects and one had no comparison group (i.e., Sterekhova et al. [1978]).

Table 4-1. IARC-reviewed epidemiologic studies of cancer in workers in chromate-producing industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs			Cancer at other sites			Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
			Site	Number of deaths or cases	Estimated relative risk	Site	Number of deaths or cases	Estimated relative risk		
Alderson et al. [1981], United Kingdom	Same UK chromate-producing factories as Bidstrup & Case1956]; employed ≥ 1 yr between 1948 and 1977; 2715 males.	Cancer mortality: England, Wales, Scotland	Lung	116 deaths	2.4*	Other sites Nasal cancer	80 2	1.2 7.1*	No	No
Baetjer [1950], United States	290 male lung cancer patients admitted to two hospitals near US chromate plant from 1925 to 1948.	Random sample of hospital admissions	Lung or bronchi	11 reported exposure to chromium	Reported as statistically significant	—	—	—	No	No
Bidstrup and Case [1956], United Kingdom	Three UK chromate factories; mortality followup of 723 men employed 1949—1955.	Cancer mortality: England and Wales	Lung	12	3.6*	Other sites	9	1.1	No	No
Brinton et al. [1952], United States	Male workers in seven chromate plants; active employees 1940-1950.	US male mortality, white, nonwhite	Respiratory system, except larynx	10 white; 16 nonwhite	14.3* 80.0*	Other sites	5 white; 1 nonwhite	1.0	No	No

Continued

Table 4-1 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-producing industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
De Marco et al. [1988], Italy	540 Italian chromate producers employed 1948—1985 with ≥ 1 year cumulative exposure entered into study ≥ 10 years after starting work.	Italian cause-specific death rates	Lung Highly exposed (qualitative estimate of CrVI exposure)	14 6	2.2* 4.2*	Larynx Pleura	3 3	2.9 30.0*	No	No
Federal Security Agency [1953], United State	Health survey of 897 chromate workers in six chromate-producing plants.	Boston chest X-ray survey	Bronchiogenic/ Lung	7 white; 3 nonwhite	53.6 (prevalence ratio)	—	—	—	No	Yes
Hayes et al. [1979], United States	2,101 male workers (restricted to 1,803 workers) employed in a U.S. chromate plant ≥ 90 days 1945—1974, working in new and/or old production sites.	Baltimore city mortality	Trachea, bronchus, lung	59	2.0*	Digestive system Other	13 14	0.60 0.40	No	No
Korallus et al. [1982], Germany	1,140 male workers employed more than one year 1934—1979 at two German chromate plants.	North-Rhine Westphalia mortality	Respiratory organs	51	2.1*	Stomach	12	0.94	No	No

Continued

Table 4-1 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-producing industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
Machle and Gregorius [1948], United States	Male workers in seven chromate plants; active employees 1930—1947; 193 deaths.	Male oil refinery workers 1933—1938	Respiratory system	42	20.7	Digestive tract Oral region (also included in respiratory system)	13 3	2.0 5.4*	No	Reported as "chromates" (see NIOSH [1975])
Mancuso and Hueper [1951]; Mancuso [1975], United States	332 U.S. chromate plant workers employed ≥ one year 1931—1937; all jobs related to exposure to soluble and insoluble chromium; mortality followed through 197	No independent comparison group	Lung	41	—	—	—	—	No	Soluble chromium described as "chiefly hexavalent"

Table 4-1 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-producing industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
Satoh et al. [1981], Japan	896 male workers in chromium manufactur–ing plant in Japan employed ≥ one year between 1918 and 1975; mortality followed until 1978, or death. 84% of chromium compounds manufactured from 1934—1975 were hexavalent compounds.	Age-, cause-specific mortality, Japanese males	Respiratory cancer Years worked: 1—10 11—20 ≥ 21	31 (includes six sinonasal) 5 9 17	9.2* 4.2* 7.5* 17.5*	Stomach	11	1.0	No	No
									Continued	
Taylor [1966]; Enterline [1974], United States Watanabe and Fukuchi [1984], Japan	1,200 males [Enterline 1974] from three U.S. chromate plants, employed 1937—1940 and surveyed 1941—1960.	Cancer mortality; U.S. males 1950, 1953, 1958	Respiratory cancer	69 (2 maxillary sinus)	9.4*	Digestive system	16	1.5	No	No

Source: Adapted from IARC [1990].
*Significant at 95% level.

Table 4-1 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-producing industries.

Table 4-2. IARC-reviewed epidemiologic studies of cancer in workers in chromate-pigment industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
Davies [1978, 1979, 1984], United Kingdom	1002 male workers in three chromate pigment factories: A, lead and zinc chromate; B, lead and zinc chromate; C, lead chromate; followed up to 1981.	Mortality, England and Wales	Lung: ≥ one year worked, "high" or "medium" exposure to chromate-containing dust:			Nasal sinuses	1	5	No (Smoking habits of lung cancer cases reported only)	No
						Larynx	2	2.15		
			A (entered 1932—1954):	21	2.2*					
			B (1948-1967):	11	4.4*					
			"high", "medium", or "low" exposure: C (1946—1960)	7	1.1					
Frentzel-Beyme [1983], Germany, Netherlands	978 male workers from five factories employed > six months in three German or Dutch factories manufactur–ing zinc and lead chromates and followed for 15,076 person-years.	Local death rates for Federal Republic of Germany and the Netherlands	Lung	19	2.0*	—	—	—	No	No

Continued

Table 4-2 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-pigment industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs			Cancer at other sites			Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
			Site	Number of deaths or cases	Estimated relative risk	Site	Number of deaths or cases	Estimated relative risk		
Haguenoer et al. [1981], France	251 male workers in a lead and zinc chromate pigment factory employed > six months between 1958 and 1977.	Standard death rates, northern France 1958—1977	Lung	11	4.6*	—	—	—	No (Smoking habits of ancer cases reported only)	No
Langård and Norseth [1975, 1979]; Langård and Vigander [1983], Norway	133 Norwegian workers producing zinc chromate pigments employed between 1948 and end of 1972. Twenty-four workers had more than three years of employment to 1972. Cohort was observed to the end of 1980.	Cancer incidence, Norway 1955—1976	Lung	6 (excluding one case with < three years' employment)	44	Gastroin-testinal Nasal cavity	3 1	6.4 —	No (Smoking habits of cancer cases reported only)	No and Yes: Exposure reported as µg/m^3 or mg/m^3 of chromium by Langård and Norseth [1975] and Langård and Vigander [1983]; later reported as mg/m^3 of Cr (VI) in a review by Langård [1993].

Table 4-2 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromate-pigment industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
								Continued		
Sheffet et al. [1982]; Hayes et al. [1989], United States	1,181 white and 698 nonwhite males employed in a lead and zinc chromate pigment factory for ≥ 1 month between 1940 and 1969; followed to end of 1982.	Mortality, U.S. white and nonwhite males	Lung	24	1.4	Stomach	6	1.8	No	No
			≥ 30 years after initial employment and:							
			< one year employment	3	1.4†					
			1—9 years' employment	3	2.0†					
			> 10 years' employment	6	3.2†					

Source: Adapted from IARC [1990].
Dash in "Estimated relative risk" indicates not reported.
*Significant at 95% level.
† *p* for trend <0.01.

Table 4-3. IARC-reviewed studies of workers in chromium plating industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs			Cancer at other sites			Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) Identified
			Site	Number of deaths or cases	Estimated relative risk	Site	Number of deaths or cases	Estimated relative risk		
Franchini et al. [1983], Italy	178 male workers from nine chrome plating plants (116 in "thick" plating; 62 in "thin") employed ≥ one year between 1951 and 1981.	Italy, male mortality	Lung	3	3.3 (4.3* for "thick" platers")	All sites	2	1.9	No	Yes; Chromium trioxide CrO_3) 1980 averages: 7µg/m^3 near plating baths; 3 µg/m^3 in middle of the room.
						Stomach	2	4		
						Pancreas	2	18*		
Okubo and Tsuchiya [1977; 1979; 1987], Japan	Japanese chromium platers; 952 male and female workers with > six months' experience. Average follow-up period was 5.2 years for the chromium workers and 5.1 years for controls.		Lung	0	—	All sites	5	0.5	No	No

Continued

Table 4-3 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromium plating industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Number of deaths or cases	Estimated relative risk	Cancer at other sites: Site	Number of deaths or cases	Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) Identified
Royle [1975a,b], United Kingdom	Mortality study of 1,056 past and current male platers in 54 chromium-plating plants, employed ≥ 3 months; 130 men had died by May 31, 1974 (Females were also studied).	1,099 non-exposed males in the plants and in two nonplating industries.	Lung and pleura	24	1.4	All sites (including lung)	44	1.7*	Yes. Information available; smoking habits of platers were compared with controls—"no important differences."	Yes, at 42 plants. Reported "chromic acid air content" at breathing zone height was generally <0.03 mg/m^3.
						Gastro-intestinal	8	1.5		
						Other sites (excluding lung, gastro-intestinal)	12	1.9		
Silverstein et al. [1981], United States	Workers with ≥ 10 years of service in a die-casting and nickel and chrome electroplating plant; 238 deaths (white and nonwhite) between 1974 and 1978.	U.S. national mortality statistics	Lung: White men White women	28 10	1.9* 3.7*	All sites (men)	53	1.4*	No	Limited to only a few samples of airborne chromic acid.
						Larynx (men)	2	3.3		
						Stomach (men)	4	2.5		
						Lympho-sarcoma, reticulo-sarcoma (men)	2	2.9		

Continued

Table 4-3 (continued). IARC-reviewed epidemiologic studies of cancer in workers in chromium plating industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Number of deaths or cases	Estimated relative risk	Cancer at other sites: Site	Number of deaths or cases	Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) Identified
Sorahan et al. [1987], United Kingdom	2,689 nickel and chromium platers (1,288 men; 1,401 women).	Mortality, England and Wales	Lung, bronchus:			Stomach (men and women)	25	1.5	No	Yes, as chromic acid. Median value of 60 "measure–ments" before 1973 was "not detectable or trace". After 1973, majority of measure-ments were recorded in factory records as "less than 0.05 mg/m^3."
			Men	63	1.6*					
			Women	9	1.1					
	First employed 1946—1975 for ≥ six months and observed 1946—1983.		Larynx:			Liver				
			Men	3	3.0	Men	4	6.7*		
			Women	0	—	Women	0	—		
						All sites (men and women)	213	1.3*		
			Nose, nasal cavities (men and women)	3	10*					

Source: Adapted from IARC [1990].
*Significant at 95% level.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs			Cancer at other sites			Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
			Site	Number of deaths or cases	Estimated relative risk	Site	Number of deaths or cases	Estimated relative risk		
Axelsson et al. [1980], Sweden	1,876 male workers employed ≥ one year from 1930 to 1975 in a ferrochromium plant; traced by parish lists and cancer registry.	County deaths, male or national statistics (incidence)	Lung, trachea, bronchus, pleura: All workers Maintenance workers Arc furnace workers	 7 4 (2 meso-theliomas) 2 (1 meso-thelioma)	 1.2 4.0* 1.0	Prostate (all workers)	23	1.2	No	Yes (Cr^{6+} and Cr^{3+}). Cr^{6+} exposures ranged from 0-0.25 mg/m^3. Sampling method not described.
Langård et al. [1980, 1990]; Norway	1,235 male ferrochromium and ferrosilicon workers employed > one year 1928—1965 and observed from 1953 to 1985.	General population and internal comparison group	Lung (ferro-chromium workers)	10	1.5	All sites (all workers) Ferro-chromium workers: Kidney Prostate Stomach	132 5 12 7	0.8 2.8 1.5 1.4	No	Yes, in 1975 survey, mean atmospheric concentration of chromium ranged from 0.01 mg/m^3 to 0.29 mg/m^3 with a water-soluble content of 11%-33%. Authors stated "Water soluble chromium compounds are considered to be in the hexavalent state."

Continued

Table 4-4 (Continued). IARC-reviewed studies of workers in ferrochromium industries.

Reference and country	Study population and followup	Reference population	Cancer of respiratory organs: Site	Cancer of respiratory organs: Number of deaths or cases	Cancer of respiratory organs: Estimated relative risk	Cancer at other sites: Site	Cancer at other sites: Number of deaths or cases	Cancer at other sites: Estimated relative risk	Cohort smoking information available and analyzed	Sampling conducted and Cr(VI) identified
Pokrovskaya and Shabynina [1973], USSR	Male and female chromium ferroalloy production workers employed between 1955 and 1969.	Mortality, general population of municipality	Lung (men)	Not reported	4.4 (age 30-39) 6.6* (age 50-59)	All sites (men) Esophagus (men)	Not reported Not reported	3.3* (age 50-59) 2.0* (age 50-59) 11.3* (age 60-69)	No	Yes, specific concentrations and sampling methods not reported—average hexavalent concentrations were 2—7 times greater than allowed.

Source: Adapted from IARC [1990].
*Significant at 95% level.

CHAPTER FIVE: EXPERIMENTAL STUDIES

Experimental studies provide important information about the pharmacokinetics, mechanisms of toxicity, and dermal effects of Cr(VI) compounds. Studies using cell culture and in vitro techniques, animal models, and human volunteers provide data about the dermal effects of these compounds. The results of these experimental studies, when combined with those of other health effects studies, provide a more comprehensive database for the evaluation of the mechanisms and health effects of occupational exposure to Cr(VI) compounds.

5.1 PHARMACOKINETICS

Inhalation is the most common route of occupational exposure to Cr(VI) compounds. Large particles (>10 μm) of inhaled Cr(VI) compounds are deposited in the upper respiratory tract; smaller particles can reach the lower respiratory tract. Some of the inhaled Cr(VI) is reduced to Cr(III) in the epithelial or interstitial lining fluids within the bronchial tree. The extracellular reduction of Cr(VI) to Cr(III) reduces the cellular uptake of chromium as Cr(III) compounds cannot enter cells as readily as Cr(VI) compounds. At physiological pH most Cr(VI) compounds are tetrahedral oxyanions that can cross cell membranes. Cr(III) compounds are predominantly octahedral structures to which the cell membrane is practically impermeable. Cr(III) can enter the cell only via pinocytosis [Jennette 1979]. The Cr(VI) ions that cross the cell membrane become a target of intracellular reductants. The Cr(VI) concentration decreases with increasing distance from the point of entry as Cr(VI) is reduced to Cr(III). The Cr(III) ions are transported to the kidneys and excreted.

Inhaled Cr(VI) that is not absorbed in the lungs may enter the gastrointestinal tract following mucociliary clearance. Much of this Cr(VI) is rapidly reduced to Cr(III) by reductants in the saliva and gastric juice and excreted in the feces. The remaining 3% to 10% of the Cr(VI) is absorbed from the intestines into the blood stream, distributed throughout the body, transported to the kidneys, and excreted in the urine [Costa 1997;

Weber 1983].

5.2 MECHANISMS OF TOXICITY

The exact mechanism of Cr(VI) carcinogenicity is not fully understood. A significant body of research suggests that Cr(VI) carcinogenicity may result from damage mediated by the bioreactive products of Cr(VI) reduction, which include the Cr(VI) intermediates (Cr(V) and Cr(IV)), and reactive oxygen species (ROS). Factors that may affect the toxicity of a chromium compound include its bioavailability, oxidative properties, and solubility [Långard 1993; Katz and Salem 1993; De Flora et al. 1990; Luo et al. 1996; Klein et al. 1991].

Intracellular Cr(VI) undergoes metabolic reduction to Cr(III) in microsomes, in mitochondria, and by cellular reductants such as ascorbic acid, lipoic acid, glutathione, cysteine, reduced nicotinamide adenine dinucleotide phosphate (NADPH), ribose, fructose, arabinose and diol- and thiol-containing molecules as well as NADPH/flavoenzymes. While the extracellular reduction of Cr(VI) to Cr(III) is a mechanism of detoxification as it decreases the number of bioavailable Cr(VI) ions, intracellular reduction may be an essential element in the mechanism of intracellular Cr(VI) toxicity.

The intracellular Cr(VI) reduction process generates products including Cr(V), Cr(IV), Cr(III) molecular oxygen radicals and other free radicals. The molecular oxygen is reduced to O_{-2}, which is further reduced to H_2O_2 by superoxide dismutase (SOD). H_2O_2 reacts with Cr(V), Cr(IV) or Cr(III) to generate ˙OH radicals via the Fenton-like reaction and undergoes reduction-oxidation cycling. The high concentration of oxygen radicals and other free radical species generated in the process of Cr(VI) reduction may result in a variety of lesions on nuclear chromatin leading to mutation and ultimately to neoplastic transformation [Liu et al. 1997b; Kasprzak 1991].

In the presence of cellular reducing systems that generate chromium intermediates and hydroxyl radicals, Cr(VI) salts induce various types of DNA damage, resulting either from the breakage of existing covalent bonds or the formation of new covalent bonds among molecules; e.g., DNA interstrand crosslinks, DNA-protein crosslinking, DNA double strand breaks, and depurination. Such lesions could lead to mutagenesis and ultimately to carcinogenicity [Shi et al. 1994; Tsapakos and Wetterhahn [1983]; Tsapakos et al. [1983]; Sterns et al. 1995; Sugiyama et al. 1986; Singh et al. 1998; Ding and Shi 2002; Fornace et al. 1981]. The oxidative damage may result from a direct binding of the reactive Cr(VI) intermediates to the DNA or may be due to the indirect effect of ROS interactions with nuclear chromatin, depending on their intracellular location and proximity to DNA [Ding and Shi 2002; Shi and Dalal 1990a,b,c; Singh et al. 1998; Liu et al. 1997b]. Cr(VI) does not bind irreversibly to native DNA and does not produce DNA lesions in the absence of the microsomal reducing systems in vitro [Tsapakos and Wetterhahn 1983].

In addition to their oxidative properties, the solubility of Cr(VI) compounds is another important factor in the mechanism of their carcinogenicity. Animal studies indicate that insoluble and sparingly soluble Cr(VI) compounds may be more carcinogenic than soluble chromium compounds [Levy et al. 1986].

Particles of lead chromate, a relatively insoluble Cr(VI) compound, when added directly to the media of mammalian cell culture, induced cell transformation [Douglas et al. 1980]. When injected into whole animals, the particles produced tumors at the site of injection [Furst et al. 1976]. Several hypotheses have been proposed to explain the effects of insoluble Cr(VI) compounds. One hypothesis proposes that particles dissolve extracellularly, resulting in chronic, localized exposure to ionic chromate. This hypothesis is consistent with studies demonstrating that particle-cell contact and extracellular dissolution were required for lead chromate-induced clastogenesis [Wise et al. 1993, 1994; Xie et al. 2004].

Another hypothesis suggests that a high Cr(VI) concentration is created locally inside the cell during internalization of Cr(VI) salt particles by phagocytosis [Leonard et al. 2004]. High intracellular local Cr(VI) concentrations can generate high concentration of ROS inside the cell, which may overwhelm the local ROS scavenging system and result in cytotoxicity and genotoxicity [Kasprzak 1991]. Highly soluble compounds do not generate such high local concentrations of Cr(VI). However, once inside the cell, both soluble (sodium chromate) and insoluble (lead chromate) Cr(VI) compounds induce similar amounts and types of concentration-dependent chromosomal damage in exposed cultured mammalian cells [Wise et al. 1993, 2002, 2003]. Pretreatment of these cells with ROS scavengers such as vitamin E or C prevented the toxic effects of both sodium chromate and lead chromate.

Numerous studies report a broad spectrum of cellular responses induced by exposure to various Cr(VI) compounds. All these responses are consistent with mechanistic events associated with carcinogenesis. Barium chromate induced concentration-dependent chromosomal damage, including chromatid and chromosomal lesions, in human lung cells after 24-hr exposure [Wise et al. 2003]. Lead chromate and soluble sodium chromate induced concentration-dependent chromosomal aberration in human bronchial fibroblast after 24-hr exposure [Wise et al. 2002; Xie et al. 2004]. Cotreatment of cells with vitamin C blocked the chromate induced toxicity. Calcium chromate induced DNA single-strand breaks and DNA protein cross-links in a dose-dependent manner in three cell lines. Human osteosarcoma cells were four times more sensitive to calcium chromate than Chinese hamster ovary cells and mouse fibroblast cells [Sugiyama et al. 1986]. Sodium dichromate generated ROS that increased the level and activity of the protein p53 in human lung epithelial cells. In normal cells the protein p53 is usually inactive. It is usually activated to protect cells from tumorigenic alterations in response to oxidative stress and other stimuli such as ultraviolet or gamma radiation. An increased $^{\cdot}OH$ concentration activated p53; elimination of $^{\cdot}OH$ by H_2O_2 scavengers inhibited p53

activation [Ye et al. 1999; Wang et al. 2000; Wang and Shi 2001].

The ROS (mainly H_2O_2) formed during potassium chromate reduction induced the expression of vascular endothelial growth factor (VEGF) and hypoxia-induced factor 1 (HIF)–1 in DU145 human prostate carcinoma cells. VEGF is the essential protein for tumor angiogenesis. HIF–1, a transcription factor, regulates the expression of many genes including VEGF. The level of HIF–1 activity in cells correlates with the tumorigenic response and angiogenesis in nude mice, is induced by the expression of various oncogenes, and is overexpressed in many human cancers [Gao et al. 2002; Ding and Shi 2002].

Early stages of apoptosis have been induced in human lung epithelial cells in vitro following exposure to potassium dichromate. Scavengers of ROS, such as catalase, aspirin, and N-acetyl-L-cysteine, decreased Cr(VI)-induced apoptosis; reductants such as NADPH and glutathione enhanced it. Apoptosis can be triggered by oxidative stress. Agents that promote or suppress apoptosis may change the rates of cell division and lead to the neoplastic transformation of cells [Singh et al. 1998; Ye et al. 1999; Chen et al. 1999].

The treatment of mouse macrophage cells in vitro with sodium chromate induced a dose-dependent activation of the transcription enhancement factors NF-κB and AP–1 [Chen et al. 1999, 2000]. Activation of these factors represents a primary cellular oxidative stress response. These factors enhance the transcription of many genes and the enhanced expression of oncogenes [Ji et al. 1994].

Sodium dichromate increased tyrosine phosphorylation in human epithelial cells. The phosphorylation could be inhibited by antioxidants [Wang and Shi 2001]. Tyrosine phosphorylation is essential in the regulation of many cellular functions including cancer development [Qian et al. 2001].

Human lung epithelial A549 cells exposed to potassium dichromate in vitro generated ROS-induced cell arrest at the G2/M phase of the cell proliferation cycle at relatively low concentrations and apoptosis at high concentrations. Interruption of the proliferation process is usually induced in response to cell damage, particularly DNA damage. The cell remains arrested in a specific cell cycle phase until the damage is repaired. If damage is not repaired, mutations and cell death or cancer may result [Zhang et al. 2001].

Gene expression profiles indicate that exposing human lung epithelial cells to potassium dichromate in vitro resulted in up regulation of the expression of 150 genes, and down regulation of 70 genes. The analysis of gene expression profiles indicated that exposure to Cr(VI) may be associated with cellular oxidative stress, protein synthesis, cell cycle regulation, and oncogenesis [Ye and Shi 2001].

These in vitro studies have limitations of models of human exposure as they cannot account for the detoxification mechanisms that take place in intact physiological systems. However, these studies represent a body of data on cellular responses to Cr(VI) that provide important information regarding the potential genotoxic mechanisms of Cr(VI) compounds. The cellular damage induced by these compounds is consistent with the mechanisms of oncogenesis.

5.3 HEALTH EFFECTS IN ANIMALS

Chronic inhalation studies provide the best data for extrapolation to occupational exposure. Unfortunately, only a few of these studies have been conducted using Cr(VI) compounds. Glaser et al. [1985, 1990] conducted subchronic inhalation studies of sodium dichromate exposure in rats. Adachi et al. [1986, 1987] and Glaser et al. [1986] conducted chronic inhalation studies of chromic acid mist exposure in mice, and sodium dichromate exposure in rats, respectively. Steinhoff et al. [1986] conducted an intratracheal study of sodium dichromate exposure in rats. Levy et al. [1986] conducted

an intrabronchial implantation study of various Cr(VI) materials in rats. The results of these animal studies support the classification of Cr(VI) compounds as occupational carcinogens.

5.3.1 Subchronic inhalation studies

Glaser et al. [1985] exposed male Wistar rats to whole body aerosol exposures of sodium dichromate at 0, 25, 50, 100 or 200 μg Cr(VI)/m^3 for 22hr/day, 7 days/wk for 28 or 90 days. Twenty rats were exposed at each dose level. An additional ten rats were exposed at 50 μg for 90 days followed by two months of nonexposure before sacrifice. The average mass median diameter (MMD) of the aerosol particles was 0.2 μm. Significant increases ($p<0.05$) occurred in the serum triglyceride, phospholipid contents, and mitogen-stimulated splenic mean T-lymphocyte count of rats exposed at the 200 μg/m^3 level for 90 days. Serum total immunoglobulins were statistically increased ($p<0.01$) for the 50 and 100 μg exposure groups.

To further study the humoral immune effects, half of the rats in each group were immunized with sheep red blood cells four days prior to sacrifice [Glaser et al. 1985]. The primary antibody responses for IgM B-lymphocytes were statistically increased ($p<0.05$) for the groups exposed to 25 μg Cr(VI)/m^3 and higher. The mitogen-stimulated T-lymphocyte response of spleen cells to Concanavalin A was significantly increased ($p<0.05$) for the 90-day, 200 μg/m^3 group compared to the control group. The mean macrophage cell counts were significantly lower ($p<0.05$) than control values for only the 50 and 200 μg Cr(VI)/m^3, 90-day groups. Alveolar macrophage phagocytosis was statistically increased in the 50 μg level of the 28-day study, and the 25 and 50 μg mg/m^3 Cr(VI) levels of the 90-day study ($p<0.001$). A significant depression of phagocytosis occurred in the 200 μg/m^3 group of the 90-day study versus controls.

A group of rats exposed to 200μg Cr(VI)/m^3 for 42 days and controls received an acute iron oxide particulate challenge to study lung clearance rates during a 49-day

nonexposure post-challenge period [Glaser et al. 1985]. Iron oxide clearance was dramatically and increasingly decreased in a bi-exponential manner for the Cr(VI)-exposed group compared to the controls.

Glaser et al. [1990] studied lung toxicity in animals exposed to sodium dichromate aerosols. Groups of 30 male Wistar rats were exposed to 0, 50, 100, 200, or 400 µg Cr(VI)/m^3 for 22 hr/day x 7 days/week for 30 or 90 days followed by a 30-day nonexposure recovery period. Aerosol mass median aerodynamic diameter (MMAD) ranged from 0.28 to 0.39 µm. Partial sacrifices of 10 rats occurred following experimental days 30, 90, and 120. The only sign or symptom induced was an obstructive dyspnea present at the 200 and 400 µg/m^3 levels. Statistically significant reductions in body weight gains were present at 30 days for the 200 µg level with similar reductions for the 400 µg level rats at the 30, 90, and 120-day intervals. White blood cell counts were statistically increased ($p<0.05$) for all four dichromate exposure groups for the 30 and 90-day intervals but returned to control levels following 30 days of nonexposure. The lung parameters studied had statistically significant dose-related increases following either 30 or 90 days of inhalation exposure to dichromate; some remained elevated despite the nonexposure recovery period. A No Observed Adverse Effect Level (NOAEL) was not achieved.

Bronchoalveolar lavage (BAL) provided information about pulmonary irritation induced by sodium dichromate exposure in these rats [Glaser et al. 1990]. Total protein levels present on day 30 progressively decreased at days 90 and 120 but remained above control values. Alveolar vascular integrity was compromised as BAL albumin levels were increased for all treatment groups with only the 200 and 400 µg/m^3 levels remaining above those of the controls at the end of the recovery period. Lung cell cytotoxicity as measured by cytosolic lactate dehydrogenase and lysosomal ß-glucuronidase was increased by dichromate exposure but normalized during the post-exposure period. Mononuclear macrophages comprised 90% of recovered total BAL cells. The two highest

exposure groups had equal increases throughout the treatment period but returned to normal during the recovery period. These macrophages had higher cell division rates, sometimes were multi-nuclear, and were bigger when compared to control cells. Sodium dichromate exposure induced statistically significant increased lung weights for the 100, 200 and 400 $\mu g/m^3$ groups throughout the entire study including the nonexposure period. Histopathology of lung tissue revealed an initial bronchoalveolar hyperplasia for all exposure groups at day 30 while only the 200 and 400 levels retained some lower levels of hyperplasia at study day 120. There was also an initial lung fibrosis observed in some animals at the levels above 50 $\mu g/m^3$ on day 30 which was not present during the remainder of the study. Lung histiocytosis remained elevated throughout the entire study for all treatment groups.

5.3.2 Chronic inhalation studies

Adachi et al. [1986] exposed 50 female ICR/JcI mice to 3.63 mg Cr(VI)/m^3 chromic acid mist (85% of mist measuring <5 μm) for 30 min/day, 2 days/week for 12 months followed by a 6 month nonexposure recovery period. Proliferative changes were observed within the respiratory tract following 26 weeks of chromate exposure. Pin-hole sized perforations of the nasal septum occurred after 39 weeks at this exposure level. When the incidence rates for histopathological findings (listed below) for chromate exposed animals were compared for successive study periods the treatment group data were generally similar for weeks 40-61 when compared to weeks 62-78 with the exception of the induction of 2 adenocarcinomas of the lungs present in 2 females at the terminal 78-week sacrifice. The total study pathology incidence rates for the 48 chromate exposed females were: perforated nasal septum (n=6), tracheal (n=43)/bronchial (n=19) epithelial proliferation, and emphysema (n=11), adenomatous metaplasia (n=3), adenoma (n=5), and adenocarcinoma (n=2) of the lungs. Total control incidence rates for the 20 females examined were confined to the lung: emphysema (n=1), adenomatous metaplasia (n=1), and adenoma (n=2).

Adachi [1987] exposed 43 female C57BL mice to 1.81 mg Cr(VI)/m^3 chromic acid mist (with 85% of mist measuring ~5 μm) for 120 min/day, 2 days/week for 12 months followed by a 6 month nonexposure recovery period. Twenty-three animals were sacrificed at 12 months with the following nontumorigenic histological changes observed: nasal cavity perforation (n=3); tracheal hyperplasia (n=1); and emphysema (n=9) and adenomatous metaplasia (n=4) of the lungs. A terminal sacrifice of the 20 remaining females occurred at 18 months which demonstrated perforated nasal septa (n=3) and papillomas (n=6); laryngeal/tracheal hyperplasia (n=4); and emphysema (n=11), adenomatous metaplasia (n=5), and adenoma (n=1) of the lungs. Only emphysema (n=2) and lung metaplasia (n=1) were observed in control females sacrificed after week 78.

Glaser et al. [1986] exposed groups of 20 male Wistar rats to aerosols of 25, 50, or 102 μg/m^3 sodium dichromate for 22 to 23hr/day, 7days/week for 18 months followed by a 12 month nonexposure recovery period. Mass median diameter of the sodium dichromate aerosol was 0.36 μm. No clinical sign of Cr(VI)-induced irritation was observed in any treated animal. Statistically increased liver weights (+26%) were observed at 30 months for the 102 μg/m^3 dichromate males. Weak accumulations of pigment-loaded macrophages were present in the lungs of rats exposed to 25 μg/m^3 sodium dichromate; moderate accumulations were present in rats exposed to 50 and 102 μg/m^3 sodium dichromate. Three primary lung tumors occurred in the 102 μg Cr(VI)/m^3 group: two adenomas and one adenocarcinoma. The authors concluded that the 102 μg Cr(VI)/m^3 level of sodium dichromate induced a weak lung carcinogenic effect in rats exposed under these conditions.

5.3.3 Intratracheal studies

Steinhoff et al. [1986] dosed Sprague-Dawley rats via intratracheal instillation with equal total weekly doses of sodium dichromate for 30 months: either five consecutive daily doses of 0.01, 0.05, or 0.25 mg/kg or one weekly dose of 0.05, 0.25, or 1.25 mg/kg. Each

group consisted of 40 male and 40 female rats. Groups left untreated or given saline were negative controls. Body weight gains were suppressed in males treated with single instillations of 1.25 mg/kg of sodium dichromate. Chromate-induced nonneoplastic and neoplastic lesions were detected only in the lungs. The nonneoplastic pulmonary lesions were primarily found at the maximum tolerated irritant concentration level for the high dose sodium dichromate group rather than having been dependent upon the total dose administered. The nonneoplastic pulmonary lesions occurred predominantly in the highest dose group and were characterized by fibrotic regions that contained residual distorted bronchiolar lumen or cellular inflammatory foci containing alveolar macrophages, proliferated epithelium and chronic inflammatory thickening of the alveolar septa plus atelectasis. The neoplastic lesions were non-fatal lung tumors found in these chromate-treated animals. Fourteen rats given single weekly instillations of 1.25 mg sodium dichromate/kg developed a significant ($p<0.01$) number of tumors: 12 benign bronchioloalveolar adenomas and 8 malignant tumors including 2 bronchioalveolar adenocarcinomas and 6 squamous cell carcinomas. Only one additional tumor, a bronchioalveolar adenocarcinoma, was found in a rat that had received single weekly instillations of 0.25 mg/kg sodium dichromate.

5.3.4 Intrabronchial studies

Levy et al. [1986] conducted a two year intrabronchial implantation study of 20 chromium-containing materials in Porton-Wistar rats. Test groups consisted of 100 animals with equal numbers of male and female rats. A small, hook-equipped stainless steel wire mesh basket containing 2 mg of cholesterol and test material was inserted into the left bronchus of each animal. Two positive control groups received pellets loaded with 20-methylcholanthrene or calcium chromate. The negative control group received a blank pellet loaded with cholesterol. Pulmonary histopathology was the primary parameter studied. There were inflammatory and metaplastic changes present in the lungs and bronchus with a high level of bronchial irritation induced by the presence of the basket alone. A total of 172 tumors were obtained throughout the study with only 18

found at the terminal sacrifice. Nearly all tumors were large bronchial keratinizing squamous cell carcinomas that affected a major part of the left lung and were the cause of death for most affected animals. The authors noted that no squamous cell carcinomas have been found in 500 of their historical laboratory controls.

In Table 5—1, study data from the journal publication were transformed to succinctly present the rank order of tumor induction potential for the test compounds through calculation of the mean μg of Cr(VI) required to induce a single bronchiolar squamous cell carcinoma. The rank order of tumor induction potential for the positive Cr(VI) compounds was: strontium>calcium >zinc>lead, chromic acid>sodium dichromate>barium. The role solubility played in tumor production for these test materials was inconsistent and was not able to be discerned.

5.4 DERMAL STUDIES

Dermal exposure is another important route of exposure to Cr(VI) compounds in the workplace. Experimental studies have been conducted using human volunteers, human and animal skin in vitro, animals, and cell culture to investigate the dermal effects of Cr(VI) compounds.

5.4.1 Human Dermal Studies

Mali et al. [1963] reported the permeation of intact epidermis by potassium dichromate in human volunteers in vivo. Sensitization was reported in humans exposed to this Cr(VI) compound but not Cr(III) sulfate.

Baranowska-Dutkiewicz [1981] conducted 27 Cr(VI) absorption experiments on seven human volunteers. Forearm skin absorption rates for 0.01, 0.1, and 0.2 molar solutions of sodium chromate were 1.1, 6.5, and 10.0 $\mu g/cm^2$/hr, respectively. The amount of Cr(VI) absorbed as a percent of the applied dose decreased with increasing concentration. The absorption rate increased as the Cr(VI) concentration applied increased, and decreased as

the exposure time increased.

Corbett et al. [1997] immersed four human volunteers below the shoulders in water containing 22 mg/L potassium dichromate for three hours to assess their uptake and elimination of chromium. The concentration of Cr in the urine was used as the measure of systemic uptake. The total Cr excretion above historical background ranged from 1.4 to 17.5 μg. The dermal uptake rates ranged from approximately 3.3×10^{-5} to 4.1×10^{-4} $\mu g/cm^2/hr$ with an average of 1.5×10^{-4}. One subject had a dermal uptake rate approximately seven times higher than the average for the other three subjects.

5.4.2 Animal Dermal Studies

Mali et al. [1963] demonstrated the experimental sensitization of 13 of 15 guinea pigs by injecting them with 0.5 mg potassium dichromate in Freund adjuvant subdermally twice at one week intervals.

Gad et al. [1986] conducted standard dermal LD_{50} tests to evaluate the acute toxicity of sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate salts in New Zealand white rabbits. All salts were tested at 1.0, 1.5, and 2.0 g/kg dosage with the exception of sodium chromate which was tested at the two higher doses only. In males the dermal LD_{50} ranged from a mean of 0.96 g/kg (SD=0.19) for sodium dichromate to 1.86 g/kg (SD=0.35) for ammonium dichromate. In females the dermal LD_{50} ranged from a mean of 1.03 g/kg (SD=0.15) for sodium dichromate to 1.73 g/kg (SD=0.28) for sodium chromate. Each of the four salts, when moistened with saline and occluded to the skin for four hours, caused marked irritation. Occlusion of each salt on the skin of the rabbit's back for 24 hours caused irreversible cutaneous damage.

Liu et al. [1997a] demonstrated the reduction of an aqueous solution of sodium dichromate to Cr(V) on the skin of Wistar rats using in vivo electron paramagnetic resonance spectroscopy. Removal of the stratum corneum by stripping the skin with

surgical tape ten times before the application of the dichromate solution increased the rates of formation and decay of Cr(V).

5.4.3 In Vitro Dermal Studies

Gammelgard et al. [1992] conducted chromium permeation studies on full thickness human skin in an in vitro diffusion cell system. Application of 0.034 M potassium chromate to the skin resulted in significantly higher levels of chromium in the epidermis and dermis compared to Cr(III) nitrate and Cr(III) chloride. Chromium levels in the epidermis and dermis increased with the application of increasing concentrations of potassium chromate up to 0.034 M Cr. Chromium skin levels increased with the application of potassium chromate solutions with increasing pH. The percentage of Cr(VI) converted to Cr(III) in the skin was largest at low total chromium concentrations and decreased with increasing total concentrations indicating a limited Cr(VI)-reducing ability of the skin.

Van Lierde et al. [2006] conducted chromium permeation studies on human and porcine skin using a Franz static diffusion cell. Potassium dichromate was determined to permeate human and pig skin after 168 hours of exposure while the Cr(III) compounds tested did not. Exposure of the skin to 5% potassium dichromate resulted in an increased, but not proportionally increased, amount of total Cr concentration in the skin compared to exposure to 0.25% potassium dichromate.. Exposure to 5% potassium dichromate compared to 2.5% potassium did not result in much more of an increased Cr skin concentration dichromate indicating a possible limited binding capacity of the skin. A smaller amount of Cr was bound to the skin when the salts were incubated in simulated sweat before application onto the skin. A larger accumulation of Cr was found in the skin after exposure to potassium dichromate compared to Cr(III) compounds.

5.4.4 Cell Culture Studies

Rudolf et al. [2005] reported a pronounced effect of potassium chromate on the

morphology and motile activity of human dermal fibroblasts at concentrations ranging from 1.5 to 45 μM. A time and concentration-dependent effect on cell shrinkage, reorganization of the cytoskeleton, and inhibition of fibroblast motile activity was reported. The inhibitory effect on fibroblast migration was seen at all concentrations eight hours after treatment; effects at higher doses were seen by four hours after treatment. Cr(VI) exposure also resulted in oxidative stress, alteration of mitochondrial function, and mitochondria-dependent apoptosis in dermal fibroblasts.

5.5 SUMMARY OF ANIMAL STUDIES

Cr(VI) compounds have been tested in animals using many different experimental conditions and exposure routes. Although experimental conditions are often different from occupational exposures, these studies provide data to assess the carcinogenicity of the test compounds. Chronic inhalation studies provide the best data for extrapolation to occupational exposure; unfortunately few have been conducted using Cr(VI) compounds. However, the body of animal studies support the classification of Cr(VI) compounds as occupational carcinogens.

The few chronic inhalation studies available demonstrate the carcinogenic effects of Cr(VI) compounds in mice and rats [Adachi et al. 1986, 1987; Glaser et al. 1986]. Animal studies conducted using other respiratory routes of administration have also produced positive results with some Cr(VI) compounds. Zinc chromate and calcium chromate produced a statistically significant ($p<0.05$) number of bronchial carcinomas when administered via an intrabronchial pellet implantation system [Levy et al. 1986]. Cr(VI) compounds with a range of solubilities were tested using this system. Although soluble Cr(VI) compounds did produce tumors, these results were not statistically significant. Some lead chromate compounds produced squamous carcinomas, which although not statistically significant may be biologically significant, due to the absence of this cancer in control rats.

Steinhoff et al. [1986] administered the same total dose of sodium dichromate either once-per-week or five-times-per week to rats via intratracheal instillation. No increased incidence of lung tumors was observed in animals dosed five times weekly. However, in animals dosed once per week, a statistically significant ($p<0.01$) tumor incidence was reported in the 1.25 mg/kg exposure group. This study demonstrates a dose-rate effect within the constraints of the experimental design. It suggests that limiting exposure to high Cr(VI) levels may be important in reducing carcinogenicity. However, quantitative extrapolation of these animal data to the human exposure scenario is difficult.

Animal studies conducted using non-respiratory routes of administration have also produced positive results with some Cr(VI) compounds [Hueper 1961; Furst 1976]. These studies provide another data set for hazard identification.

Most animal studies conducted on Cr(VI) compounds were published prior to the 1990 IARC evaluation of chromium. IARC review of the studies concluded "there is sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate and lead chromates. There is limited evidence in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate. There is inadequate evidence in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium[III] compounds" [IARC 1990].

Table 5-1. Single intrabronchiolar pellet implantation of Cr(VI) or Cr(III) materials and their potential to induce lung carcinomas during a two-year period in rats

Test compound	Water solubility, mg Cr(VI)/L	Cr(VI) (%)	Capsule Cr(VI) content (µg)	µg Cr(VI) to induce carcinomas*	Number of carcinomas
Strontium chromate	207000	8.7	174	4	43
Strontium chromate	63000	24.3	486	8	62
Hi Lime Residue (2.7% calcium chromate)	1820	1.2	24	24	1
Calcium chromate Positive control	181000	32.5	649	26	25
Zinc chromate	420	8.7	173	35	5
Zinc chromate	64000	9.2	184	61	3
Kiln frit†	84600	9.3	186	93	2
LD chrome yellow supra‡	<1	5.7	114	114	1
Lead chromate	17	5.7	115	115	1
Vanadium solids/leach†	54000	7.3	146	146	1
Zinc tetroxychromate	230	8.8	176	176	1
Chromic acid	400000	21.2	424	212	2
Primrose chrome yellow‡	5	12.6	252	252	1
Med chrome yellow‡	2	16.3	326	326	1
Sodium dichromate Dehydrate	328000	34.8	696	696	1
Molybdate chrome orange‡	<1	12.9	258	—	0
Light chrome yellow‡	1	12.5	250	—	
Med chrome yellow‡	17	10.5	210	—	
Barium chromate	11	6.8	135	—	0
Recycled residue	6000	0.7	14	—	0
High silica Cr(III) ore	5	13.7	750	—	0
Cholesterol Negative control**	Not reported	NA	NA	NA	0
3-Methylcholanthrene Positive control	Not reported	NA	NA	NA	22***

Source: Levy et al. [1986].
Abbreviations: NA = Not applicable.
† = This process material contained unstated amounts of calcium chromate.
‡ = Identified also as being a lead chromate containing group.
* µg Cr(VI) to induce carcinomas=capsul Cr(VI) content % number of carcinomas
** No lung tumors were previously found in 500 negative historical control rats that had basket implants.
*** 21 squamous cell carcinomas plus one anaplastic carcinoma of the lung.

CHAPTER SIX: ASSESSMENT OF RISK

The exposure and health data from two chromate production facilities have provided the bases for the quantitative risk assessments of lung cancer due to occupational and environmental Cr(VI) exposure. Data from the Painesville Ohio chromate production facility provided the basis for the risk assessments of Crump et al. [2003], K.S. Crump [1995], Gibb et al. [1986], and U.S. EPA [1984]. Data from the Baltimore, Maryland chromium chemical production facility was quantitatively assessed by Park et al. [2004], K.S. Crump [1995], and Gibb et al. [1986]. The epidemiology studies of these worker populations are described in the human health effects chapter of this document (see Chapter Four).

The occupational quantitative risk assessments demonstrate an elevated risk of lung cancer death to workers exposed to Cr(VI) at both the current OSHA PEL (100 $\mu g/m^3$ as CrO_3) and the previous NIOSH REL (1 $\mu g/m^3$ as Cr) over a working lifetime. The most recent risk assessment conducted on the Painesville data reports an excess risk estimate of lung cancer death of two per 1000 workers at the previous NIOSH REL [Crump et al. 2003]. The most recent risk assessment conducted on the Baltimore data indicates an excess risk estimate of lung cancer death of six per 1000 workers at 1 $\mu g/m^3$ and approximately one per 1000 workers at 0.2 $\mu g/m^3$ [Park et al. 2004]. These estimates of increased lung cancer risk vary depending on the data set(s) used, the assumptions made, and the models tested.

Environmental risk assessments of Cr(VI) exposure have also been conducted. These analyses assess the risk of lung cancer death or noncancer endpoints due to nonoccupational Cr(VI) exposure.

6.1 ANALYSES OF THE BALTIMORE CHROMATE PRODUCTION DATA

Assessment of the excess lifetime risk of lung cancer mortality due to occupational Cr(VI) exposure has been conducted by Park et al. [2004], Crump et al. [2003], K.S. Crump [1995], Gibb et al. [1986], DECOS [1998], and ICDA [1997]. Most of these

analyses used the data of the Baltimore Maryland or Painesville Ohio chromate production facilities.

NIOSH calculated estimates of excess lifetime risk of lung cancer death resulting from occupational exposure to chromium-containing mists and dusts in a cohort of chromate chemical production workers [Park et al. 2004]. Various models of exposure-response for soluble respirable Cr(VI) and lung cancer were evaluated and a risk assessment conducted. The excess lifetime (45 years) risk for lung cancer mortality from exposure to Cr(VI) was estimated to be 255 per thousand workers at the current OSHA PEL based on the exposure-response estimate for all men in the Baltimore cohort. At the previous NIOSH REL of 1 $\mu g/m^3$ the excess lifetime risk was estimated to be six deaths per 1000 workers and at the proposed REL of 0.2 $\mu g/m^3$ the excess lifetime risk is approximately one death per 1000 workers.

The data analyzed was from the Baltimore, Maryland cohort previously studied by Hayes et al. [1979] and Gibb et al. [2000a]. The cohort was comprised of 2357 men first hired between 1950 and 1974 whose vital status was followed through 1992. The racial makeup of the study population was: 1205 white (51%), 848 nonwhite (40%) and 304 of unknown race (13%).

This cohort had a detailed retrospective exposure assessment which was used to estimate individual worker current and cumulative Cr(VI) exposures across time. Approximately 70,000 both area and personal airborne Cr(VI) measurements of typical exposures were collected and analyzed by the employer from 1950 to 1985, when the plant closed. These samples were used to assign, in successive annual time periods, average exposure levels to exposure zones that had been defined by the employer. These job title estimated exposures were combined with individual work histories to calculate the Cr(VI) exposure of each member of the cohort.

Smoking information at hire was available from medical records for 91% of the

population, including packs per day for most workers. The cohort was largely free of other potentially confounding exposures. The mean duration of employment of workers in the cohort was 3.1 years while the median duration was only 0.39 year.

In this study population of 2357 workers, 122 lung cancer deaths were documented. This mortality experience was analyzed using Poisson regression methods. Diverse models of exposure-response for Cr(VI) were evaluated by comparing deviances and inspecting cubic splines. The models using cumulative smoking (as a linear spline) fit significantly better in comparison with models using a simple categorical classification (smoking at hire: yes, no, unknown). For this reason smoking cumulative exposure imputed from cigarette use at hire was included as a predictor in the final models despite absence of detailed smoking histories. Lifetime risks of lung cancer death from exposure to Cr(VI) were estimated using an actuarial calculation that accounted for competing causes of death.

An additive relative rate model was selected which fit the data well and which was readily interpretable for excess lifetime risk calculations:

$$\text{relative rate} = \exp(\hat{a}_0 + \hat{a}_1\,\text{Smk1} + \hat{a}_2\,\text{Smk2}) \times (1 + \hat{a}_3 X)$$

where Smk1 and Smk2 are the smoking terms (number of pack-years up to 30, and above 30, respectively) and X is the cumulative chromium exposure (lagged 5 years). The model adjusted for age, race and calendar time by incorporating national U.S. mortality rates into the model. In the final model, the estimated rate ratio (RR) for 1 mg/m^3-yr cumulative exposure to Cr(VI) was 2.44 with a 95% confidence interval of 1.54-3.83 (Δ[–2 lnL]= 15.1). Addition of a race-chromium interaction term in the preferred linear relative rate model resulted in a further reduction in deviance of 10.6, a highly statistically significant result (p=0.001), and the observed chromium effect for nonwhite workers (RR=5.31, 95% CI=2.78-10.1) was larger than for all workers combined. White workers showed only an overall excess, weakly related to measured cumulative exposure. All the well-fitting models examined had strong race-exposure interactions. This interaction was observed whether age, race and calendar time were adjusted by

stratification (internal adjustment) or by using external population rates. No other important interactions were detected.

A working lifetime of 45 years of exposure to Cr(VI) at the current OSHA PEL of 100 ug/m^3 as CrO_3 corresponds to a cumulative exposure of 4.5 mg/m^3-yr. The excess lifetime risk for lung cancer mortality from exposure to Cr(VI) at this exposure level was estimated to be 255 per thousand workers (95% CI: 109-416). At the previous NIOSH REL, 45 years of occupational exposure corresponded to a lifetime excess risk of six (95% CI: 3-12) lung cancer deaths per thousand workers.

Based on a categorical analysis, the exposure-race interaction was found to be due largely to an excess in lung cancer mortality evident among whites in the range 0.03-0.09 mg/m^3-yr of chromium cumulative exposure and a deficit in the range 0.37-1.1 mg/m^3-yr. While an explanation for this observed disparity on race was not provided it was argued that a biological basis is unlikely. Alternate explanations include exposure misclassification and failure to adequately control for important confounding. It is doubtful that confounding factors play an important role since it is unlikely that another causal risk factor is strongly and jointly associated with exposure and race. The asbestos exposure that was present was reported to be typical of industry generally at that time. Some asbestos exposure may have been associated with certain chromium process areas wherein workers were not representative of the entire workforce on race. For this to explain a significant amount of the observed lung cancer excess would require relatively high asbestos exposures correlated with Cr(VI) levels for non-white workers. It would not explain the relative deficit of lung cancer observed among white workers with high cumulative Cr(VI) exposures. Furthermore, no mesothelioma deaths were observed and the observed lung cancer excess would correspond to asbestos exposures at levels seen only in asbestos manufacturing or processing environments.

Exposure misclassification, on the other hand, is quite plausible, given the well-known disparities in exposure by race often observed in occupational settings. In this study

average exposure levels were assigned to exposure zones within which there may have been substantial race-related differences in work assignments and resulting individual exposures. Race-exposure interactions would inevitably follow. However, if the misallocation of exposure levels by race within otherwise appropriately sampled exposure zones is the source of the interaction, it follows that models without the race-chromium interaction term would provide an unbiased estimate of the exposure-response, although less precisely than if race had been taken into account in the processing of air sampling results and in the specification of exposure zone averages.

Park et al. [2006] examined the possibility of an exposure threshold in the Baltimore cohort by calculating different measures of cumulative exposure in which only concentrations exceeding some specified threshold value were summed over time. The best fitting models, evaluated with the profile likelihood method, were those with a threshold lower than 1.0 $\mu g/m^3$, the lowest threshold tested. The test was limited by statistical power but established upper confidence limits for a threshold consistent with the observed data of 16 or 29 $\mu g/m^3$ Cr(VI), for models with and without the exposure-race interaction, respectively. Other models using a cumulative exposure metric in which concentration raised to some power, X^a, is summed over time, found that the best fit corresponded to a=0.8. If saturation of some protective process were taking place, one would expect a>1.0. However, statistical power limited interpretation as a=1.0 could not be ruled out. Analyses in which a cumulative exposure threshold was tested found the best fitting models with thresholds of 0.02 or 0.3 mg/m^3-yr Cr(VI)(with and without exposure-race interaction, respectively) but could not ruleout no threshold. The retrospective exposure assessment for the Baltimore cohort, although the best available for a chromium-exposed population, has limitations which reduce the certainty of negative findings regarding thresholds. Nevertheless, the best estimate at this time is that there is no concentration threshold for the Cr(VI)-lung cancer effect.

K.S. Crump [1995] conducted an analysis of a cohort from the older Baltimore plant reported by Hayes et al. [1979]. The cumulative exposure estimates of Braver et al.

[1985] were also used in the risk assessment. From a Poisson regression model, the maximum likelihood estimate of ß, the potency parameter (i.e. unit risk), was 7.5×10^{-4} per $\mu g/m^3$-yr. Occupational exposure to Cr(VI) for 45 years was estimated to result in 88 and 1.8 excess lung cancer deaths per 1000 workers exposed at the current OSHA PEL and previous NIOSH REL, respectively.

Gibb et al. [1986] conducted a quantitative assessment of the Baltimore production workers reported by Hayes et al. [1979] whose exposure was reconstructed by Braver et al. [1985]. This cohort was divided into six subcohorts based on their period of hire and length of employment [Braver et al. 1985]. Gibb et al. [1986] calculated the lifetime respiratory cancer mortality risk estimates for the four subcohorts who were hired before 1960 and had worked in the old facility. The slopes for these subcohorts ranged from $5.1 \times 10^{-3}/\mu g/m^3$ to $2.0 \times 10^{-2}/\mu g/m^3$ with a geometric mean of $9.4 \times 10^{-3}/\mu g/m^3$.

6.2 ANALYSES OF THE PAINESVILLE CHROMATE PRODUCTION DATA

Crump et al. [2003] calculated estimates of excess lifetime risk of lung cancer death resulting from occupational and environmental exposure to Cr(VI) in a cohort of chromate chemical production workers. The excess lifetime (45 years) risk for lung cancer mortality from occupational exposure to Cr(VI) at 1 $\mu g/m^3$ (the previous NIOSH REL) was estimated to be approximately two per thousand workers for both the relative and additive risk models.

The cohort analyzed was a Painesville Ohio worker population described by Luippold et al. [2003]. The cohort was comprised of 493 workers who met the following criteria: first hired between 1940 and 1972, worked for at least one year, and did not work in any of the other Cr(VI) facilities owned by the same company other than the North Carolina plant. The vital status of the cohort was followed through 1997.

All but four members of the cohort were male. Little information was available on the racial makeup of the study population other than that available from death certificates.

Information on potential confounders such as smoking histories and other occupational exposures was limited so was not included in the mortality analysis. There were 303 deaths, including 51 lung cancer deaths, reported in the cohort. SMRs were significantly increased for: all causes combined, all cancers combined, lung cancer, year of hire before 1960, twenty or more years of exposed employment, and latency of 20 or more years. A trend test showed a strong relationship between lung cancer mortality and cumulative Cr(VI) exposure. Lung cancer mortality was statistically significantly increased for observation groups with cumulative exposures greater than or equal to 1.05 mg/m^3-years.

The exposure assessment of the cohort was reported by Proctor et al. [2003]. More than 800 Cr(VI) air sampling measurements from 21 industrial hygiene surveys were identified. These data were airborne area samples. Airborne Cr(VI) concentration profiles were constructed for 22 areas of the plant for each month from January 1940 to April 1972. Cr(VI) exposure estimates for each worker were reconstructed by correlating their job titles and work areas with the corresponding area exposure levels for each month of their employment. The cumulative exposure and highest average monthly exposure levels were determined for each worker.

K.S. Crump [1995] calculated the risk of Cr(VI) occupational exposure in its analysis of the Mancuso [1975] data. Cr(III) and Cr(VI) data from the Painesville Ohio plant [Bourne and Yee 1950] were used to justify a conversion factor of 0.4 to calculate Cr(VI) concentrations from the total chromium concentrations presented by Mancuso [1975]. The cumulative exposure of workers to Cr(VI) (μg/m^3-yr) was used in the analysis. All of the original exposure categories presented by Mancuso [1975] were used in the analysis including those that had the greatest cumulative exposure. A sensitivity analysis using different average values was applied to these highest exposure groups. U.S. vital statistics data from 1956, 1967, and 1971 were used to calculate the expected numbers of lung cancer deaths. Estimates of excess lung cancer deaths at the previous NIOSH REL ranged from 5.8 to 8.9 per 1000 workers. Estimates of excess lung cancer deaths at the current OSHA PEL ranged from 246 to 342 per 1000 workers.

DECOS [1998] used the U.S. EPA [1984] environmental risk assessment which was based on the Mancuso [1975] data to calculate the additional lung cancer mortality risk due to occupational Cr(VI) exposure. The U.S. EPA estimate that occupational exposure to 8 $\mu g/m^3$ total dust resulted in an additional lung cancer mortality risk of 1.4×10^{-2} was used to calculate occupational risk. It was assumed that total dust concentrations were similar to inhalable dust concentrations due to the small aerodynamic diameters of the particulates. Additional cancer mortality risks of 4×10^{-3} and 4×10^{-5} were calculated for 40 year occupational exposures to 2 and 0.02 $\mu g/m^3$ Cr(VI) as inhalable dust, respectively.

The U.S. EPA used the data of Mancuso [1975] to calculate a unit risk estimate for Cr(VI). A unit risk estimate is the incremental lifetime cancer risk over the background cancer risk occurring in a hypothetical population in which all individuals are exposed continuously throughout life to a concentration of 1 $\mu g/m^3$ of the agent in the air that they breathe [EPA 1984]. This unit risk quantifies the risk resulting from environmental exposure to Cr(VI) as an air pollutant. The U.S. EPA calculated a unit risk estimate for Cr(VI) of 1.2×10^{-2} for environmental exposures based on the Mancuso [1975] data. If this lifetime unit risk estimate is adjusted to a hypothetical working lifetime of Cr(VI) exposure (eight-hour work day, 250 days per year for 45 years) there would be 92.5 and 1.8 predicted additional deaths from lung cancer per 1000 workers at the previous OSHA PEL of 52 $\mu g/m^3$ and the previous NIOSH REL of 1 $\mu g/m^3$, respectively [K.S. Crump 1995].

The U.S. EPA used the age-specific lung cancer death rate data from Mancuso [1975] in its risk assessment [EPA 1984]. Data were used, assumptions were made, and calculations were performed which affected the final calculations of risk as summarized below:

- data on cumulative exposure to total chromium was used because age-specific exposure data for Cr(VI) only were not available.

- it was assumed that this cohort smoked more than the general population as worker smoking data was not available.
- the exposure data was from one 1949 survey only and it was assumed that these exposure estimates were constant over the time period of the study.
- the 1964 vital statistics were used to estimate the expected number of lung cancer deaths as Mancuso [1975] did not provide this information.
- cumulative chromium exposure was converted to average concentration.
- the highest exposure group, more than 8,000 $\mu g/m^3$-yr of cumulative exposure, was dropped from the analysis due to uncertainty in the average exposure in this group.
- 21 cumulative exposure categories were combined into 9 different groups.

Given the weaknesses of these data and their analysis as summarized above, this risk assessment does not provide the strongest quantitative assessment of occupational Cr(VI) exposure. A recent re-analysis of workplace airborne hexavalent chromium concentrations indicates that the single exposure survey conducted in 1949 was not a good representation of workplace exposures in the 1930s and early 1940s [Proctor et al. 2003].

Gibb et al. [1986] applied the same models as U.S. EPA [1984] to the data of Mancuso [1975] to derive the same lifetime respiratory unit cancer risk estimate for Cr(VI) of 1.2×10^{-2}. This analysis has the same shortcomings as those of U.S. EPA [1984] as the same data, assumptions, and calculations were used.

6.3 OTHER CANCER RISK ASSESSMENTS

The International Chromium Development Association (ICDA) [1997] used the overall SMR for lung cancer from ten Cr(VI) studies to assess the risk of occupational exposure to various levels of Cr(VI) exposure. The ten studies evaluated were those selected by Steenland et al. [1996] as the largest and best-designed studies of workers in the chromium production, chromate paint production, and chromate plating industries. It was

assumed that the mean length of employment of all workers was 15 years. Although this assumption may be appropriate for some of the cohorts , for others it is not: the mean duration of employment for the Painesville cohort was less than ten years, and for the Baltimore cohort it was less than four years. Occupational exposures to Cr(VI) were assumed to be 500 $\mu g/m^3$, 1000 $\mu g/m^3$, or 2000 $\mu g/m^3$ TWA. These are very unlikely exposure Cr(VI) levels. The mean exposure concentrations in the Painesville cohort were less than 100 $\mu g/m^3$ after 1942, and in the Baltimore cohort the mean exposure concentration was 45 $\mu g/m^3$. For these different exposure levels three different assumptions were tested: (1) the excess SMR was due only to Cr(VI) exposure, (2) Cr(VI) exposure was confounded by smoking or other occupational exposures so that the baseline SMR should be 130, or (3) confounders set the baseline SMR to 160. The investigators did not adjust for the likely presence of a healthy worker effect in these SMR analyses. A baseline SMR of 80 or 90 would have been appropriate based on other industrial cohorts and would have addressed smoking differences between industrial worker populations and national reference populations [Park et al. 1991]. The reference used for expected deaths was the 1981 life-table for males in England and Wales. The lung cancer mortality risk estimates ranged from 5 to 28 per 1000 at exposure to 50 $\mu g/m^3$ Cr(VI) to 0.1 to 0.6 per 1000 at exposure to 1 $\mu g/m^3$ Cr(VI). The assumptions made and methods used in this risk assessment make it a weaker analysis than those in which worker exposure data at a particular plant is correlated with their incidence of lung cancer. The excess lung cancer deaths may have been underestimated by at least a factor of ten given the assumptions used on duration (factor of 1.5-2.0), exposure level (factor of 10-20), and healthy worker bias (factor of 1.1-1.2).

6.4 NONCANCER RISK ASSESSMENTS

The U.S. EPA derived reference concentrations (RfCs) for chronic inhalation exposure to Cr(VI) [U.S. EPA 1998]. The RfC is an estimate of a daily inhalation exposure of a substance to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. A RfC of 8×10^{-6} mg/m^3 for chromic acid mists and dissolved Cr(VI) aerosols was calculated using the critical effect of nasal septum atrophy

reported by Lindberg and Hedenstierna [1983]. The LOAEL of 2 x 10^{-3} mg/m^3 based on a TWA exposure to chromic acid was converted to a LOAEL for continuous exposure of 7.14 x 10^{-4} mg/m^3. Applying an uncertainty factor of 90 to this LOAEL resulted in the calculation of an RfC of 8 x 10^{-6} mg/m^3.

An RfC of 1 x 10^{-4} mg/m^3 for Cr(VI) particulates was calculated using the critical effect of lactate dehydrogenase levels in bronchioalveolar lavage (BAL) fluid in rats reported by Glaser et al. [1990]. The benchmark concentration (BMC) approach of Malsch et al. [1994] was used to derive this RfC. Malsch et al. [1994] calculated an RfC of 0.34 mg/m^3 using an uncertainty factor of 3 to account for pharmacokinetic differences between species. The EPA used uncertainty factors of 10, 10, and 3 to account for extrapolation from a subchronic to a chronic study, human variability, and pharmacodynamic differences between species, respectively. The benchmark dose of 0.016 mg/m^3 and uncertainty factor of 300 resulted in the calculation of an RfC of 1 x 10^{-4} mg/m^3.

Minimal Risk Levels (MRLs) are estimates of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure [ATSDR 2000]. MRLs are based on noncancer health effects only. They are intended to serve as screening levels to identify contaminants and potential health effects that may be of concern at hazardous waste sites. They are based on the most sensitive chemical-induced end point of relevance to humans.

ATSDR [2000] derived an intermediate (15 to 364 days) inhalation MRL of 5 x 10^{-6} mg/m^3 for Cr(VI) as chromic acid (chromium trioxide mist) and other dissolved hexavalent chromium aerosols and mists using the respiratory effects data of Lindberg and Hedenstierna [1983]. These respiratory effects included nasal irritation, mucosal atrophy, ulceration, and decreases in forced vital capacity, forced expired volume in one second, and forced mid-expiratory flow. The LOAEL of 2 x 10^{-3} mg Cr(VI)/m^3 TWA was adjusted to a continuous exposure LOAEL of 5 x 10^{-4} mg Cr(VI)/m^3. Uncertainty factors of 10 and 10 were used to account for extrapolation from a LOAEL and human

variability.

ATSDR [2000] derived an intermediate inhalation MRL of 1 x 10^{-3} mg Cr(VI)/m^3 for Cr(VI) particulate compounds based on the data from the subchronic rat study of Glaser et al. [1990]. The BMC of 0.016 mg Cr(VI)/m^3 for alterations in lactate dehydrogenase levels in BAL fluid was adjusted to account for differences in rat and human inhalation exposures. Uncertainty factors of 3 and 10 were applied to account for interspecies and human variability, respectively.

6.5 SUMMARY

The data sets of the Painesville Ohio and Baltimore Maryland chromate production workers provide the bases for the quantitative risk assessments of excess lung cancer deaths due to occupational Cr(VI) exposure. In 1975 Mancuso presented the first data set of the Painesville Ohio workers which was used for quantitative risk analysis. Its deficiencies included: very limited exposure data, information on total chromium only, and no reporting of the expected number of deaths from lung cancer. Proctor et al. [2003] presented over 800 airborne Cr(VI) measurements from 23 newly identified surveys conducted between 1943 and 1971 at the Painesville plant. These data and the mortality study of Luippold et al. [2003] provided the basis for an improved lung cancer risk assessment of the Painesville workers.

In 1979 Hayes presented the first data of the Baltimore Maryland production facility workers which was later used for quantitative risk assessment. In 2000 Gibb and coworkers provided additional exposure data for an improved cancer risk assessment of this cohort [Gibb et al. 2000a]. These data were used by Park et al. [2004] to derive their Cr(VI) lung cancer risk assessment.

In spite of the different data sets analyzed, and the use of different assumptions, models, and calculations, all of these risk assessments have estimates of excess risk that are within an order of magnitude of each other (see Tables 6—1, 6—2). All of these risk

assessments indicate considerable excess risk of lung cancer death to workers exposed to Cr(VI) at the current OSHA PEL and previous NIOSH REL. The risk assessments of Crump et al. [2003] and Park et al. [2004] analyzed the most complete data sets available on occupational exposure to Cr(VI). These risk assessments estimated excess risks of lung cancer death of two and six per 1000 workers, respectively, at a working lifetime exposure to 1 $\mu g/m^3$. Park et al. [2004] estimated an excess risk of lung cancer death of approximately one per 1000 workers at a steady 45 year workplace exposure to 0.2 $\mu g/m^3$.

Park and Stayner [2006] evaluated the possibility of a threshold concentration for lung cancer in the Baltimore cohort. Although a threshold could not be ruled out due to the limitations of the analysis, the best estimate at this time is that there is no concentration threshold for the Cr(VI)-lung cancer effect.

Table 6–1. Cr(VI) Risk assessments based on the Mancuso cohort estimated additional deaths from lung cancer per 1000 workers

Cr(VI) exposure µg/m^{3*}	U.S. EPA [1984]	KS Crump [1995]†	Crump et al. [2003]
0.25	0.44	1.4–2.2	
0.5		2.9–4.4	
1.0**	1.8	5.8–8.9	1.2 (0.2–2.1) – 2.2 (1.5–3.1)‡
2.5	4.4	14.0–22.0	
5.0***	8.8	28.0–43.0	
52.0	91.5	246–342	

* Assumes steady working lifetime exposure
**Previous NIOSH REL
***OSHA PEL
† Range results from different treatments of high-exposure groups

Table 6-2. Cr(VI) Risk assessments based on the Hayes cohort estimated additional deaths from lung cancer per 1000 workers

Cr(VI) exposure µg/m^{3*}	Gibb et al. [1986]	KS Crump [1995]	Park et al. [2004] linear model	Park et al. [2004] log-linear model
0.25	0.34	0.45	1.5	____
0.5	____	0.90	3 (1–6)†	3 (1–4)
1.0**	1.4	1.8	6 (3–12)	5 (3–8)
2.5	3.4	4.5	16 (6–30)	14 (7–20)
5.0***	6.8	9.0	31 (12–59)	28 (13–43)
52.0	70.2	88.0	255 (109–416)	281 (96–516)

* Assumes steady working lifetime exposure
**Previous NIOSH REL
***OSHA PEL
†95% confidence interval

CHAPTER SEVEN: RECOMMENDATIONS FOR AN EXPOSURE LIMIT

NIOSH is mandated under the authority of the Occupational Safety and Health Act of 1970 (Public Law 91-596) to develop and recommend criteria for identifying and controlling workplace hazards that may result in occupational illness or injury. NIOSH evaluated the available literature on Cr(VI) compounds including quantitative risk assessment, epidemiologic, toxicologic, and industrial hygiene studies to develop recommendations for occupational exposure to Cr(VI) compounds. This chapter summarizes the information relevant to the NIOSH REL for Cr(VI) compounds and the scientific data used to derive and support the revised REL. More detailed information on the studies summarized here is available in the respective document chapters.

7.1 THE NIOSH REL FOR Cr(VI) COMPOUNDS

NIOSH recommends that airborne exposure to all Cr(VI) compounds be limited to a concentration of 0.2 μg Cr(VI)/m^3 for an 8-hr TWA exposure, during a 40-hr workweek. The use of NIOSH Methods 7605 or 7703 (or validated equivalents), is recommended for Cr(VI) determination in the laboratory and field, respectively. The REL represents the upper limit of exposure for each worker during each work shift. Due to the residual risk of lung cancer at the REL, NIOSH further recommends that all reasonable efforts be made to reduce exposures to Cr(VI) compounds below the REL through the use of work practices and engineering controls. The available scientific evidence supports the inclusion of all Cr(VI) compounds into this recommendation. The REL is intended to reduce workers' risk of death from lung cancer associated with occupational exposure to Cr(VI) compounds over a working lifetime. Although the quantitative analysis is based on lung cancer data, it is expected that reducing airborne workplace exposures will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa. Additional controls are needed or administrative actions should be taken to reduce 8-hr TWA exposure to Cr(VI) compounds when the results of the exposure monitoring plan do not produce a high degree of confidence that a high percentage of daily 8-hr TWA exposures are below the REL.

In addition to limiting airborne concentrations of Cr(VI) compounds, NIOSH recommends that dermal exposure to Cr(VI) be prevented in the workplace to reduce the risk of adverse dermal health effects including irritation, ulcers, skin sensitization, and allergic contact dermatitis. Based on the draft NIOSH Current Intelligence Bulletin, *A Strategy for Improvement of Skin Notations*[†], skin notations of SK-DIR(COR) and SK-SEN are recommended for all Cr(VI) compounds [NIOSH 2008 draft]. The SK-DIR notation identifies Cr(VI) compounds as substances known to cause direct damage to the skin. The sub-category (COR) identifies Cr(VI) compounds as corrosive. The SK-SEN identifies Cr(VI) compounds as substances that cause skin sensitization or allergic contact dermatitis.

7.2 BASIS FOR NIOSH STANDARDS

In the 1973 *Criteria for a Recommended Standard: Occupational Exposure to Chromic Acid*, NIOSH recommended that the Federal standard for chromic acid, 0.1 mg/m^3 as a 15-minute ceiling concentration, be retained due to reports of nasal ulceration occurring at concentrations only slightly above this concentration [NIOSH 1973]. In addition, NIOSH recommended supplementing this ceiling concentration with a time-weighted average of 0.05 mg/m^3 for an 8-hour work day to protect against possible chronic effects, including lung cancer and liver damage.

In the 1975 *Criteria for a Recommended Standard for Occupational Exposure to Chromium(VI)*, NIOSH supported two distinct recommended standards for Cr(VI) compounds [NIOSH 1975]. Some Cr(VI) compounds were considered to be noncarcinogenic at that time, including the chromates and bichromates of hydrogen, lithium, sodium, potassium, rubidium, cesium, and ammonium, and chromic acid anhydride. These Cr(VI) compounds were relatively soluble in water. It was recommended that a 10-hr TWA limit of 25 µg Cr(VI)/m^3 and a 15-minute ceiling limit

[†] The draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals,* is in the NIOSH review and clearance process. The skin notations are included here for review with the expectation that the revised dermal policy will be approved prior to final publication of this Cr(VI) criteria document update.

of 50 µg Cr(VI)/m^3 be applied to these Cr(VI) compounds.

All other Cr(VI) compounds were considered carcinogenic [NIOSH 1975]. These Cr(VI) compounds were relatively insoluble in water. At that time NIOSH had a carcinogen policy which called for "no detectable exposure levels for proven carcinogenic substances" [Fairchild 1976]. Thus the basis for the REL for carcinogenic Cr(VI) compounds, 1 µg Cr(VI)/m^3 TWA, was the quantitative limitation of the analytical method available for measuring workplace exposures to Cr(VI) at that time.

NIOSH revised its policy on Cr(VI) compounds in its 1988 testimony to OSHA on the Proposed Rule on Air Contaminants [NIOSH 1988b]. NIOSH testified that while insoluble Cr(VI) compounds had previously been demonstrated to be carcinogenic, there was now sufficient evidence that soluble Cr(VI) compounds were also carcinogenic. Human studies cited in support of this position included Blair and Mason [1980], Franchini et al. [1983], Royle [1975a,b], Silverstein et al. [1981], Sorahan et al. [1987], and Waterhouse [1975]. In addition, the animal studies of Glaser et al. [1986] and Steinhoff et al. [1986] were cited as demonstrating that lifespan exposure of rats to soluble chromates could induce statistically significant excess cancer rates. NIOSH recommended that all Cr(VI) compounds, whether soluble or insoluble in water, be classified as potential occupational carcinogens based on the OSHA carcinogen policy. The adoption of the most protective of the available standards, the NIOSH RELs, was recommended. Consequently the REL of 1 µg Cr(VI)/m^3 TWA was adopted by NIOSH for all Cr(VI) compounds.

NIOSH reaffirmed its policy that all Cr(VI) compounds be classified as occupational carcinogens in its response to the 2002 OSHA Request for Information on Occupational Exposure to Hexavalent Chromium and in its testimony to OSHA on the Proposed Rule on Occupational Exposure to Hexavalent Chromium [NIOSH 2002; 2005] (see Appendix A).

This Criteria Document Update describes the most recent NIOSH scientific evaluation of occupational exposure to Cr(VI) compounds, including the justification for a revised REL derived using current quantitative risk assessment methodology on human health effects data. The policies and recommendations in this document are consistent with those of the January 2005 NIOSH testimony on the OSHA Proposed Rule on Occupational Exposure to Hexavalent Chromium and the corresponding NIOSH Post-Hearing Comments (Appendices A and B, respectively). Derivation of the REL follows the criteria established by NIOSH in 1995 in which RELs, including those for carcinogens, would be based on risk evaluations using human or animal health effects data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques [NIOSH 1995].

7.3 EVIDENCE FOR THE CARCINOGENICITY OF Cr(VI) COMPOUNDS

Hexavalent chromium is a well-established occupational carcinogen associated with lung cancer and nasal and sinus cancer [ATSDR 2000; EPA 1998; IARC 1990]. Toxicologic studies, epidemiologic studies and lung cancer meta-analyses provide evidence for the carcinogenicity of Cr(VI) compounds.

7.3.1 Epidemiologic Lung Cancer Studies

In 1989, the IARC critically evaluated the published epidemiologic studies of chromium compounds including Cr(VI), and concluded that "there is sufficient evidence in humans for the carcinogenicity of chromium[VI] compounds as encountered in the chromate production, chromate pigment production and chromium plating industries" (i.e., IARC category "Group 1" carcinogen) [IARC 1990]. Results from two recent lung cancer mortality studies of chromate production workers support this evaluation [Gibb et al. 2000a; Luippold et al. 2003].

Gibb et al. [2000a] conducted a retrospective analysis of lung cancer mortality in a cohort of Maryland chromate production workers. The cohort of 2,357 male workers first

employed between 1950 and 1974 was followed until 1992. Workers with short-term employment (i.e., <90 days) were included in the study group to increase the size of the low exposure group. The mean length of employment was 3.1 years. A detailed retrospective assessment of Cr(VI) exposure based on over 70,000 personal and area samples (short term and full-shift) and information about most workers' smoking habits at hire was available.

Lung cancer standardized mortality ratios increased with increasing cumulative exposure (i.e., mg CrO_3/m^3-years, with five-year exposure lag)—from 0.96 in the lowest quartile to 1.57 (95% CI 1.07—2.20) and 2.24 (95% CI 1.60—3.03) in the two highest quartiles. The number of expected lung cancer deaths was based on age-, race-, and calendar year-specific rates for Maryland. Proportional hazards models that controlled for the effects of smoking predicted increasing lung cancer risk with increasing Cr(VI) cumulative exposure (relative risks: 1.83, 2.48, and 3.32 for second, third, and fourth exposure quartiles, respectively, compared with first quartile of cumulative exposure; confidence intervals not reported; five-year exposure lag).

Luippold et al. [2003] conducted a retrospective cohort study of lung cancer mortality in 493 chromate production workers employed for at least one year between 1940 and 1972 in a Painesville, Ohio plant. Their mortality was followed from 1941 to the end of 1997 and compared with U.S. and Ohio rates. The effects of smoking could not be assessed because of insufficient data. More than 800 area samples of airborne Cr(VI) from 21 industrial hygiene surveys were available for formation of a job-exposure matrix [Proctor et al. 2003]. Cumulative Cr(VI) exposure was divided into five categories: 0.00—0.19, 0.20—0.48, 0.49—1.04, 1.05—2.69, and 2.70—23.0 mg/m^3-years (a rationale for selection of these categories was not described) [Luippold et al. 2003]. Person-years in each category ranged from 2,369 to 3,220 and the number of deaths from trachea, bronchus, or lung cancer ranged from three in the lowest exposure category to 20 in the highest (n=51). The SMRs were statistically significant in the two highest cumulative exposure categories (3.65 (95% CI 2.08—5.92) and 4.63 (2.83—7.16), respectively).

SMRs were also significantly increased for year of hire before 1960, ≥20 years of employment, and ≥20 years since first exposure. The tests for trend across increasing categories of cumulative exposure, year of hire, and duration of employment were statistically significant ($p \leq 0.005$). A test for departure of the data from linearity was not statistically significant (χ^2 goodness of fit of linear model; $p=0.23$).

7.3.2 Lung Cancer Meta-analyses

Meta-analyses of epidemiologic studies have been conducted to investigate cancer risk in chromium-exposed workers. Most of these studies also provide support for the classification of Cr(VI) compounds as occupational lung carcinogens.

Sjögren et al. [1994] reported a meta-analysis of five lung cancer studies of Canadian and European welders exposed to stainless steel welding fumes. The meta-analysis found an estimated relative risk of 1.94 (95% CI 1.28—2.93) and accounted for the effects of smoking and asbestos exposure.

Steenland et al. [1996] reported overall relative risks for specific occupational lung carcinogens identified by IARC, including chromium. Ten epidemiologic studies were selected by the authors as the largest and best-designed studies of chromium production workers, chromate pigment production workers, and chromium platers. The summary relative risk for the ten studies was 2.78 (95% confidence interval 2.47—3.52; random effects model), which was the second highest relative risk among the eight carcinogens summarized.

Cole and Rodu [2005] conducted meta-analyses of epidemiologic studies published in 1950 or later to test for an association of chromium exposure with all causes of death and death from malignant diseases (i.e., all cancers combined, lung cancer, stomach cancer, cancer of the central nervous system (CNS), kidney cancer, prostate gland cancer, leukemia, Hodgkin's disease, and other lymphatohematopoietic cancers (OLHC)).

Available papers (n=114) were evaluated independently by both authors on eight criteria that addressed study quality. In addition, papers with data on lung or stomach cancer were assessed for control of cigarette smoking effects or economic status, respectively. Forty-nine epidemiologic studies based on 84 papers published were used in the meta-analyses. The number of studies in each meta-analysis ranged from 9 for Hodgkin's disease to 47 for lung cancer. Association was measured by an author-defined "SMR" which included odds ratios, proportionate mortality ratios, and most often, standardized mortality ratios. Mortality risks were not significantly increased for most causes of death. However, SMRs were significantly increased in all lung cancer meta-analyses (smoking controlled: 26 studies; 1,325 deaths; SMR=118; 95% CI 112-125) (smoking not controlled: 21 studies; 1,129 deaths; SMR=181; 95% CI 171-192) (lung cancer—all: 47 studies; 2,454 deaths; SMR=141; 95% CI 135-147). Stomach cancer mortality risk was significantly increased only in meta-analyses of studies that did not control for effects of economic status (economic status not controlled: 18 studies; 324 deaths; SMR=137; 95% 123-153). The authors stated that statistically significant SMRs for "all cancer" mortality were due mainly to lung cancer (all cancer: 40 studies; 6,011 deaths; SMR=112; 95% CI 109-115). Many of the studies contributing to the meta-analyses did not address bias from the healthy worker effect and thus the results are likely underestimates of the cancer mortality risks. Other limitations of these meta-analyses include lack of (1) exposure characterization of populations such as the route of exposure (i.e., airborne versus ingestion) and (2) detail of criteria used to exclude studies based on "no or little chrome exposure" or "no usable data".

7.3.3 Animal Experimental Studies

Cr(VI) compounds have been tested in animals using many different experimental conditions and exposure routes. Although experimental conditions are often different from occupational exposures, these studies provide data to assess the carcinogenicity of the test compounds. Chronic inhalation studies provide the best data for extrapolation to occupational exposure; unfortunately few have been conducted using Cr(VI) compounds. However, the body of animal studies support the classification of Cr(VI) compounds as

occupational carcinogens.

The few chronic inhalation studies available demonstrate the carcinogenic effects of Cr(VI) compounds in mice and rats [Adachi et al. 1986, 1987; Glaser et al. 1986]. Female mice exposed to 1.8 mg/m^3 chromic acid mist (two hours per day, two days per week for up to 12 months) developed a significant number of nasal papillomas compared to control animals [Adachi 1987]. Female mice exposed to a higher dose of chromic acid mist, 3.6 mg/m^3 (30 minutes per day, two days per week for up to 12 months) developed an increased, but not statistically significant, number of lung adenomas [Adachi et al. 1986]. Glaser et al. [1986] reported a statistically significant number of lung tumors in male rats exposed for 18 months to 100 $\mu g/m^3$ sodium dichromate; no tumors were reported at lower dose levels.

Animal studies conducted using other routes of administration have also produced adverse health effects with some Cr(VI) compounds. Zinc chromate and calcium chromate produced a statistically significant ($p<0.05$) number of bronchial carcinomas when administered to rats via an intrabronchial pellet implantation system [Levy et al. 1986]. Cr(VI) compounds with a range of solubilities were tested using this system. Although some soluble Cr(VI) compounds did produce bronchial carcinomas, these results were not statistically significant. Some lead chromate compounds produced bronchial squamous carcinomas which, although not statistically significant, may be biologically significant due to the absence of this cancer in control rats.

Steinhoff et al. [1986] administered the same total dose of sodium dichromate either once-per-week or five-times-per week to male and female rats via intratracheal instillation. No increased incidence of lung tumors was observed in animals dosed five times weekly. However, in animals dosed once per week, a statistically significant tumor incidence was reported in the 1.25 mg/kg exposure group. This study demonstrates a dose-rate effect within the constraints of the experimental design. It suggests that limiting exposure to high Cr(VI) concentrations may be important in reducing carcinogenicity.

However, quantitative extrapolation of these animal data to the human exposure scenario is difficult.

Animal studies conducted using non-respiratory routes of administration have also produced injection-site tumors with some Cr(VI) compounds [Hueper 1961; Furst 1976]. These studies provide another data set for hazard identification.

Most animal studies conducted on Cr(VI) compounds were published prior to the 1990 IARC evaluation of chromium. IARC review of the studies concluded "there is sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate and lead chromates. There is limited evidence in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate. There is inadequate evidence in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium[III] compounds" [IARC 1990].

7.4 BASIS FOR THE NIOSH REL

The primary basis for the revised NIOSH REL is the results of the Park et al. [2004] quantitative risk assessment of lung cancer deaths of Baltimore MD chromate production workers. The revised REL has an associated excess risk of lung cancer death of approximately one per 1000 workers which is a level of risk consistent with those for other carcinogens in recent OSHA rules [71 Fed. Reg. 10099 (2006)]. The results of the NIOSH risk assessment are supported by other quantitative Cr(VI) risk assessments (see Chapter Six). Additional considerations in the derivation of the REL include analytical feasibility and the ability to achieve exposure concentrations to the REL in the workplace. The REL is intended to reduce workers' risk of death from lung cancer over a 45-year working lifetime. Although the quantitative analysis is based on lung cancer mortality data, it is expected that reducing airborne workplace exposures will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa.

The skin notations for Cr(VI) compounds are based on epidemiologic and experimental studies described in Chapters Four and Five documenting the adverse dermal health effects of irritation, ulceration, allergic contact dermatitis, and skin sensitization.

The available scientific evidence supports the inclusion of all Cr(VI) compounds into this recommendation. All Cr(VI) compounds studied have demonstrated their carcinogenic potential in animal, in vitro, or human studies [NIOSH 1988b; 2002; 2005a,b]. Recent molecular toxicology studies provide support for classifying all Cr(VI) compounds as occupational carcinogens without providing sufficient data to quantify different RELs for specific compounds [NIOSH 2005a,b]. Although there is inadequate epidemiologic data to quantify the risk of human exposure to insoluble Cr(VI) compounds, the results of animal studies indicate that this risk is likely as great as, if not greater than, exposure to soluble Cr(VI) compounds [Levy et al. 1986]. Due to the similar mechanisms of action of soluble and insoluble Cr(VI) compounds, and the quantitative risk assessments demonstrating significant risk of lung cancer death resulting from occupational lifetime exposure to soluble Cr(VI) compounds, it is prudent public health practice to include all Cr(VI) compounds under this recommendation until further data is available.

7.4.1 Park et al. [2004] Risk Assessment

NIOSH calculated estimates of excess lifetime risk of lung cancer death resulting from occupational exposure to water-soluble chromium-containing mists and dusts in a cohort of Baltimore, MD chromate chemical production workers [Park et al. 2004]. This cohort, originally studied by Gibb et al. [2000a], was composed of 2357 men first hired between 1950 and 1974 whose vital status was followed through 1992. The mean duration of employment of workers in the cohort was 3.1 years and the median duration was 0.39 year.

This cohort had a detailed retrospective exposure assessment of approximately 70,000 measurements which was used to estimate individual worker current and cumulative

Cr(VI) exposures across time. Smoking information at hire was available from medical records for 91% of the population, including packs per day for most workers. In this study population of 2357 workers, 122 lung cancer deaths were documented.

The excess working lifetime (45 years) risk estimates of lung cancer death associated with occupational exposure to water-soluble Cr(VI) compounds using the linear risk model are 255 (95% CI: 109-416) per 1000 workers at 52 μg Cr(VI)/m^3, 6 (95% CI: 3-12) per 1000 workers at 1 μg Cr(VI)/m^3, and approximately one per 1000 workers at 0.2 μg Cr(VI)/m^3.

7.4.2 Crump et al. [2003] Risk Assessment

Crump et al. [2003] analyzed data from the Painesville OH chromate production worker cohort described by Luippold et al. [2003]. The cohort was comprised of 493 workers who met the following criteria: first hired between 1940 and 1972, worked for at least one year, and did not work in any of the other Cr(VI) facilities owned by the same company other than the North Carolina plant. The vital status of the cohort was followed through 1997.

Information on potential confounders (e.g., smoking) and other occupational exposures was limited and not included in the mortality analysis. There were 303 deaths reported, including 51 lung cancer deaths. SMRs were significantly increased for: all causes combined, all cancers combined, lung cancer, year of hire before 1960, twenty or more years of exposed employment, and latency of 20 or more years. A trend test showed a strong relationship between lung cancer mortality and cumulative Cr(VI) exposure. Lung cancer mortality was increased for cumulative exposures greater than or equal to 1.05 mg/m^3-years.

The estimated lifetime additional risk of lung cancer mortality associated with 45 years of occupational exposure to water-soluble Cr(VI) compounds at 1 μg/m^3 was approximately 2 per 1000 (0.00205 (90% CI: 0.00134, 0.00291) for the relative risk model and 0.00216

(90% CI: 0.00143, 0.00302) for the additive risk model assuming a linear dose response for cumulative exposure with a five-year lag).

7.4.3 Risk Assessment Summary

Quantitative risk assessments of the Baltimore MD and Painesville OH chromate production workers, including those most recently conducted by Park et al. [2004] and Crump et al. [2003], demonstrate significant risk of lung cancer mortality to workers exposed to Cr(VI) at the previous NIOSH REL of 1 μg Cr(VI)/m^3. These results justify lowering the REL to decrease the risk of lung cancer deaths in Cr(VI)-exposed workers. The risk assessment of Park et al. [2004] was used to derive the current REL as it analyzes a more extensive database of workplace exposure measurements that includes smoking data on most workers.

7.5 APPLICABILITY OF THE REL TO ALL Cr(VI) COMPOUNDS

NIOSH recommends that the REL of 0.2 ug/m^3 be applied to all Cr(VI) compounds. There is currently inadequate data to exclude any single Cr(VI) compound from this recommendation.

Epidemiologic studies were often unable to identify the specific Cr(VI) compound responsible for the excess risk of cancer. However, these studies have documented the carcinogenic risk of occupational exposure to soluble Cr(VI). Gibb et al. [2000a] and Luippold et al. [2003] reported the health effects of chromate production workers with sodium dichromate being their primary Cr(VI) exposure. These studies, and the risk assessments done on their data, demonstrate the carcinogenic effects of this soluble Cr(VI) compound. The NIOSH risk assessment on which the REL is based evaluated the risk of exposure to sodium dichromate [Park et al. 2004].

Although there is inadequate epidemiologic data to quantify the risk of human exposure to insoluble Cr(VI) compounds, the results of animal studies indicate that this risk is likely as great, if not greater than, exposure to soluble Cr(VI) compounds [Levy et al.

1986]. The carcinogenicity of insoluble Cr(VI) compounds has been demonstrated in animal and human studies [NIOSH 1988b]. Animal studies have demonstrated the carcinogenic potential of soluble and insoluble Cr(VI) compounds [NIOSH 1988b, 2002, 2005a; ATSDR 2000]. Recent molecular toxicology studies provide further support for classifying all Cr(VI) compounds as occupational carcinogens without providing sufficient data to quantify different RELs for specific compounds [NIOSH 2005a]. The cytotoxicity and genotoxicity of both soluble (sodium chromate) and insoluble (lead chromate) Cr(VI) compounds have been demonstrated in human lung cells [Wise et al. 2002]. Phagocytosis is one mechanism by which lead chromate particles, an insoluble Cr(VI) compound, may enter cells and cause damage [Leonard et al. 2004]. Barium chromate is the only Cr(VI) compound for which IARC concluded that there were insufficient data from animal studies to evaluate its carcinogenicity. However, the cytotoxicity and genotoxicity of this compound has been demonstrated in human lung cells [Wise et al. 2003]. With the data currently available for Cr(VI) compounds it is prudent public health practice to include all Cr(VI) compounds in the revised REL. There is inadequate data to exclude any single Cr(VI) compound from this recommendation.

7.6 ANALYTICAL FEASIBILITY

There are several validated methods to quantify airborne exposures to Cr(VI) in workplace air. The limits of detection (LODs) for NIOSH Methods 7605, 7604, and 7600 are 0.02 µg, 3.5 µg, and 0.05 µg per sample, respectively [NIOSH 1994a,b; NIOSH 2003b]. OSHA Method ID-215 has an LOD of 0.01 µg per sample. NIOSH methods 7605 or 7600, or OSHA Method ID-215, can quantitatively assess worker exposure to Cr(VI) at the REL of 0.2 µg Cr(VI)/m^3. Thus, monitoring exposures over a work shift poses no problem in assessing exposures at the NIOSH REL. Sampling considerations to ensure accurate workplace Cr(VI) measurements are discussed in Chapter Three.

7.7 CONTROLLING WORKER EXPOSURE BELOW THE REL

Elimination of and substitution for Cr(VI) compounds, and the use of engineering controls and good work practices for controlling Cr(VI) exposure should be the highest

priorities. However, the use of respirators may be required for some workers exposed to Cr(VI) compounds. Respirators may be required for those industries or job tasks where there are routinely and unavoidably high Cr(VI) concentrations, or where the airborne concentration of Cr(VI) is unknown, unpredictable,or highly variable.

An analysis of the need for respirator use in Cr(VI) industries at various potential PELs after engineering and work practice controls have been applied indicate that in some industries a large percentage of workers would need to wear respirators at an exposure limit of 0.25 μg/m^3 for a full-workshift TWA exposure to Cr(VI) in air [71 Fed. Reg. 10099 (2006)]. In other industries an appreciable but smaller proportion of the workers would need to wear respirators at this exposure limit [71 Fed. Reg. 10099 (2006)]. The latter conclusion is consistent with a separate, qualitative analysis of NIOSH field-survey exposure data collected at "hard" chromium electroplating, chromate-paint spray application, atomized-alloy spray-coating, and some types of welding operations which concluded that it may be difficult for these operations to consistently achieve exposures at or below 1 μg Cr(VI)/m^3 by means of engineering controls and work practices alone [Blade et al. 2007]. The NIOSH field-survey data reveal very low existing Cr(VI) exposures in some workplaces and the potential for relatively easy control of exposures in others. The NIOSH REL of 0.2 μg Cr(VI)/m^3 is therefore achievable in some workplaces where Cr(VI) compounds are used without the need for extensive, if any, respirator use. However, it will be difficult to reduce exposures below the REL at some electroplating, spray painting, welding, and atomized-alloy spray-coating operations using existing, and perhaps even improved, exposure control methods as observed at these operations. There are other operations evaluated by NIOSH in which control of exposures to the REL using only engineering and work-practice controls also may prove difficult.

7.8 CONTROLLING DERMAL EXPOSURE

NIOSH recommends that dermal exposure to Cr(VI) be prevented by elimination or substitution of Cr(VI) compounds. When this is not possible, appropriate sanitation and

hygiene procedures, and appropriate PPE should be used (see Chapter Eight for specific PPE recommendations). Preventing dermal exposure is important to reduce the risk of adverse dermal health effects including dermal irritation, ulcers, skin sensitization, and allergic contact dermatitis. The prevention of dermal exposure to Cr(VI) compounds is critical in preventing Cr(VI)-related skin disorders.

7.9 SUMMARY

The NIOSH quantitative risk assessment indicates that the previous REL for airborne Cr(VI) compounds, 1 µg Cr(VI)/m^3 as a TWA concentration for up to a 10-hr day within a 40-hr workweek, is associated with a significant excess risk of lung cancer death of approximately six per 1000 workers [Park et al. 2004]. This assessment of risk is based on the most comprehensive data set available on occupational exposure to Cr(VI), including an extensive exposure assessment database and smoking information on workers. Based on the results of this risk assessment NIOSH recommends a REL of 0.2 µg Cr(VI)/m^3 for an 8-hr TWA exposure within a 40-hr workweek, for all airborne Cr(VI) compounds to reduce workers' risk of lung cancer death over a working lifetime. The excess risk of lung cancer death at the revised REL is approximately one per 1000 workers. This risk estimate is consistent with those of other carcinogens recently regulated by OSHA. Analytical methods are available to accurately and reliably quantitate occupational Cr(VI) exposures in this range. Results from epidemiologic and toxicologic studies provide the scientific evidence to classify all Cr(VI) compounds as occupational carcinogens and support the recommendation of having one REL for controlling exposures to all Cr(VI) compounds [NIOSH 2005a,b, 2002, 1988b].

Exposure to Cr(VI) compounds should be eliminated from the workplace where possible due to their carcinogenic potential. Where possible, less toxic compounds should be substituted for Cr(VI) compounds. Where elimination or substitution of Cr(VI) compounds is not possible, attempts should be made to control workplace exposures at the REL. Compliance with the REL for Cr(VI) compounds is currently achievable in some industries and tasks. Other workplaces will require the use of engineering controls

to achieve the REL. It may be difficult to achieve the REL in several workplaces or during certain job tasks including welding, electroplating, spray painting, and atomized-alloy spray-coating operations. Where airborne exposures to Cr(VI) cannot be reduced to the REL through the use of state-of-the-art engineering controls and work practices, the use of respiratory protection will be required.

The REL may not be sufficiently protective to prevent all occurrences of lung cancer and other adverse health effects among workers exposed for a working lifetime. NIOSH therefore recommends that worker exposures be maintained as far below the REL as achievable during each work shift. NIOSH also recommends that a comprehensive safety and health program be implemented that includes worker education and training, exposure monitoring, and medical monitoring.

In addition to controlling airborne exposures at the REL, NIOSH recommends that dermal exposures to Cr(VI) compounds be prevented to reduce the risk of adverse dermal health effects including dermal irritation, ulcers, skin sensitization, and allergic contact dermatitis. Skin notations of SK-DIR(CORR) and SK-SEN are recommended.

CHAPTER EIGHT: RISK MANAGEMENT

NIOSH recommends the following guidelines to control and minimize occupational exposure to Cr(VI) compounds. Adherence to these recommendations should decrease the risk of lung cancer death in workers exposed to Cr(VI) compounds. It is expected that reducing airborne workplace exposures will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa. Although workplaces in which workers are exposed to Cr(VI) levels above the REL warrant particular concern and attention, all workplaces should attempt to decrease worker exposures to Cr(VI) compounds to the lowest level which is reasonably achievable to minimize adverse health effects, including lung cancer, in workers. The following recommendations should be incorporated into a comprehensive safety and health plan in each workplace in which workers manufacture, use, handle, or dispose of Cr(VI) compounds, or perform any other activity which involves exposure to Cr(VI) compounds.

OSHA has a standard for occupational exposure to hexavalent chromium compounds which covers occupational exposure to hexavalent chromium (Cr(VI)) in general industry, construction and shipyards. There are many OSHA standards related to Cr(VI) compounds. For a full list and explanation of relevant standards see the OSHA topic page on Hexavalent Chromium: OSHA Standards (http://www.osha.gov/SLTC/hexavalentchromium/standards.html).

8.1 THE NIOSH RECOMMENDED EXPOSURE LIMIT

8.1.1 The NIOSH REL

NIOSH recommends that airborne exposure to all Cr(VI) compounds be limited to a concentration of 0.2 µg Cr(VI)/m^3 for an 8-hr TWA exposure, during a 40-hr workweek. The use of NIOSH Methods 7605 or 7703 (or validated equivalents), is recommended for Cr(VI) determination in the laboratory and field, respectively. The REL represents the upper limit of exposure for each worker during each work shift. Due to the residual risk of lung cancer at the REL, NIOSH further recommends that all reasonable efforts be

made to reduce exposures to Cr(VI) compounds below the REL through the use of work practices and engineering controls. The available scientific evidence supports the inclusion of all Cr(VI) compounds into this recommendation. The REL is intended to reduce workers' risk of death from lung cancer associated with occupational exposure to Cr(VI) compounds over a 45-year working lifetime. Although the quantitative analysis is based on lung cancer mortality data, it is expected that reducing airborne workplace exposures will also reduce the nonmalignant respiratory effects of Cr(VI) compounds including irritated, ulcerated, or perforated nasal septa.

In addition to limiting airborne concentrations of Cr(VI) compounds, NIOSH recommends that dermal exposure to Cr(VI) be prevented in the workplace to reduce the risk of adverse dermal health effects including irritation, ulcers, allergic contact dermatitis, and skin sensitization. Based on the draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals*[†], skin notations of SK-DIR(COR) and SK-SEN are recommended for all Cr(VI) compounds [NIOSH 2008 draft]. The SK-DIR notation identifies Cr(VI) compounds as substances known to cause direct damage to the skin. The sub-category (COR) identifies Cr(VI) compounds as corrosive. The SK-SEN identifies Cr(VI) compounds as substances that cause skin sensitization or allergic contact dermatitis.

8.1.2 Sampling and analytical methods

The sampling and analysis of Cr(VI) in workplace air should be performed using precise, accurate, sensitive and validated methods. The use of NIOSH Methods 7605 or 7703 is recommended for Cr(VI) determination in the laboratory and field, respectively. Other standardized methods for Cr(VI) analysis include OSHA Method ID-215 [OSHA 1998], ASTM Method D6832-02 [ASTM 2002], and ISO Method 16740 [ISO 2005]. More detailed discussion of sampling and analytical methods for Cr(VI) is provided in Chapter Three, Measurement of Exposure.

[†] The draft NIOSH Current Intelligence Bulletin, *A Strategy for Assigning the New NIOSH Skin Notations for Chemicals,* is in the NIOSH review and clearance process. The revised skin notations are included here for review purposes with the expectation that the revised dermal policy will be approved prior to final publication of this Cr(VI) criteria document update.

8.2 INFORMING WORKERS ABOUT THE HAZARD

8.2.1 Safety and Health Programs

Employers should establish a comprehensive safety and health training program for all workers who manufacture, use, handle, or dispose of Cr(VI) compounds or perform any other activity which involves exposure to Cr(VI) compounds. This program should include employee training on the hazards of occupational Cr(VI) exposure, workplace monitoring of airborne Cr(VI) levels, and medical surveillance of Cr(VI)-exposed employees.

Workers should receive training as mandated by the OSHA Hazard Communication Standard (29 CFR 1910.1200) which contains information including: the Cr(VI) compounds to which they are exposed; the physical and chemical properties of these compounds; explanation of the corresponding material safety data sheets (MSDSs); appropriate routine and emergency handling procedures; and recognition of the adverse health effects of Cr(VI) exposure. Workers should be trained in the appropriate use, maintenance, and storage of PPE to minimize Cr(VI) exposure. Employees should be trained to report promptly to their supervisor any leaks observed, failures of equipment or procedures, wet or dry spills, cases of gross contact, and instances of suspected overexposure to Cr(VI) compounds. Employees should be trained to report to their supervisor or the director of the medical monitoring program any symptoms or illnesses associated with Cr(VI) exposure and any workplace events involving accidental or incidental exposures to Cr(VI) compounds. A medical monitoring program should be in place for all workers exposed to Cr(VI) compounds in the workplace (see section 8.6).

Safety and health programs should also include workers involved in cleaning, repair, and maintenance procedures who may be exposed to Cr(VI) compounds. Attempts should be made to minimize Cr(VI) exposures to these workers by the exposure control measures recommended in this chapter. When possible these duties should be performed when the work area or facility is not in operation to minimize these workers' airborne and dermal

Cr(VI) exposures.

8.2.2 Labeling and Posting

Receptacles containing Cr(VI) compounds used or stored in the workplace should carry a permanently attached label that is readily visible. The label should identify Cr(VI) compounds and provide information on their adverse health effects, including cancer, and appropriate emergency procedures.

Signs containing information about the health effects of Cr(VI) compounds should be posted at the entrances to work areas or building enclosures and in visible locations throughout the work areas where there is a potential for exposure to Cr(VI) compounds. Since Cr(VI) compounds are carcinogenic, the following warning sign, or a sign containing comparable information that is consistent with the workplace hazard communication program, should be posted:

DANGER
CHROMIUM(VI)
MAY CAUSE CANCER
CAN DAMAGE SKIN, EYES, NASAL PASSAGES AND LUNGS
AUTHORIZED PERSONNEL ONLY

In areas where respirators and/or chemical protective clothing are needed the following statement should be added:

RESPIRATORY PROTECTION AND CHEMICAL PROTECTIVE CLOTHING REQUIRED IN THIS AREA

Information on emergency first-aid procedures and the locations of emergency showers and eyewash fountains should be provided where needed.

All signs should be printed both in English and in the predominant language of non-English-speaking workers. All workers who are unable to read should receive oral instruction on the content and instructions on any written signs. Signs using universal safety symbols should be used wherever possible.

8.3 EXPOSURE CONTROL MEASURES

Many exposure control measures are used to protect workers from potentially harmful exposures to hazardous workplace chemical, physical, or biological agents. These control measures include, in order of priority: engineering controls, administrative controls and appropriate work practices, and the use of protective clothing and equipment [NIOSH 1983b]. The occupational exposure routes of primary concern for Cr(VI) compounds are the inhalation of airborne particulate containing Cr(VI) and direct skin contact. This section provides information on general exposure control measures that can be used in many workplaces and specific control measures for controlling Cr(VI) exposures in some workplaces.

8.3.1 Engineering Controls

Engineering controls are the first choice for reducing worker exposure to Cr(VI) compounds. These controls should be considered when new facilities are being designed, or when existing facilities are being renovated to maximize their effectiveness, efficiency, and economy. Engineering measures to control potentially hazardous workplace exposures to Cr(VI) compounds may include substitution, isolation, and ventilation.

8.3.1.1 Substitution

Using substitution as an engineering control may include substitution of equipment, materials, or less hazardous processes. Equipment substitution is the most common type of substitution [Peterson 1973]. It is often less costly than process substitution, and may be easier than finding a suitable substitute material. An example that applies to Cr(VI) exposure reduction is the substitution of an enclosed and automated spray paint booth for a partially enclosed work station.

Material substitution is the second most common type of substitution after equipment substitution. It has been used to improve the safety of a process or lower the intrinsic toxicity of its materials. However, evaluation of potential substitutes is essential as one

hazard may be replaced with a different one [Peterson 1973].

Material substitution was reported in some processes with potential worker exposures to Cr(VI) compounds investigated by NIOSH between 1999 and 2001 [Blade et al. 2007]. A reduction in the use of chromate-containing paints was reported in construction (i.e., bridge repainting) and vehicle manufacturing (i.e., the manufacture of automobiles and most trucks reportedly no longer uses chromate paints). However, chromate-containing paints reportedly remain without satisfactory substitute in aircraft manufacture and refurbishing. Chromium electroplating industry representatives also report steady demand for hard chrome finishes for mechanical parts such as gears, molds, etc., due to a lack of economical alternatives for this durable finish.

Many examples of process substitution have been considered. A change from an intermittent or batch-type process to a continuous-type process often reduces the potential hazard, particularly if the latter process is more automated [Peterson 1973; Soule 1978]. Dipping objects into a coating material, such as paint, usually causes less airborne material and is less of an inhalation hazard than spraying the material. Mechanical stirring of process materials requiring mixing usually offers a similar benefit over sparging with compressed gas [Peterson 1973].

8.3.1.2 Isolation

Isolation as an engineering control may involve the erection of a physical barrier between the worker and the hazard. Isolation may also be achieved by the appropriate use of distance or time [Soule 1978]. Examples of hazard isolation include the isolation of potentially hazardous materials into separate structures, rooms, or cabinets; and the isolation of potentially hazardous process equipment into dedicated areas or rooms that are separate from the general process areas [Peterson 1973]. Separate ventilation of the isolated area(s) may be needed to maintain the isolation of the hazard from the rest of the facility [Soule 1978]. Complete isolation of an entire process also may be achieved using automated, remote operation methods [Peterson 1973].

An example of using isolation to control Cr(VI) exposure is the use of a separate, ventilated mixing room for mixing batches of powdered materials containing chromate pigments.

8.3.1.3 Ventilation

Ventilation may be defined as the strategic use of airflow to control the environment within a space—to provide thermal control within the space, remove an air contaminant near its source of release into the space, or dilute the concentration of an air contaminant to an acceptable level [Soule 1978]. When controlling a workplace air contaminant such as Cr(VI), a specific ventilation system or assembly may be designed primarily to provide local or general control, using air exhaust or supply [Peterson 1973].

Local exhaust ventilation (LEV) is primarily intended to capture the contaminant at specific points of release into the workroom air through the use of exhaust hoods, enclosures, or similar assemblies. LEV is appropriate for the control of stationary point sources of contaminant release.

General ventilation, often called dilution ventilation, is primarily intended to dilute the concentration of the contaminant within the general workroom air. It controls widespread problems such as generalized or mobile emission sources [Peterson 1973].

Whenever practicable, point-source emissions are most effectively controlled by LEV, which is designed to remove the contaminant at the source before it emanates throughout the work space. Dilution ventilation is less effective because it merely reduces the concentration of the contaminant after it enters the workroom air, rather than preventing much of the emitted contaminant from ever entering the workroom air, and it also is much less efficient in terms of the much-greater volumetric air flow required. However, for non-point sources of contaminant emission, dilution ventilation may be required to reduce exposures.

It is important to recognize that LEV and general ventilation are not, and cannot be, exclusive. The air exhausted by a local exhaust system must be replaced, and the replacement air will usually be supplied by a general system that is not associated with any particular exhaust inlet and/or by simple infiltration through building openings. Whether exhausted air is made up by infiltration or a mechanical supply-air system, this general supply of replacement air will provide general ventilation to the space even if all the exhaust is considered local. The designation of a particular ventilation system or assembly as local or general, exhaust or supply, is governed by the primary intent of the design [Peterson 1973].

8.3.1.4 Engineering controls to reduce Cr(VI) exposures

Many engineering controls can reduce workplace Cr(VI) exposures. Some of the general engineering controls recommended by NIOSH in 1975 are still valid and in use today. The use of closed systems and operations is applicable in many cases. Tight and reliable seals, joints, covers, and similar assemblies must be ensured. The maintenance of negative static pressure within the closed equipment, relative to the surroundings, is preferable.

The use of local exhaust ventilation may be needed even with closed systems to control workers' exposures during operations such as unloading, charging, and packaging. The use of protective clothing and equipment may also be needed. Ventilation systems should be regularly inspected and maintained to assure effective operation. Work practices which may obstruct or interfere with ventilation effectiveness must be avoided. The effects of any changes to a ventilation system must be systematically evaluated by a qualified professional.

The use of clean areas such as control rooms with uncontaminated air is one method of isolating the workers from the hazard. An area to which workers may retreat for periods of time when they are not needed at the process equipment also may be configured as a

clean area.

The most difficult exposures to control often are those of repair and maintenance workers who may be working in emergency conditions in close contact with grossly contaminated equipment or surfaces. Their exposures may be variable in nature and irregular in frequency. Controls such as ventilation should be used where practicable, but careful use of PPE, work practices, and administrative controls may be essential to control exposures to below the REL.

From 1999 through 2001, NIOSH conducted field surveys in 21 workplaces across a variety of industrial operations and economic sectors with potential worker exposures to Cr(VI) compounds [Blade et al. 2007]. Many of the observed processes and equipment applications are typical of those throughout industry, such as dip tanks, paint booths, and grinding, sanding, and welding operations. In some of these sectors and operations, the application of general engineering controls were observed or recommended. In contrast, unique or specialized engineering measures were not observed in these processes. Accepted practices for the design and operation of local-exhaust ventilation enclosures for operations such as these and others are available in any comprehensive manual of industrial ventilation practice such as that published by the American Conference of Governmental Industrial Hygienists [ACGIH 2004].

Contrasting with what was observed in the previously mentioned relatively common types of processes and operations, some specialized engineering measures for Cr(VI) exposure control were observed or recommended during the NIOSH field surveys in some sectors and operations with other, less common types of processes. The following are examples:

Chromium electroplating. A combination of engineering measures may be needed to effectively control potential exposures from hard chrome plating tanks. Hard chrome is a relatively thick coating of chromium that provides an extremely durable, wear-resistant

surface for mechanical parts. At one facility, push-pull ventilation systems, polyethylene tarpaulins, and a foam-blanket mist-suppressant product were used, and workers' exposures still exceeded the existing NIOSH REL. Qualitative airflow visualization with smoke tubes suggested that the push-pull ventilation systems were generally effective in moving air away from workers' breathing zones. However, maintenance problems also were found suggesting that the effectiveness of the systems was not optimal. Reportedly, floating plastic balls also had been used in the past but proved impractical, while surface-tension-reducing mist suppressants were not used because of concerns that they may induce pitting in the hard-chrome plated finish.

In contrast with hard chrome plating tanks, control of bright chrome plating-tank emissions is less problematic. Bright chrome plating provides a thin chromium coating for appearance and corrosion protection to non-mechanical parts. The use of a wetting agent as a surface-tension-reducing fume suppressant provided very effective control of emissions [Blade et al. 2007].

At another facility, a hard chrome plating tank was equipped with a layer of a newly developed, proprietary viscous liquid and a system to circulate it [Blade et al. 2007]. This system effectively reduced Cr(VI)-containing mist emission from the tank but proved not to be durable over time.

Spray application of chromate-containing paints. At one facility where chromate-containing paints were applied to aircraft parts, the survey found that the most effective measure for reducing workers' Cr(VI) exposures would be the substitution of paints with lower chromate content (in this case, 1% to 5%) for those with higher content (in this case, 30%) wherever possible [Blade et al. 2007]. In addition, results indicated that partially enclosed paint booths for large-part painting may not provide adequate contaminant capture. The facility also used fully enclosed paint booths with single-pass ventilation, with air entering one end and exhausted from the other. The survey also indicated the need for average internal air velocities within these booths to exceed the

speed with which the workers walk while spraying paint so that the plume of paint overspray moves away from the workers.

Removal of chromate-containing paints. At another facility where chromate-containing paints were applied to aircraft parts, subsequent assembly tasks necessitated the removal of the newly applied paint from portions of the parts [Blade et al. 2007]. One specialized engineering measure used for exposure control was a rotary-disc sander with an integral vacuum attachment which provided local exhaust ventilation for this tool. The exposure of one worker using a 5-inch-diameter vacuum-equipped disc sander was 2.1 μg Cr(VI)/m^3 TWA on one of two days of exposure monitoring despite the presence of an additional local exhaust-ventilation inlet positioned close to the sanding operation.

At a construction site where a bridge was to be repainted the removal of the existing chromate-containing paint was accomplished by abrasive blasting. An enclosure of plastic sheeting was constructed to contain the spent abrasive and paint residue and prevent its release into the surrounding environment [Blade et al. 2007]. No mechanical ventilation was provided to the containment structure. NIOSH recommended that this type of containment structure be equipped with general-dilution exhaust ventilation that discharges the exhausted air through a high-efficiency particulate air (HEPA) filtration unit.

Mixing of chromate-containing pigments. At a colored-glass manufacturing facility, Cr(VI)-containing pigments were weighed in a separate room, with generally effective LEV, then moved to a production area for mixing into batches of materials [Blade et al. 2007]. Cr(VI) exposures at the facility were very low to not detectable.

At a screen-printing-ink manufacturing facility, there was no dedicated pigment-mixing room; LEV was used at the ink-batch mixing and weighing operation but capture velocities were inadequate [Blade et al. 2007]. Almost all the Cr(VI) exposures of the ink-batch weighers exceeded the existing REL.

Operations creating concrete dust. Portland cement contains Cr(VI), so operations that create concrete dust may lead to worker exposures. In one operation, the use of water to suppress dust during cleanup was observed to result in visibly lower dust concentrations [Blade et al. 2007]. All Cr(VI) exposures at the facility were low. At a construction-rubble crushing and recycling facility, a water-spray system was used on the crusher at various locations, and the operator also used a hand-held water hose [Blade et al. 2007]. All Cr(VI) exposures at this facility also were low.

8.3.2 Administrative Controls and Work Practices

Administrative controls are measures designed to minimize exposure times such as adjusting task schedules. Appropriate work practices may include proper material handling techniques, good personal hygiene and sanitation practices, and good housekeeping in the work area.

Workers should not be allowed to smoke, eat, or drink in work areas where Cr(VI) compounds are used or stored. Smoking should be prohibited in workplaces in which workers are exposed to Cr(VI). Emergency showers and eye-flushing fountains should be provided by the employer in areas where there is the potential for skin or eye contact with Cr(VI). This equipment should be properly maintained and inspected regularly. If Cr(VI) gets on the skin the affected area must be flushed promptly with large amounts of mild soap and running water for at least 15 minutes. If the eyes are contaminated with Cr(VI) they should be flushed immediately for at least 15 minutes with a copious flow of water and promptly examined by a physician.

Clean work clothing should be put on before each work shift. The clothing should be changed whenever it becomes wetted or grossly contaminated with Cr(VI)-containing compounds. Work clothing should not be worn home. Workers should be provided with showering and changing areas free from contamination where they may store and change into street clothes before leaving the worksite. Employers should provide services for

laundering work clothing so that contaminated clothes are not taken home. These precautions will protect the worker and people outside the workplace, including the worker's family, from being exposed to Cr(VI)-contaminated clothing. Laundry personnel should be informed about the potential hazards of handling contaminated clothing, and they should be instructed about measures to minimize their health risk.

8.3.3 Protective Clothing and Equipment

The use of protective clothing and PPE is another way to create a physical barrier between the worker and the hazard. The use of different types of protective clothing and PPE, such as chemically impervious gloves and clothing and respirators, may be appropriate. Employers are responsible for the selection of PPE, training in the proper use of PPE, ensuring the PPE is properly used, maintenance of PPE, and providing and paying for all PPE [NIOSH 1999]. The use of respirators to control inhalation exposures to air contaminants is considered a last resort for cases where engineering and other measures cannot provide sufficient control. Workers should be trained in the proper use, maintenance, and storage of all protective clothing worn in the workplace.

Workers and persons responsible for worker health and safety should be informed that protective clothing may interfere with the body's heat dissipation, especially during hot weather or in hot work situations. Additional monitoring is required to prevent heat-related illness when protective clothing is worn under these conditions [NIOSH 1986].

8.3.3.1 Protective Clothing and Gloves

NIOSH recommends the use of gloves and chemical protective clothing (CPC) with maximum body coverage for all employees exposed to Cr(VI) compounds. Protective clothing and gloves made from PVC or Saranex® can be used for an eight-hour exposure while those made from butyl or Viton can be used for a four-hour exposure [Forsberg and Keith 1999]. While the selection of this CPC is based on permeation properties, other selection factors, including size, dexterity, cut and tear resistance, should be considered as well. Contaminated CPC, gloves, and shoes must be removed and decontaminated

with proper methods before reuse. If Cr(VI) gets on the skin the affected area must be flushed immediately with large amounts of mild soap and running water for at least 15 minutes.

Further information on chemical protective clothing can be obtained on the NIOSH Protective Clothing topic page: http://www.cdc.gov/niosh/npptl/topics/protclothing Additional information is also available in the OSHA Technical Manual, Section VIII, Chapter 1, Chemical Protective Clothing [OSHA 1999]: http://www.osha-slc.gov/dts/osta/otm/otm_viii/otm_viii_1.html

8.3.3.2 Face and Skin Protection

Cr(VI) compounds cause irritation of the skin, skin ulcers, allergic contact dermatitis and skin sensitization. In workplaces where skin contact is possible, dermal and mucous membrane contact with Cr(VI) compounds should be prevented by full-body protective clothing consisting of: head, neck, and face protection; coveralls or similar protective body clothing; impermeable gloves with gauntlets; and shoes and apron where solutions or dry materials containing Cr(VI) may be contacted.

The proper use of this protective clothing requires that all openings be closed and that all garments fit snugly about the neck, wrists, and ankles whenever the wearer is in an exposure area. Care must be exercised to keep work clothing separate from street clothing to avoid contamination. All protective clothing must be maintained properly in an uncontaminated environment. Protective clothing should be inspected prior to each use and cleaned or replaced regularly.

Eye protection should be provided by the employer and used by the employees where eye contact with Cr(VI) is possible. Selection, use, and maintenance of eye protective equipment should be in accordance with the provisions of the American National Standard Practice for Occupational and Educational Eye and Face Protection, ANSI Z87.1-1989 [ANSI 1989]. In work environments where Cr(VI) levels are above the

NIOSH REL and respiratory protection is required, NIOSH recommends that eye protection be incorporated into PPE by the use of tight-fitting full facepiece respirators, or tight-fitting half-mask respirators used in conjunction with safety spectacles or goggles.

8.3.3.3 Respiratory Protection

NIOSH recommends respirator use while performing any task for which the exposure level is either unknown, or has been documented to be higher than the NIOSH REL of 0.2 µg Cr(VI)/m^3 8-hr TWA. Respirators should not be used as the primary means of controlling worker exposures. Other exposure control methods such as engineering controls, administrative controls and changes in work practices should be implemented in an attempt to lower exposures before the use of respirators is required. The use of respirators may be necessary when these other control measures do not control Cr(VI) levels to below the REL. NIOSH recognizes this may be a particular challenge in electroplating, spray painting, atomized-alloy spray-coating operations, some types of welding operations, and other industries or tasks with routinely and uncontrollably high Cr(VI) exposures. When respiratory protection is needed, the employer should establish a comprehensive respiratory protection program as described in the OSHA respiratory protection standard [29 CFR 1910.134]. Elements of a respiratory protection program, established and described in a written plan that is specific to the workplace, must include the following:

- Procedures for selecting respirators
- Medical evaluations of employees required to wear respirators
- Fit-testing procedures
- Routine-use procedures and emergency respirator use procedures
- Procedures and schedules for cleaning, disinfecting, storing, inspecting, repairing, discarding, and maintaining respirators
- When applicable, procedures for ensuring adequate air quality for supplied air respirators (respirable air should meet the requirements of Compressed Gas Association Specification G-7.1 Grade D or higher quality)

- Training in respiratory hazards
- Training in proper use and maintenance of respirators
- Program evaluation procedures
- Procedures for ensuring that workers who voluntarily wear respirators (excluding filtering-facepiece respirators) comply with the medical evaluation and cleaning, storing, and maintenance requirements of the standard
- A designated program administrator who is qualified to administer the respiratory protection program.

The written program should be updated as necessary to account for changes in the workplace that affect respirator use. All equipment, training, and medical evaluations required under the respiratory protection program should be provided at no cost to workers.

When conditions of exposure to airborne Cr(VI) compounds exceed the REL of 0.2 µg Cr(VI)/m^3 for an 8-hr TWA exposure during a 40-hr workweek NIOSH recommends that the selection of the minimum respiratory protective equipment to be used should be determined using the following equation:
APF > (Workplace Airborne Concentration / REL) [NIOSH 2004]
as described in Table 8–1. A comprehensive assessment of all workplace exposures should be performed to determine the presence of other possible contaminants to ensure that the proper respiratory protection is used.

For information and assistance in establishing a respiratory protection program and selecting appropriate respirators, employers are directed to the OSHA *Respiratory Protection Advisor* on the OSHA Web site at http://www.osha.gov

Additional information is also available from the NIOSH respirators topic page [http://www.cdc.gov/niosh/npptl/topics/respirators/], the *NIOSH Guide to Industrial Respiratory Protection* [NIOSH 1987a], the *NIOSH Guide to the Selection and Use of*

480 *Particulate Respirators Certified under 42 CFR 84* [NIOSH 1996b], and *NIOSH*
481 *Respirator Selection Logic* [2004].

1

Table 8-1. Respiratory protection recommendations for Cr(VI) exposure

Airborne Cr(VI)concentration	Minimum respiratory protection
<0.002 mg/m^3 (APF = 10)	Any half mask particulate air-purifying respirator with N, R, or P100 filters worn in combination with eye protection If Chromyl Chloride is present: Any half mask particulate air-purifying respirator with canisters providing Acid Gas protection and N, R, or P100 filters worn in combination with eye protection
<0.005 mg/m^3 (APF = 25)	Any supplied-air respirator with loose-fitting hood or helmet operated in a continuous-flow mode; any PAPR with HEPA particulate filter with loose-fitting hood or helmet If Chromyl Chloride is present: Any PAPR with canisters providing Acid Gas protection and HE particulate filters with loose-fitting hood or helmet
<0.010 mg/m^3 (APF = 50)	Any full facepiece particulate air-purifying respirator with N, R, or P100 filters; any PAPR respirator with full facepiece and HE particulate filters ; any full facepiece supplied-air respirator operated in a continuous-flow mode If Chromyl Chloride is present: Any full facepiece particulate air-purifying respirator with cartridges or canisters providing Acid Gas protection and N, R, or P100 filters; any full facepiece PAPR with cartridges or canisters providing Acid Gas protection and HE particulate filters
< 0.4 mg/m^3 (APF = 2,000)	Any supplied-air, pressure-demand respirator with full facepiece
< 2.0 mg/m^3 (APF=10,000)	Any self-contained breathing apparatus that is operated in a pressure-demand or other positive-pressure mode or any supplied-air respirator with a full facepiece that is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained positive-pressure breathing apparatus
$\geq$ 2.0 mg/m^3 (IDLH $\geq$15 mg/m^3) (APF = 10,000)	Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode

2 Abbreviations: APF = assigned protection factor; HEPA = High Efficiency Particulate Aerosol;
3 IDLH = Immediately Dangerous to Life and Health; PAPR = powered air-purifying respirator.
4

8.4 EMERGENCY PROCEDURES

Emergency plans and procedures should be developed for all work areas where there is a potential for exposure to Cr(VI). Workers should be trained in the effective implementation of these plans and procedures. These plans should be reviewed regularly for their effectiveness and updated when warranted due to changes in the facility, operating procedures, or chemical types or uses. Necessary emergency equipment, including appropriate respiratory protective devices, should be kept in readily accessible locations. Appropriate respirators should be available for use during evacuation. A full facepiece respirator with a 100-level filter may be used for escape-only situations. When chromyl chloride is present, a full facepiece gas mask (14G) with an AG canister and 100-level filter should be used for escape-only situations.

Any spills of Cr(VI) compounds should be promptly cleaned up by means that minimize the inhalation of, or contact with, the spilled material. No dry sweeping should be performed. Wet vacuuming is preferred for spills of dry material. Wet spills and flushing of wet or dry spills should be channeled for appropriate treatment or collection for disposal. They should not be channeled directly into the sanitary sewer system. Dry vacuuming is acceptable only if an adequately filtered system is used: either a HEPA-filtered system or a single-pass externally-exhausted system.

8.5 EXPOSURE MONITORING STRATEGY

The workplace exposure monitoring program for sites where workers are exposed to Cr(VI) compounds should include routine environmental and personal monitoring of airborne exposure levels. The monitoring strategy should be designed for use in assessing the effectiveness of engineering controls, work practices, PPE, training, and other factors in controlling airborne concentrations. The monitoring program should also be used to identify specific work areas or job tasks where worker exposures are routinely high and therefore require additional efforts to reduce them. A focused sampling strategy may be more practical than a random sampling approach. A focused sampling strategy, targeting workers with perceived highest exposure concentrations, is most efficient for identifying

exposure above the REL if maximum-risk workers and time periods are accurately identified.

Employers should implement an exposure monitoring plan that produces a high degree of confidence that a high percentage of daily 8-hr TWA exposures are below the REL. The probability that even a very low percentage of actual daily employee 8-hr TWA exposures will exceed the REL should be minimized. In statistical terms, the employer should try to attain 95% confidence that workers' 8-hr TWA exposures exceed the REL on no more than 5% of days in which there is an exposure [NIOSH 1977]. Additional controls are needed or administrative actions should be taken to reduce 8-hr TWA exposures to Cr(VI) compounds when the results of the exposure monitoring plan do not produce this level of confidence.

An exposure monitoring plan should be developed and implemented for each specific process and group of workers exposed to Cr(VI) compounds. The details of the plan will depend on a number of factors including the number of workers in the group and variability in exposure. It is well known that workers' exposures vary from day to day, and the daily exposures are typically log normally distributed. Exposures in well-controlled processes and environmental conditions vary less than in poorly controlled processes and where the environmental conditions change considerably, such as outdoors. As the day-to-day variability of 8-hr TWA exposures increases, more daily 8-hr TWA exposures must be assessed to achieve the needed level of confidence. More detailed information on developing exposure monitoring plans for specific situations is available from NIOSH [1977] and the AIHA [2006].

The goal of the exposure monitoring program is to ensure a more healthful work environment where worker exposure does not exceed the REL. The exposure sampling survey should be performed by collecting representative personal samples over the entire work shift. Periodic sampling should then be performed at least annually and whenever any major process change takes place or there is another reason to suspect that exposure

concentrations may have changed. All routine personal samples should be collected in the breathing zone of the worker. For workers exposed to concentrations above the REL more frequent exposure monitoring should be performed as engineering changes are implemented, and until an adequate number of consecutive samples indicate that the workers' exposures no longer exceed the REL. All workers should be notified of monitoring results and of any actions taken to reduce their exposure. An environmental sampling strategy should consider variations in work and production schedules and the inherent variability in most environmental sampling.

NIOSH Method No. 7605 or 7703 (or validated equivalents) should be used for the collection and analysis of airborne Cr(VI) samples in the workplace or in the field, respectively. Area sampling may be useful to determine sources of airborne Cr(VI) exposures and assessing the effectiveness of engineering controls.

The employer should also monitor, evaluate, and record the potential for skin exposure to any particular worker, task, or location.

8.6 MEDICAL MONITORING

The employer should establish a medical monitoring program for all workers with occupational exposure to Cr(VI) compounds, including personnel involved with routine or emergency repair or maintenance. Medical monitoring represents secondary prevention and should not replace the primary prevention efforts mentioned in previous sections of this chapter to minimize occupational exposure to Cr(VI). The goal of a workplace medical monitoring program is the early identification of adverse health effects that may be related to Cr(VI) exposure such as dermatitis, respiratory irritation, airway obstruction and other local or systemic effects. It is hoped that early detection of adverse health effects, subsequent treatment, and workplace interventions will minimize the adverse health effects of Cr(VI) exposure. Medical monitoring data may also be used for the purposes of medical surveillance to identify work areas, tasks, and processes that require additional primary prevention efforts.

8.6.1 Medical Monitoring Program Director

The employer should assign responsibility for the medical monitoring program to a qualified physician or other qualified health care provider (as determined by appropriate State laws and regulations) who is informed and knowledgeable about the following:

- The administration and management of a medical monitoring program for occupational hazards
- The establishment of a respiratory protection program, based on an understanding of the requirements of the OSHA respiratory protection standard and types of respiratory protection devices available at the workplace
- The identification and management of occupational skin disease
- The identification and management of occupational respiratory effects or illnesses, including lung cancer.

8.6.2 Medical Monitoring Program Elements

Recommended elements of a medical monitoring program for workers exposed to Cr(VI) compounds include: worker education, a preplacement medical examination, and regularly scheduled follow-up medical examinations. Based on the findings from these examinations more frequent and detailed medical examination may be necessary.

8.6.2.1 Worker Education

All workers in the medical monitoring program should be provided with the following information: the purposes of the program, the potential health benefits of participation, and program procedures. Workers should be trained in the potential symptoms, findings, and diseases associated with Cr(VI) exposure. They should also be trained in procedures to avoid and minimize their Cr(VI) exposures. They should be instructed to inform their supervisor or the medical director of any symptoms consistent with Cr(VI) procedure. They should be instructed to report any accidental exposures to Cr(VI) or incidents involving potentially high exposure levels.

8.6.2.2 Preplacement Medical Examination

A preplacement examination should be conducted on all workers included in the medical monitoring program. This medical examination should include:

- A standardized occupational history questionnaire that gathers information on all past jobs, a description of all duties and potential exposures for each job, and a description of all protective equipment the worker has used
- A standardized respiratory symptom questionnaire
- A detailed medical history including information on conditions such as skin sensitization, occupational asthma, and other dermatologic or respiratory symptoms or disorders that may be exacerbated by exposure to Cr(VI)
- A physical examination of all systems with careful inspection of the integumentary system for evidence of irritation, ulceration, sensitization, or dermatitis and the ears, optic membranes and upper respiratory tract for evidence of irritation, bleeding, ulcerations, or perforation
- An evaluation of the worker's ability to use negative or positive pressure respirators
- A baseline spirometric test. Anyone administering spirometric testing as part of the medical monitoring program should have completed a NIOSH-approved training course in spirometry or other equivalent training.
- A baseline chest radiograph
- Worker education on the potential risks of Cr(VI) exposure including symptoms, findings, and diseases that may occur from exposure and training on how to minimize exposures.

If a preplacement spirometric test or chest radiograph is not conducted, then a baseline spirometric test should be conducted within three months of assignment, and a chest radiograph within three to six months of assignment.

8.6.2.3 Follow-up Medical Examinations

All workers in the medical monitoring program should be provided with follow-up

medical examinations conducted by a physician or other qualified health care provider. The following recommendations are suggested for workers in good health. Any worker with adverse health effects associated with Cr(VI) exposure such as respiratory or dermatologic effects should be examined immediately and may require more frequent monitoring and extensive testing.

Each worker should have a thorough medical evaluation of the upper respiratory tract conducted every six months for the first two years of employment and annually thereafter unless adverse health effects warrant more frequent monitoring. An annual medical examination should be conducted and include: a physical examination with emphasis on the skin and respiratory system, respiratory symptom update questionnaire, and occupational history update questionnaire.

Spirometric testing should be conducted annually for the first three years and every two to three years thereafter, or as indicated by current medical recommendations and the scientific literature. Based on the findings from these examinations, more frequent and detailed medical examination or testing may be necessary. Interpretation of annual lung function changes within an individual worker are specified and updated by professional organization such as the American Thoracic Society (ATS) and the American College of Occupational and Environmental Medicine (ACOEM) [ATS 1995; ACOEM 2004].

The value of periodic chest radiographs in a medical surveillance program should be evaluated by a qualified health care professional, in consultation with the worker, based on current medical recommendations and the scientific literature to assess whether the benefits of testing warrant the additional exposure to radiation. Although lung cancer is often first detected on chest radiographs, the utility of either routine radiographic or tomographic lung images in early detection of cancer remains uncertain. If the qualified health care professional deems periodic chest radiographs useful, their timing and frequency should take into account the observed latency and natural history of occupational lung cancer associated with Cr(VI) and the symptoms of other relevant

findings.

Any worker may require more frequent and/or more detailed medical evaluation if he or she has any of the following indications:

- A prior history of exposure to Cr(VI) compounds, asbestos, any other lung carcinogen, or other respiratory hazard
- A past or present history of smoking
- New or worsening dermatologic or respiratory symptoms
- Other medically significant reason(s) for more detailed assessment.

8.6.3 Medical Reporting

Following each medical examination the physician or other qualified health care provider should provide each worker with a written report containing:

- The results of any medical tests performed on the worker
- A medical opinion in plain language about any medical condition that would increase the worker's risk of impairment from exposure to Cr(VI) compounds
- Recommendations for limiting the worker's exposure to Cr(VI) compounds including the use of appropriate respiratory protective devices or protective clothing
- Recommendations for further evaluation and treatment of medical conditions detected.

Following each medical examination the physician should provide a written report to the employer which contains:

- Occupationally pertinent results of the medical evaluation
- A medical opinion about any medical condition that would increase the worker's risk of illness or disease as a result of exposure to Cr(VI) compounds
- Recommendations for limiting the worker's exposure to Cr(VI) compounds which may include the use of appropriate respiratory protective devices or protective

clothing or reassignment to another job, as warranted

- A statement that the worker has been informed about the results of the medical examination and about medical condition(s) that should have further evaluation or treatment

Specific findings, test results, or diagnoses that have no bearing on the worker's ability to work with Cr(VI) compounds should not be included in the report to the employer. Safeguards to protect the confidentiality of the worker's medical records should be enforced in accordance with all applicable regulations and guidelines.

8.6.4 Employer Actions

The employer should assure that the qualified health care provider's recommended restriction of a worker's exposure to Cr(VI) compounds or other workplace hazards is followed, and that the REL for Cr(VI) compounds is not exceeded without requiring the use of personal protective equipment. Efforts to encourage worker participation in the medical monitoring program and to report any symptoms promptly to the program director are important to the program's success. Medical evaluations performed as part of the medical monitoring program should be provided by the employer at no cost to the participating workers. Where medical removal or job reassignment is indicated the affected worker should not suffer loss of wages, benefits, or seniority.

The employer should ensure that the program director regularly collaborates with the employer's safety and health personnel (e.g. industrial hygienists) to identify and control work exposure and activities that pose a risk of adverse health effects.

8.7 SMOKING CESSATION

Smoking should be prohibited in all areas of any workplaces in which workers are exposed to Cr(VI) compounds. As cigarette smoking is an important cause of lung cancer, NIOSH recommends that all workers who smoke should participate in a smoking cessation program. Employers are urged to establish smoking cessation programs which

inform workers about the hazards of cigarette smoking and provide assistance and encouragement for workers who want to quit smoking. These programs should be offered at no cost to the participants. Information about the carcinogenic effects of smoking should be disseminated. Activities promoting physical fitness and other health lifestyle practices that affect respiratory and overall health should be encouraged through training, employee assistance programs, and/or health education campaigns.

8.8 RECORD KEEPING

Employers should keep employee records on exposure and medical monitoring according to the requirements of 29 CFR 1910.20(d), Preservation of Records.

Accurate records of all sampling and analysis of airborne Cr(VI) conducted in a workplace should be maintained by the employer for at least 30 years. These records should include the name of the worker being monitored, social security number, duties performed and job locations, dates and times of measurements, sampling and analytical methods used, type of personal protection used, and number, duration and results of samples taken.

Accurate records of all medical monitoring conducted in a workplace should be maintained by the employer for 30 years beyond the employee's termination of employment.

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Appendix A

Testimony to DOL

Testimony of the
National Institute for Occupational Safety and Health
on the
Occupational Safety and Health Administration
Proposed Rule
Occupational Exposure to Hexavalent Chromium

29 CFR Parts 1910, 1915, 1917, 1918, and 1926
Docket No. H054A

Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

January 3, 2005

The National Institute for Occupational Safety and Health (NIOSH) has reviewed the Occupational Safety and Health Administration (OSHA) proposed rule *Occupational Exposure to Hexavalent Chromium* published in the Federal Register (FR) on October 4, 2004 [69 FR 59306]. NIOSH supports OSHA's effort to amend the existing standard for occupational exposure to hexavalent chromium [Cr(VI)], including revisions to methods for controlling exposure, respiratory protection, protective work clothing and equipment, hygiene areas and practices, medical surveillance, hazard communication, and recordkeeping. The proposed rule is important because Cr(VI) workers exposed at the current permissible exposure limit (PEL) have a significant health risk. NIOSH agrees with OSHA's determination that the proposed standard will substantially reduce that risk.

NIOSH has reviewed the basis for OSHA's determination that a Cr(VI) PEL of 1 $\mu g/m^3$ will substantially reduce the risk posed to workers exposed to Cr(VI) at the current OSHA PEL of 52 $\mu g/m^3$ as a ceiling limit in general industry and 52 $\mu g/m^3$ as a time-weighted average (TWA) in construction. NIOSH agrees with OSHA's statement in the Preamble that the risk of lung cancer mortality remaining at the proposed PEL of 1 $\mu g/m^3$ is significant and encourages OSHA to consider a lower PEL to reduce the excess risk. NIOSH anticipates revising the recommended exposure limit (REL) for Cr(VI) to 0.2 $\mu g/m^3$.

Due to the large number of workers exposed, the severity of the adverse health effects, and the lack of data on a Cr(VI) concentration below which dermal effects will not occur, it would be useful for the proposed construction standard to include portland cement.

Since NIOSH's November 2002 submission to OSHA's public docket in response to the Request for Information on Occupational Exposure to Hexavalent Chromium [NIOSH 2002], NIOSH scientists have participated in the publication of the following Cr(VI)-related publications (enclosed):

- Ashley K, Howe AM, Demange M, Nygren O. [2003]. Sampling and analysis considerations for the determination of hexavalent chromium in workplace air**.** Environ Monit *5*(5):707–716.

- Hazelwood KJ, Drake PL, Ashley K, Marcy D. [2004]. Field method for the determination of insoluble or total hexavalent chromium in workplace air. J Occup Environ Hyg *1*:613–619.

- NIOSH [2003a]. Hexavalent chromium by ion chromatography: method 7605. 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 94–113.

- NIOSH [2003b]. Hexavalent chromium by field-portable spectrophotometry: method 7703. 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention,

National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 94–113.

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

OSHA may also find helpful the NIOSH topic page on Cr(VI) which contains links to NIOSH Cr(VI) publications including sampling and analysis, journal articles, and health hazard evaluations: http://www.cdc.gov/niosh/topics/hexchrom/

NIOSH comments to specific OSHA questions follow (NIOSH only addressed those OSHA questions for which it had either data or expertise to respond. This explains why the numbering of the following responses is not consecutive).

II. Issues

OSHA requests comment on all relevant issues, including health effects, risk assessment, significance of risk determination, technological and economic feasibility, and the provisions of the proposed regulatory text. OSHA is especially interested in responses, supported by evidence and reasons, to the following questions:

Health Effects

***1*. OSHA has described a variety of studies addressing the major adverse health effects that have been associated with exposure to Cr(VI). Has OSHA adequately identified and documented all critical health impairments associated with occupational exposure to Cr(VI)? Are there any additional studies or other data that would controvert the information discussed or significantly enhance the determination of material health impairment or the assessment of exposure-response relationships? Submit any relevant information, and explain your reasoning for recommending the inclusion of any studies you suggest.**

OSHA has adequately identified and documented the major adverse health effects that have been associated with exposure to Cr(VI) in its discussion of the health effects of Cr(VI). However, OSHA's discussion of Material Impairment of Health could be expanded to include allergic contact dermatitis. Dermal exposure to Cr(VI) through skin contact with portland cement or other Cr(VI)-containing products may lead to sensitization or allergic contact dermatitis. This condition, while not life-threatening, is debilitating and marked by significant discomfort and long-lasting adverse effects; it can have adverse occupational and social consequences and should be considered a material impairment to the health of affected workers. As stated in the Preamble (page 59358), ***"****Cr(VI)-related dermatitis tends to become more severe and persistent with continuing exposure. Once established, the condition may persist even if occupational exposure ceases."* The Preamble also notes that a majority of contact dermatitis experts indicated that chromate was one of the allergens associated with the "worst possible prognosis" for dermatitis (page 59358). Including allergic contact dermatitis in

OSHA's determination of material impairment of health draws attention to the fact that Cr(VI) is both a dermal exposure hazard and an inhalation hazard, and alerts employers that they should seek to minimize exposures by both routes.

NIOSH knows of no additional substantive studies that would add to or alter OSHA's analysis of the health effects of Cr(VI).

***2*. Using currently available epidemiologic and experimental studies, OSHA has made a preliminary determination that all Cr(VI) compounds (e.g., water soluble, insoluble and slightly soluble) possess carcinogenic potential and thus present a lung cancer risk to exposed workers. Is this determination correct? Are there additional data OSHA should consider in evaluating the carcinogenicity or relative carcinogenic potencies of different Cr(VI) compounds?**

The epidemiologic and experimental studies cited by OSHA support the carcinogenic potential of all Cr(VI) compounds (i.e., water soluble, insoluble, and slightly soluble). NIOSH is not aware of additional data beyond that data already submitted to the docket to consider in evaluating the carcinogenicity or relative carcinogenic potencies of different Cr(VI) compounds.

Risk Assessment

***3*. In its preliminary assessment of risk, OSHA has relied primarily on two epidemiologic cohort studies of chromate production workers to estimate the lung cancer risk to workers exposed to Cr(VI) (Exs. 31-22-11; 33-10). Are there any other studies that you believe are better suited to estimating the risk to exposed workers; if so, please provide the studies and explain why you believe they are better.**

NIOSH concurs that the Baltimore and Painesville cohorts [Gibb et al. 2000a; Luippold et al. 2003] noted in this question are the best studies for predicting cancer risks because of the quality of the exposure estimation, large numbers of workers available for analysis, extent of exposure, and years of follow-up. NIOSH selected the Baltimore cohort for analysis [Park et al. 2004] because it has a greater number of lung cancer deaths, better smoking histories, and a more comprehensive retrospective exposure archive.

***4*. OSHA is aware of two cohorts (i.e., Alexander cohort, Ex. 31-16-3, and Pastides cohort, Ex. 35-279) in which a sizable number of workers were probably exposed to low Cr(VI) air levels (e.g., < 10 µg/m^3) more consistent with concentrations found in the workplace today. However, OSHA believes the period of follow-up observation (median < 10 yr), the young age (< 45 yr at end of follow-up) and the low number of observed lung cancers (< =15 lung cancers) severely limits these cohorts as primary data sets for quantitative risk analysis. Other limitations to the Alexander study include a lack of data on workers who were employed between 1940 and 1974, but whose employment ended prior to 1974, and on exposures prior to 1974. Are there updated analyses available for the Alexander and Pastides cohorts? How many years do these cohorts need to be**

followed and how many lung cancers need to be observed in order for these data sets to provide insight into the shape of the exposure-response curve at lower levels of Cr(VI) exposure (e.g., 0.5 to 5 µg/m^3)? In the case of the Alexander cohort, is there additional information on cohort members' exposures prior to 1974 or workers who left prior to 1974 that could improve the analysis? Are there other cohorts available to look at low exposures?

NIOSH is not aware of any updated analyses of the Alexander or Pastides cohorts.

The Pastides [1994a] cohort consisted of a small number of workers with very low exposures to Cr(VI). Even if the cohort was followed until all workers were deceased, the study would have insufficient power to describe with any certainty the effects of low Cr(VI) exposures. Specifically, 92% of the cohort had cumulative Cr(VI) exposures less than 30 µg/m^3–yr. The mean cumulative exposure was less than 10 µg/m^3-yr (estimated from Pastides et al. [1994b]). In comparison, the mean cumulative Cr(VI) exposure in the Baltimore cohort was 134 µg/m^3–yr [Gibb et al. 2000a]. With the Cr(VI) exposures present in the Pastides cohort, less than 10 additional cancers attributable to Cr(VI) would be expected, an insufficient number to make any valid statistical inferences about the effects of low levels of Cr(VI) exposures.

The Alexander et al. [1996] study of lung cancer incidence has an inadequate exposure assessment, especially for possibly confounding exposures such as epoxy resins, welding, solvents, other pigments, and other work in aircraft manufacturing. Alexander et al. [1996] reported that exposure data needed to improve the retrospective exposure assessment prior to 1974 do not exist. In addition, as in the Pastides [1994a] study, the exposures are too low and the numbers of workers too small for the study to have sufficient power to draw statistically valid conclusions about the effects of low Cr(VI) exposures. Among incident lung cancer cases, the median cumulative exposure was only 9.8 µg/m^3–yr. Only 15 incident lung cancer cases were observed which is substantially fewer than the 122 lung cancer deaths observed in the Baltimore cohort. Further investigation of this cohort would not significantly improve the current assessment of risk for Cr(VI).

NIOSH is not aware of additional information on the Alexander cohort members' exposures prior to 1974 or workers who left prior to 1974.

NIOSH is not aware of any other cohorts available to study low exposures.

5. **OSHA has relied upon a linear relative risk model and cumulative Cr(VI) exposure for estimating the lifetime occupational lung cancer risk among Cr(VI)-exposed workers. In particular, OSHA has made a preliminary determination that a threshold model is not appropriate for estimating the lung cancer risk associated with Cr(VI). However, there is some evidence that pathways (e.g., extracellular reduction, DNA repair, cell apoptosis, etc.) may exist within the lung that protect against Cr(VI)-induced respiratory carcinogenesis, and may potentially introduce non-linearities into the Cr(VI) exposure-cancer response. Is there convincing scientific evidence of a non-linear exposure-response**

relationship in the range of occupational exposures of interest to OSHA? If so, are there sufficient data to define a non-linear approach that would provide more reliable predictions of risk than the linear relative risk model used by OSHA?

It is not appropriate to employ a threshold dose-response approach to estimate cancer risk from a genotoxic carcinogen such as Cr(VI) [Park et al. 2004]. The scientific evidence for a carcinogenicity threshold for Cr(VI) described in the Preamble consists of the absence of an observed effect in epidemiology studies and animal studies at low exposures, and *in vitro* evidence of intracellular reduction. The epidemiologic and animal studies lack the statistical power to detect a low-dose threshold. In both the NIOSH and OSHA risk assessments, linear no-threshold risk models provided good fit to the observed cancer data. The *in vitro* extracellular reduction studies which suggested a theoretical basis for a non-linear response to Cr(VI) exposure were conducted under non-physiologic conditions. These results do not demonstrate a threshold of response to Cr(VI) exposure.

6. **OSHA's estimates of lung cancer risk are based on workers primarily exposed to highly water-soluble sodium chromate and sodium dichromate. OSHA has preliminarily concluded that the risk for workers exposed to equivalent levels of other Cr(VI) compounds will be of a similar magnitude or, in the case of some Cr(VI) compounds, possibly greater than the risks projected in the OSHA quantitative risk assessment. Is this determination appropriate? Are there sufficient data to reliably quantify the risk from occupational exposure to specific Cr(VI) compounds? If so, explain how the risk could be estimated.**

NIOSH supports OSHA's determination that the risk for workers exposed to Cr(VI) compounds other than water-soluble sodium chromate and sodium dichromate is comparable or possibly greater. There have been few experimental studies that directly address the issue of the relative potencies of inhaled Cr(VI) compounds. However, NIOSH supports OSHA's conclusions drawn from the studies cited in the Preamble in which Cr(VI) compounds were instilled in the respiratory tracts of rodents. The results of these studies demonstrated that equivalent doses of the less water soluble Cr(VI) compounds produced more lung tumors than compounds with higher water solubility, such as sodium dichromate and chromic acid. This suggests that the less water soluble compounds may be more potent carcinogens than the more water soluble compounds.

NIOSH is not aware of studies with sufficient data to reliably quantify the potential differences in risk of lung cancer from these other Cr(VI) compounds.

7. **The preliminary quantitative risk assessment relies on two (Gibb and Luippold) cohort studies in which most workers were exposed higher Cr(VI) levels than the PEL proposed by OSHA, for shorter durations than a working lifetime exposure. The risks estimated by OSHA for lifetime exposure to the proposed PEL, therefore, carry the assumption that a cumulative exposure achieved by short duration exposure to higher Cr(VI) air levels (e.g., exposed 3 years to 15 µg/m^3) leads to the same risk as an equivalent cumulative exposure achieved by longer duration exposure to lower Cr(VI) exposure (e.g, exposed**

45 years to 1 µg/m^3). OSHA preliminarily finds this assumed exposure equivalency to represent an uncertainty in the estimates of risk but does not have information that indicates this uncertainty introduces serious error in its predictions of risk. Does the OSHA exposure-response assessment based on the higher Cr(VI) air levels and/or shorter durations experienced by the Gibb and Luippold cohorts lead to a serious underprediction or overprediction in estimated risks for the occupational exposure scenarios of interest to OSHA? Please provide any data to support your rationale.

NIOSH supports OSHA's approach in using cumulative exposure as the dose metric in its quantitative risk assessment. Theories of chemical carcinogenesis predict that, in the absence of metabolic non-linear effects, the carcinogenic effect should be linear with exposure intensity and should accumulate over time [Crump et al. 1976]. This implies that timing of exposure is not important except for the lag between initiation of the cancer and its clinical appearance or resulting death. NIOSH finds no convincing evidence of metabolic nonlinearities in the exposure-response relationship for Cr(VI). Additionally, the observation from the Painesville [Crump et al. 2003] and Baltimore [Park et al. 2004] studies that linear, cumulative exposure-response models fit the mortality data well supports the assumption of low-dose linearity.

***8*. OSHA has made a preliminary determination that suitable data are not available for making quantitative risk estimates for the non-cancer adverse health effects associated with exposure to Cr(VI) (e.g., nasal septum ulcerations and perforations, asthma, irritant and allergic contact dermatitis). Are there suitable data for a quantitative estimation of risk for non-cancer adverse effects that OSHA should include in its final quantitative risk assessment? If so, what models or approaches should be used?**

Both human and animal data do exist that would support a quantitative risk assessment of the non-cancer health effects from occupational exposure to Cr(VI), but the available human data have serious limitations making it unlikely that such an analysis would provide useful information for OSHA in their deliberations. Specifically, the Gibb et al. [2000b] study of non-cancer outcomes in chromate production workers has been considered for a quantitative risk assessment. Although a large number of workers experienced nasal irritation/ulceration, and these effects occurred within a short period after hire, several factors limit the usefulness of these health effects for quantitative analysis. For instance, the high turn-over of employees in the population, possibly related to adverse health effects, would bias the analysis, seriously limiting its usefulness for quantitative risk assessment. Furthermore, the investigators were not able to link many morbidity outcomes usually associated with chromium to the exposure measures available, suggesting that there was considerable exposure misclassification. In addition, the median exposure levels at the time of diagnosis of a variety of chromium related morbidities were 20-28 µg/m^3. Few non-cancer effects would be observable at the levels being proposed by OSHA for a PEL based on lung cancer, resulting in low statistical power for characterizing the low exposure-response.

An alternative approach would be to use the Glaser et al. [1990; 1985] multidose subchronic rat inhalation studies, described on pages 59355–59356 of the Preamble, for a quantitative estimation of risk from non-cancer adverse health effects. Dose-response data are available on several endpoints indicating pulmonary toxicity, including significantly elevated levels of lactate dehydrogenase, protein, and albumin in bronchioalveolar lavage fluid. The benchmark concentration approach is an appropriate method to analyze these data [ATSDR 2000; EPA 1998; Malsch et al. 1994].

***9*. Are there other factors OSHA should take into consideration in its final quantitative risk assessment to better characterize the risks associated with exposure to Cr(VI)?**

One additional factor that should be systematically considered is the impact of the healthy worker effect. Discussion in the Preamble (pages 59318–59341) of results from cohort studies using national or regional reference populations does not take into account the healthy worker effect bias. Accounting for this bias would result in the conclusion that some estimates of exposure effect whose lower 95% confidence limits are <1.0 are in fact statistically significantly elevated.

The NIOSH analysis [Park et al. 2004] was based on regression models that performed internal comparisons on exposure that accounted for the healthy worker effect bias. The model also estimated how the study population adjusted for race differed from expected based on national lung cancer mortality rates. It also allowed for a general departure of the baseline rates from national rates with increasing age.

Technologic and Economic Feasibility

15. OSHA requests the following information regarding engineering and work practice controls in your workplace or industry:

***e*. When these additional controls are implemented, to what levels can exposure be expected to be reduced, or what per cent reduction is expected to be achieved?**

and

***16*. OSHA requests information on whether there are any limited or unique conditions or job tasks in Cr(VI) manufacture or use where engineering and work practice controls are not available or are not capable of reducing exposure levels to or below the proposed PEL most of the time. Provide data and evidence to support your response.**

From 1999 through 2001, NIOSH conducted 21 site surveys in a variety of establishments to characterize occupational exposures to Cr(VI) compounds and the existing exposure control measures associated with these exposures. Reports for all of these site visits were previously submitted to OSHA and are included in the docket for this proposed rule. Although the information in each report submitted to OSHA deals exclusively with the relevant site survey, NIOSH researchers have evaluated the data from all site visits and reached preliminary conclusions about the types of processes

and operations for which it may be most difficult to reduce exposure levels to or below the existing NIOSH REL and the proposed PEL.

For the analysis of the combined results of the 21 site surveys, NIOSH researchers have qualitatively evaluated the extent to which exposures might be reduced in various industrial sectors, processes, and operations that were studied. Specifically, this evaluation addresses the difficulty in reducing exposures to less than the existing NIOSH REL of 1 μg/m^3 for a 10-hour TWA exposure to Cr(VI) in air, which is similar to the proposed OSHA permissible exposure limit for an 8-hour TWA exposure. The NIOSH researchers have developed a classification scheme for the various industrial processes and operations studied based on the relative difficulty in reducing exposures.

The following is the preliminary categorization of the processes and operations evaluated at the 21 sites included in the NIOSH study. This analysis considers only conditions observed and measured during the site surveys that usually lasted two days. Wherever possible, the sites selected were "typical" of their industrial sector, and qualitative information to help evaluate the extent to which each selected facility is representative of its sector is presented in the 21 site-survey reports. The sites selected do not represent a statistical sampling of conditions in all facilities within the sectors.

Category 4. Control of workers' airborne-Cr(VI) exposures to the approximate magnitude of the current NIOSH REL *is considered most difficult* for the processes and operations in this category because of one or both of the following two factors: (1) the measured exposures exceeded by a substantial margin the existing REL of 1 μg/m^3 for a full-shift average exposure; (2) the engineering and other exposure-control measures already in use and characterized during the field surveys, although not necessarily the best available, were judged to be providing reasonably substantial reductions in exposures below what otherwise would be experienced, and the extent to which additional controls would reduce exposures in the processes and operations in this category all of the time was uncertain.

- Spray application and re-sanding of chromate-containing paints (in manufacturing)

- "Hard" chromium electroplating, and facilities with both "hard" and "bright" chromium electroplating (manufacturing)

- Atomized Cr-alloy spray-coating "metallization" operation (industrial maintenance)

Category 3. Workers' exposures to Cr(VI) in air for the processes and operations in this category are expected to be *moderately difficult to control to the approximate magnitude of the current NIOSH REL.* In this category the existing exposures do not exceed that level by a substantial margin and/or improvements or additions to the engineering

exposure-control measures in use and characterized during the field surveys are reasonably anticipated to further reduce worker exposures.

- Manufacturing of screen-printing inks containing chromate pigments
- Metal-inert-gas (MIG) welding on stainless steel, and operations involving MIG and tungsten-inert-gas (TIG) welding and plasma-arc cutting on stainless-steel (in manufacturing)
- Metal cutting (torch and carbon-arc) in ship demolition (shipyard)
- Repair welding and cutting on alloy and stainless-steel castings in foundries (manufacturing)

Category 2. Workers' exposures to Cr(VI) in air are anticipated to be *easier to control to the current NIOSH REL or below* for the processes and operations in this category compared to those in categories 3 and 4 because existing exposures are near that level and/or exceed it by a modest amount, and/or improvements or additions to the engineering exposure-control measures in use and characterized during the field surveys are expected to further reduce worker exposures.

- Alodyne/anodize chromium-coating processes (in manufacturing)
- TIG welding on stainless steel in sheet-metal fabrication (manufacturing)
- Manufacturing of refractory brick using chromic oxide
- Manufacturing of chromium sulfate from sodium dichromate
- Removal of chromate-containing paint by abrasive blasting (in construction)
- Operations involving shielded-metal arc welding (SMAW), flux-core arc welding (FCAW), dual-shield, TIG, and MIG welding on stainless and other steels (in shipyard operations)
- Manufacturing of products from wood treated with chromium-copper-arsenate (CCA)

Category 1. *Worker exposure to Cr(VI) was limited* for the processes and operations in this category. Specifically, full-shift exposures were well below the existing NIOSH REL and in many cases were below the level detectable by the sampling and analytical method used.

- "Bright" chromium electroplating alone (in manufacturing)
- Other non-electroplating chromium coating processes not named above (in manufacturing)

- Selected welding and cutting operations: Operations involving TIG, fusion, and dual-shield welding and submerged-arc plasma cutting (in manufacturing), and stick and MIG welding on steel and galvanized piping and sheet metal (in construction)

- Foundry casting operations involving stainless steel and other ferrous alloys, and ductile iron foundries (in manufacturing)

- Manufacturing of pre-cast concrete products; and, crushing and recycling of concrete from demolition

- Manufacturing of colored glass products, using chromate pigments

- Screen printing with inks containing chromate pigments (in manufacturing)

- Chromate-conversion treatment process (manufacturing) for electronic-component boards

Provisions of the Standard

***24*. OSHA's safety and health advisory committees for Construction and Maritime advised the Agency to take into consideration the unique nature of their work environments by either settings separate standards or making accommodations for the differences in work environments in construction and maritime. To account for differences in the workplace environment for these different sectors OSHA has proposed separate standards for general industry, construction, and shipyards. Is this approach appropriate? What other approaches should the Agency consider? Please provide a rationale for your response.**

Construction and maritime work environments can differ from general industry; OSHA has used separate standards for many substances during previous rulemakings. Both environments lend themselves to worker protection strategies based on job and task-based approaches, and OSHA has previously used such approaches in the construction asbestos and lead standards. Task-based strategies (e.g. addressing tasks such as applying wet cement, welding, spray painting, abrasive blasting) may offer additional opportunities for tailoring construction and maritime standard components for Cr(VI).

***25*. OSHA has not proposed to cover agriculture, because the Agency is not aware of significant exposures to Cr(VI) in agriculture. Is this determination correct?**

The sources of agricultural workers' exposures to Cr(VI) would most likely be from chromate-based paints from agricultural machinery and welding fume from welding of some metals or with welding rods that contain Cr(VI). Population-based studies of agriculture indicate that farmers tend to do relatively little painting of equipment, but a

very large percentage of farmers do their own repair, including welding [Sanderson W. personal communication, 2004]. This group would benefit from guidance materials identifying sources of exposure and methods of reducing exposure. NIOSH is available to assist OSHA in developing guidance or educational materials about preventing exposure from welding.

***26*. OSHA has proposed to regulate exposures to all Cr(VI) compounds. As discussed in the health effects section of this preamble, the Agency has made a preliminary determination that the existing data support coverage of all Cr(VI) compounds in the scope of the proposed standard. Is this an appropriate determination or are there additional data that support the exclusion of certain compounds from the scope of the final standard? If so, describe specifically how these data would support a decision to exclude certain compounds from the scope of the final rule.**

The existing data reviewed by OSHA support coverage of all Cr(VI) compounds in the scope of the proposed standard. NIOSH is not aware of any data beyond that data already submitted to the docket that would exclude any Cr(VI) compound from the scope of the final standard.

***27*. OSHA has made a preliminary determination to exclude Cr(VI) exposures due to work with portland cement from the scope of the construction standard. OSHA believes that guidance efforts by the Agency may be more suitable for addressing the dermal hazards associated with portland cement use in construction settings. OSHA's Advisory Committee for Construction Safety and Health (ACCSH) advised OSHA to include construction cement work under the proposed standard because of the known hazards associated with wet cement and the large number of workers exposed to wet cement in construction work settings. In particular ACCSH advised OSHA that only certain provisions might be necessary for workers exposed to wet cement (e.g., protective work clothing, hygiene areas and practices, medical surveillance for signs and symptoms of adverse health effects only, communication of hazards and recordkeeping for medical surveillance and training). Other provisions, ACCSH advised, might not be necessary (e.g., permissible exposure levels, exposure assessment, methods of compliance and respiratory protection). Should OSHA expand the scope of the construction proposal to include Cr(VI) exposures from portland cement? If so, what would be the best approach for addressing the dermal hazards from Cr(VI) faced by these workers?**

NIOSH agrees with the ACCSH advice that construction cement work be included in the scope of the standard. To our knowledge, previous OSHA 6(b) standards have taken a comprehensive approach to reducing all known hazards associated with a given substance. Standards for other occupational carcinogens have included provisions to address serious non-cancer health effects. For example, both formaldehyde and 4, 4' methylenedianiline (MDA) are known skin sensitizers, as is Cr(VI), and in both cases the resulting OSHA standards included language to address dermal hazards. These provisions were also included in the construction versions of the standards.

Large numbers of workers have potential dermal exposures to portland cement. For example, the Center to Protect Workers' Rights has estimated that more than 1,300,000 construction workers are employed in occupations with exposure to wet cement [CPWR 1999a]. Exposures can occur from working with a variety of construction materials that contain portland cement. These include: concrete, mortar, stucco, and terrazzo. Examples of construction trades with potential exposure to wet cement include: bricklayers, cement masons, concrete finishers, construction craft laborers, hod carriers, plasterers, terrazzo workers, and tile setters. The Bureau of Labor Statistics reports that cement masons, concrete finishers, segmental pavers, and terrazzo workers held about 190,000 jobs in 2002 [BLS 2004].

Adverse health effects associated with wet cement exposure include irritant contact dermatitis and allergic contact dermatitis. As noted in the NIOSH response to question 1, Cr(VI)-related allergic contact dermatitis is a major adverse health effect that represents a material impairment of health for affected workers. Sensitized workers can expect long bouts of dermatitis, even if they leave the industry [Halbert et al. 1992; Cooley and Nethercott 1994]. Allergic contact sensitization is considered to last life-long, thus making life-long allergen avoidance necessary [Uter et al. 2004]. Since there are no known cures for contact allergy, primary prevention is of utmost importance [Uter et al. 2004].

The dermal hazards faced by construction workers can be addressed by providing training, appropriate protective equipment (see responses to questions 53 and 62), and washing facilities. The training required by proposed paragraph (l) *Communication of chromium (VI) hazards to employees*, including hygienic practices, adverse associated health effects, and use of personal protective equipment, and a medical surveillance program provide an appropriate approach for addressing dermal hazards.

In 1984, NIOSH provided testimony on the OSHA proposed rule *Field Sanitation.* NIOSH concluded in our submission to OSHA during the Field Sanitation hearings that *….a standard for field sanitation could and should be supported on the basis of the well known and long-documented sanitary requirements of public health practice and the need for equalization of working conditions with other occupational groups.* To that end, NIOSH recommended simple and well accepted public health practices such as hand washing and protecting the skin by wearing appropriate clothing. The circumstances of exposure between agricultural field workers and portland cement workers are similar. Thus those recommendations are also appropriate for workers exposed to portland cement.

At a minimum, containers of water should be available to exposed workers so that they may wash skin that has come in contact with portland cement (either dry or wet). It would be useful for OSHA to develop training materials that provide information to portland cement workers on how to prevent allergic contact dermatitis. NIOSH can assist OSHA in the development of such information. The Center to Protect Workers' Rights, in collaboration with NIOSH, has developed educational documents for employers and health practitioners related to skin protection and work with wet cement in construction [CPWR 1999a,b].

***28*. OSHA has proposed to include exposure to Cr(VI) from portland cement in the scope of the standard for general industry. The Agency believes that the potential for airborne exposure to Cr(VI) in general industry due to work with portland cement, as indicated by the profile of exposed workers presented in Table IX-2 of this preamble, is higher than in the construction industry. OSHA acknowledges, however, that the exposure profile indicates that no workers are exposed to Cr(VI) at levels over the proposed action level. Given the low level of airborne exposure among cement workers in general industry, should OSHA exclude exposures to Cr(VI) from portland cement from the scope of the general industry standard?**

NIOSH supports the OSHA proposal to include exposure to Cr(VI) from portland cement in the general industry standard due to the significant risk of excess lung cancer even at the low exposure levels reported in the exposure profile presented in the Preamble on pages 59405–59406. The risk assessment conducted by NIOSH using the linear model estimates excess lung cancer risks of approximately three per thousand at the proposed action level of 0.5 μg/m^3. Exposure to Cr(VI) levels as low as 0.2 μg/m^3 have an estimated excess lung cancer risk of approximately one per 1000 workers [Park et al. 2004].

***30*. Describe any additional industries, processes, or applications that should be exempted from the Cr(VI) standard and provide detailed reasons for any requested exemption. In particular, are the epidemiologic and experimental studies sufficient to support OSHA's the inclusion of various industries or processes under the scope of the proposed standard? Please provide the rationale and supporting data for your response.**

NIOSH reviewed the experimental and epidemiologic studies of carcinogenic effects, non-cancer respiratory effects, dermal effects, and other health effects discussed in the Preamble on pages 59314–59360. These studies provide support for the inclusion of the industries and processes identified in the scope of the proposed standard. In addition, as stated previously, portland cement should be included in the scope of the proposed Cr(VI) construction standard.

NIOSH is not aware of any industries or processes that should be exempted.

***31.* Can the proposed Cr(VI) standard for the construction industry be modified in any way to better account for the workplace conditions in that industry, while still providing appropriate protection to Cr(VI)-exposed workers in that industry? Would an alternative approach similar to that used in OSHA's asbestos standard, where the application of specified controls in certain situations would be considered adequate to meet the requirements of the standard, be useful?**

The approach used for the asbestos standard, where specified controls were applied for certain situations, deserves consideration, as it may provide a useful approach for tailoring controls to the construction tasks associated with Cr(VI) exposures. Additional relevant information is also provided in response to questions 35 and 43. Provisions for

"competent persons," also used in the construction asbestos standard and many construction safety standards, may also be appropriate.

As discussed in the response to question 27, inclusion of portland cement in the standard would better protect the large number of workers exposed and address the severity of the adverse health effects associated with Cr(VI) exposure in wet cement. NIOSH notes that the OSHA construction standard for MDA [29 CFR 1926.60] provides a useful example of a comprehensive standard that includes provisions targeting prevention and control of dermal exposures. For example, sections such as 1926.60(f)(8) [Visual monitoring], 1926.60(g)(1)(ii) [Dermal exposures], 1926.60(h)(2) [Special Provisions], 1926.60(h)(3) [Prohibitions], and 1926.60(j) [Protective work clothing and equipment] provide relevant language for further consideration.

***32*. Can the proposed Cr(VI) standard for shipyards be modified in any way to better account for the workplace conditions in that industry, while still providing appropriate protection to Cr(VI)-exposed workers in that industry?**

As with construction, operation-specific provisions would provide useful approaches for worker protection in shipyards. The existing maritime standards include several operation-specific provisions. For example, Subpart D of 1915 requires the use of ventilation when welding, cutting, or heating metals of toxic significance in enclosed spaces. Section 1915.51(d)(1)(iv) explicitly mentions "Chromium-bearing metals or metals coated with chromium-bearing materials." Section 1915.34 includes provisions such as air line respirators for mechanical paint removal operations, e.g., abrasive blasting. Additional examples that can be used to modify the proposed Cr(VI) standard for shipyards are provided in response to questions 35 and 43.

***33*. OSHA has proposed a TWA PEL for Cr(VI) of 1.0 µg/m^3. The Agency has made a preliminary determination that this is the lowest level that is both technologically and economically feasible and is necessary to reduce significant risks of material health impairment from exposure to Cr(VI). Is this PEL appropriate and is it adequately supported by the existing data? If not, what PEL would be more appropriate or would more adequately protect employees from Cr(VI)-associated health risks? Provide evidence to support your response.**

As presented on pages 59369–59370 of the Preamble, NIOSH conducted a quantitative risk assessment analyzing the excess risk of lung cancer mortality in chromate production workers from the Baltimore, Maryland, chromium chemical production facility [Park et al. 2004]. Results of this risk assessment indicate excess lung cancer deaths of approximately 6 per 1000, 3 per 1000, and 1 per 1000 at working lifetime Cr(VI) exposure levels of 1 µg/m^3, 0.5 µg/m^3, and 0.2 µg/m^3, respectively. The NIOSH risk assessment concludes that at 0.2 µg Cr(VI)/m^3 the lifetime risk of lung cancer death from Cr(VI) exposure will range from 0.47 cases to 2.5 cases per 1000 workers. Therefore, NIOSH encourages OSHA to consider a lower PEL to reduce the excess risk and to control Cr(VI) exposures in the workplace. In addition to reducing the risk of lung cancer deaths, a PEL of 0.2 µg/m^3 would likely result in a reduction of the non-cancer health effects associated with Cr(VI) exposure.

`Paragraph *(c) Permissible exposure limit (PEL)* of the proposed rule requires the following:

> *The employer shall ensure that no employee is exposed to an airborne concentration of chromium (VI) in excess of 1 microgram per cubic meter of air (1µg/m^3), calculated as an 8-hour time-weighted average (TWA).*

Proposed paragraph (c) should include wording to clarify that the proposed PEL refers to the concentration of Cr(VI) measured and reported on the basis of the mass of Cr(VI) ion per cubic meter of air rather than the entire mass of any compounds which contain Cr(VI).

***34*. Should different PELs be established for different Cr(VI) compounds?**

As noted in the responses to Questions 2 and 6, the available data are not sufficient to establish separate PELs for different Cr(VI) compounds.

***35*. OSHA has proposed an action level for Cr(VI) exposure in general industry, but not in construction or shipyards. Is this an appropriate approach? Should OSHA set an action level for exposure to Cr(VI) in construction and shipyards? Should the proposed action level in general industry be retained in the final rule?**

An exposure assessment requirement with an action level is advisable for construction and shipyards. The use of an action level provides a mechanism to trigger protective requirements such as exposure monitoring and medical surveillance and as a means to assess the need for improving existing controls. This is especially important for substances such as Cr(VI) where significant risks remain at the PEL.

OSHA has previously incorporated an action level for construction in the construction lead standard (29 CFR 1926.62). NIOSH notes that OSHA did not include an action level in the construction asbestos standard (29 CFR 1926.1101) due to limitations in sampling accuracy at one-half the PEL. However, OSHA used an alternative approach for that standard by incorporating provisions such as classifying jobs into four classes by task and likelihood of exposure, and using a presumption of exposure approach (e.g. 29 CFR 1926.1101(f)(2)(ii)) by including operation-specific work practices and controls. Those provisions provided alternative mechanisms in that training and medical surveillance were triggered by exposure or the type of work being done. A similar approach might be advisable for workers exposed to Cr(VI) if routine monitoring of exposures is not feasible.

In summary, adding an action level to the construction and shipyard standards would enhance the protection provided to workers and would provide a traditional trigger for medical surveillance coverage and for other measures (e.g., PPE) that may be needed to protect the health of workers. The current medical surveillance proposal relies on signs and symptoms of adverse effects being observed in employees before medical surveillance for non-emergency purposes is triggered. An alternative approach such as that taken for the construction asbestos standard is an additional option for OSHA to consider, and operation-specific work practices (such as those used in 29 CFR

1926.1101) would need to be added for this approach to work.

NIOSH also agrees that an action level equal to one half of the PEL should be retained in the final rule.

***36*. If an action level is included in the final rule, is the proposed action level for general industry (0.5 µg/m^3) the appropriate level for the PEL under consideration? If not, at what level should the action level be set?**

The proposed action level for general industry of one-half the PEL is the appropriate level to indicate sufficient probability that an employee's exposure does not exceed the proposed PEL on other days [NIOSH 1977].

***37.* If an action level is included in the final rule, which provisions should be triggered by exposure above the action level? Indicate the basis for your position and include any supporting information.**

Provisions triggered by exposure above the action level could include additional worker training, medical surveillance and exposure monitoring for employees with potential airborne exposure to Cr(VI) compounds in general industry, construction and shipyards.

***39*. Should OSHA set a short-term exposure limit (STEL) or ceiling for exposure to Cr(VI)? If so, please specify the appropriate air concentration and the rationale for its selection.**

There is evidence that short-term exposures to high levels of Cr(VI) can cause severe upper and lower respiratory effects in humans and in animal models [ATSDR 2000]. In previous comments to OSHA, NIOSH indicated that short-term peak exposures may be important in causing adverse health effects because they may overwhelm the reducing abilities and defense mechanisms of the body [NIOSH 2002].

***40*. Do you conduct initial air monitoring or do you rely on objective data to determine Cr(VI) exposures? Describe any other approaches you have implemented for assessing an employee's initial exposure to Cr(VI).**

and

***41*. Describe any follow-up or subsequent exposure assessments that you conduct. How often do you conduct such follow-up or subsequent exposure assessments?**

NIOSH suggests that air monitoring is the most appropriate means of estimating airborne exposure to Cr(VI). NIOSH further suggests that the use of objective data may not be appropriate for some industries and processes because of the variability of the conditions surrounding exposures (See Question 44).

A review of the previously mentioned 21 NIOSH site-survey reports indicates that 8 of the 21 sites had developed Cr(VI) exposure data. The following processes or operations

were conducted at these sites: painting, chromium-sulfate manufacturing, printing, welding, foundry operations, electroplating, and shipbreaking. None of the information is explicitly identified as resulting from “initial” or “follow-up” monitoring, and only one site clearly had a routine monitoring program. Thus the frequency of exposure assessment is not known by NIOSH.

The following summarizes the exposure-assessment efforts at the 8 sites:

- Four of the eight sites provided information from one monitoring survey for Cr(VI), each with results from two, three, or four air samples.

- Two sites provided information from one monitoring survey, each with several air samples for surrogate indicators of Cr(VI) exposure: in one case total welding fume and in the other, lead along with bulk-material analysis to provide a lead-to-Cr(VI) ratio.

- One site with a welding operation provided information from two monitoring surveys, each with several air samples for total chromium.

- One site, a shipbreaking operation, provided extensive, routine air-monitoring data for Cr(VI) stretching across years of time.

NIOSH does not have information on employer costs of exposure-assessment programs.

43. **OSHA has proposed specific requirements for exposure assessment in general industry, but has not proposed that these requirements apply to construction or shipyard employers. Should requirements for exposure assessment in construction or shipyards be included in the final Cr(VI) standard? Are there any advantages to requiring construction or shipyard employers to measure their employees' exposures to Cr(VI)? If so, would the exposure assessment requirements proposed for general industry be appropriate? Indicate the basis for your position and include any supporting information. What types of exposure assessment strategies are effective for assessing worker exposures at construction and shipyard worksites?**

It is prudent public health practice to monitor worker exposure to Cr(VI) whenever feasible. Exposure measurement data are important for determining the potential health risks to workers associated with their occupation [NIOSH 1988b]. Information obtained from exposure monitoring provides the means to assess the effectiveness of control measures and to determine whether alternative approaches to controlling exposures and protecting workers are needed.

Exposure assessment is the traditional mechanism for identifying the jobs and tasks that require a risk management approach to protect the health of employees; this approach is typically included in OSHA standards. Construction and shipyard employers, especially small employers, need a mechanism for making initial determinations on the need and type of actions that should be taken to prevent

employee exposure. Information obtained from exposure monitoring provides the most sensitive measure for evaluating the potential health risk to employees. NIOSH has developed a field portable method (NIOSH 7703) that has been validated for determining soluble Cr(VI) concentrations in the field where the use of other Cr(VI) monitoring methods may be difficult. This method has a limit of quantitation of 0.27 µg of Cr(VI), a working range of at least 0.05 to 1000 $\mu g/m^3$, and is capable of providing a quicker analysis than other available methods [NIOSH 2003; Boiano et al. 2000]. This method has also been modified for the on-site analysis of insoluble Cr(VI) compounds [Hazelwood et al. 2004].

Because obtaining timely exposure assessment on construction jobs can be challenging, OSHA may want to further develop other approaches for employers to choose from. As described in the response to question 35, NIOSH recognizes that OSHA has used other options to complement traditional exposure assessment in previous construction standards. For example OSHA included interim protection provisions until employers conduct exposure assessments for certain tasks such as welding or abrasive blasting in the construction lead standard (29 CFR 1926.62(d)). OSHA grouped tasks and job types into classes based on exposure potential in the construction asbestos standard (29 CFR 1926.1101). OSHA provided language to clarify when exposure assessment data from previous operations conducted under workplace conditions "closely resembling" a current work operation could be used to demonstrate that the PEL would not be exceeded. OSHA also included “competent person” provisions in the asbestos standard to make use of a common construction approach to making safety and health determinations.

In summary, when feasible, exposure monitoring would be appropriate in the construction and shipyard industry. Supplementing exposure monitoring requirements with other performance provisions (e.g., required use of PPE) has been used by OSHA for previously regulated health hazards, and can provide additional flexibility for construction and shipyard employers in protecting the health of employees. Tailoring provisions to commonly expected tasks and operations that may have exposures exceeding the PEL might be one way to enhance the effectiveness of control strategies. Task-based approaches enable the employer to focus on activities most likely to lead to exposures [Susi et al. 2000].

44. **Should requirements for exposure assessment in general industry be included in the final Cr(VI) standard, or would the performance-oriented requirement proposed for construction and shipyards be more appropriate? Indicate the basis for your position and include any supporting information.**

Inclusion of the requirements for initial, periodic, and additional exposure assessment in general industry would facilitate the measurement and evaluation of employee exposures, an important aspect in reducing the risk of impaired health resulting from inhalation of Cr(VI). This evaluation is the first step in an employee exposure monitoring program that minimizes employer sampling burden while providing adequate employee protection [NIOSH 1977].

Personal sampling and breathing zone sampling have been shown to be most

representative of workers' exposures [NIOSH 1977]. Other methods, such as observational schemes, used to estimate and extrapolate personal exposures, are not as reliable in accurately measuring a worker's exposure [Rappaport et al. 1993; Kromhout 2002]. In the 1975 criteria document for Cr(VI), NIOSH recommended that, "In all monitoring, samples representative of the exposures in the breathing zone of employees shall be collected by personal samplers." [NIOSH 1975].

***45*. OSHA has proposed that exposure monitoring in general industry be conducted at least every six months if exposures are above the action level but below the PEL, and at least every three months if exposures are at or above the PEL. Are these proposed frequencies appropriate? If not, what frequency of monitoring would be more appropriate, and why?**

In the1975 NIOSH criteria document for Cr(VI), NIOSH recommended that surveys be repeated annually and when any process change indicates a need for reevaluation. The first determination of the workers' exposures should be completed within 6 months after the promulgation of a standard. Surveillance exposure monitoring should be conducted every 2 months, and if exposures exceed the 1975 REL of 1 µg/m^3, monitoring is to be conducted at 1-week intervals until 3 consecutive surveys indicated the adequacy of controls.

***46.* OSHA has proposed that regulated areas be established in general industry wherever an employee's exposure to airborne concentrations of Cr(VI) is, or can reasonably be expected to be, in excess of the PEL.**

and

***47*. OSHA has not proposed requirements for establishment of regulated areas in construction or shipyards. Should requirements for regulated areas for construction or shipyards be included in the final Cr(VI) standard?**

Regulated areas are important on construction and shipyard worksites because of the potential for "bystander" exposures given that it is common for employees from different trades to work in close proximity. For construction, bystander employees may work for different employers, thus complicating control efforts. In addition, outdoor work is common to construction work and air currents can contribute to the spread of air contaminants. Regulated areas help minimize unintended exposures to bystander workers.

***48.* Under the proposed standard, employers are required to use engineering and work practice controls to reduce and maintain employee exposure to Cr(VI) to or below the PEL unless the employer can demonstrate that employees are not exposed above the PEL for 30 or more days per year, or the employer can demonstrate that such controls are not feasible. Is this approach appropriate for**

Cr(VI)? Indicate the basis for your position and include any supporting information.

NIOSH supports the use of engineering controls and work practices as primary methods to reduce and maintain employee exposure to Cr(VI) to or below the REL in accordance with industrial hygiene best practices. Personal protective equipment, such as respiratory protection, should be the last line of defense to control exposures to Cr(VI). Respirators should be worn only when engineering controls are not feasible in controlling exposures [NIOSH1983; 1989].

OSHA has proposed (pages 59454–59455) that respiratory protection may be used exclusively to protect workers exposed above the PEL if they are exposed for fewer than 30 days to Cr(VI). Relying on respirators would be a significant weakening of the requirement for priority use of engineering controls in preference to respirators. It goes beyond the normal permissive use of respirators in work situations where engineering controls are not feasible, or during the time necessary to install or implement engineering controls, or in emergencies [NIOSH 1983]. In addition, NIOSH is concerned about the routine use of respirators during brief duration jobs/tasks where respiratory protection is less expensive than engineering controls or where feasible engineering controls result in only a negligible reduction in exposure [NIOSH 1989].

***50*. The proposed standard prohibits the use of job rotation for the sole purpose of lowering employee exposures to Cr(VI). Are there any circumstances where this practice should be allowed in order to meet the proposed PEL?**

NIOSH supports the prohibition of job rotation for the sole purpose of meeting the proposed PEL [NIOSH 1987]. Because Cr(VI) is a potential occupational carcinogen and a potent dermal sensitizing agent with no known safe level of exposure, the prudent public health practice is to minimize the number of workers potentially at risk of material impairment to their health. Although they are exposed for shorter durations, job rotation increases the total number of workers exposed. In addition, job rotation schedules set to reduce exposures may not do so if they are not followed rigorously or workers are rotated to other equally hazardous jobs.

***51.* OSHA is proposing that employers provide appropriate protective clothing and equipment when a hazard is present or is likely to be present from skin or eye contact with Cr(VI). OSHA would expect an employer to exercise common sense and appropriate expertise to determine if a hazard is present or likely to be present. Is this approach appropriate? Are there other approaches that would be better for characterizing eye and skin contact with Cr(VI)? For example, . . . are there methods to measure dermal exposure that could be used to routinely monitor worker exposure to Cr(VI) that OSHA should consider including in the final standard?**

NIOSH supports the proposed measures for use of appropriate protective clothing and equipment to protect against skin and eye contact.

NIOSH is not aware of any validated methods to measure Cr(VI) contamination of the skin surface. However, it is possible to measure Cr(VI) in the worker's environment to assess potential dermal exposure using OSHA's Method W-4001, a wipe sampling method for Cr(VI).

53. **Should OSHA require the use of protective clothing and equipment for those employees who are exposed to airborne concentrations of Cr(VI) in excess of the PEL? If so, what type of protective clothing and equipment might be necessary?**

NIOSH recommends the use of appropriate chemical protective clothing (CPC) and gloves with maximum body coverage for all employees exposed to Cr(VI) compounds where skin contact is possible. In workplaces where skin contact is possible, dermal and mucous membrane contact with all Cr(VI) compounds should be prevented by full-body protective clothing consisting of head, neck, and face protection; coveralls or similar protective body clothing; impermeable gloves with gauntlets; and shoes and apron where solutions or dry materials containing Cr(VI) may be contacted [NIOSH 1975]. Protective clothing and gloves made from PVC or Saranex® can be used for an eight-hour exposure, while those made from butyl or Viton can be used for a four-hour exposure [Forsberg and Keith 1999; Mansdorf 1998]. While the selection of this CPC is based on permeation properties, other selection factors, including size, dexterity, and cut and tear resistance should be considered as well.

Eye protection should be provided by the employer and used by employees where eye contact with solutions or particulates containing Cr(VI) is possible [NIOSH 1975]. The American National Standard Practice for Occupational and Educational Eye and Face Protection, ANSI Z87.1-1989, includes provisions for selection, use, and maintenance of eye protective equipment. In work environments where Cr(VI) levels are above the NIOSH REL and respiratory protection is required, NIOSH recommends that eye protection be incorporated by the use of tight-fitting full facepiece respirators, or tight-fitting half-mask respirators used in conjunction with safety spectacles or goggles.

NIOSH recommends appropriate respirator use while performing any task for which the exposure level is either unknown or has been documented to be higher than the NIOSH REL. The use of respirators may be necessary when other control measures do not control Cr(VI) levels below the REL.

54. **OSHA has proposed to require that employers pay for protective clothing and equipment provided to employees. The Agency seeks comment on this provision, in particular:**

b. **Are there circumstances where employers should not be required to pay for clothing and equipment used to protect employees from Cr(VI) hazards, such as situations where it is customary for employees to provide their own protective clothing and equipment (i.e., "tools of the trade")?**

Since 1971, NIOSH has recommended that PPE be a part of the hierarchy of controls for worker protection. Employer provision of PPE is similar to employer provision of

engineering controls for controlling workplace hazards [NIOSH 1999]. NIOSH criteria documents have consistently provided recommendations for the use of PPE, including respiratory protection; eye, face, and head protection; skin protection; fall protection; safety shoes; and hearing protection. NIOSH has previously commented to OSHA that employers are responsible for all PPE required for the work setting, including:

- the selection of PPE
- training in the proper use of PPE
- ensuring the PPE is properly used
- maintenance of PPE
- providing and paying for the PPE

***55*. OSHA is proposing that washing facilities capable of removing Cr(VI) from the skin be provided to affected employees, but does not propose that showers be required. Should OSHA include requirements to provide showers to employees exposed to Cr(VI)? If so, under what circumstances should showers be required?**

At the end of each shift, employees should wash any exposed skin areas with soap and copious amounts of water. A complete shower is preferred after anything but limited, minor contact with Cr(VI) [NIOSH 1975].

***57*. Is medical surveillance being provided to Cr(VI)-exposed employees at your worksite?**

NIOSH conducted 21 site visits to a variety of industries that use Cr(VI)-containing materials under an Interagency Agreement with OSHA. The reports of these site visits were reviewed to ascertain information related to medical surveillance. Since evaluation of medical surveillance programs was not the purpose of the site visits, only summary information can be abstracted from the full reports. Of the 21 sites, two performed chromium-specific medical surveillance; one performed medical surveillance, but it could not be determined whether it was chromium-specific;17 sites performed some type of medical surveillance, but it was not chromium-specific; and two sites lacked a medical surveillance program of any kind. The sites with medical surveillance programs would be familiar with the concepts behind such programs and have infrastructure to support requirements for chromium-specific medical surveillance.

***58.* OSHA has proposed that medical surveillance be triggered in general industry in the following circumstances: (1) When exposure to Cr(VI) is above the PEL for 30 days or more per year; (2) after an employee experiences signs or symptoms of the adverse health effects associated with Cr(VI) exposure (e.g., dermatitis, asthma); or (3) after exposure in an emergency. OSHA seeks comments as to whether or not these are appropriate triggers for offering medical surveillance and whether there are additional triggers that should be included. Should OSHA require that medical surveillance be triggered in general industry**

only upon an employee experiencing signs and symptoms of disease or after exposure in an emergency, as in the construction and maritime standards? OSHA also solicits comment on the optimal frequency of medical surveillance.

and

***59*. OSHA has proposed that medical surveillance be triggered in construction and shipyards in the following circumstances: (1) after an employee experiences signs or symptoms of the adverse health effects associated with Cr(VI) exposure (e.g., dermatitis, asthma); or (2) after exposure in an emergency. Should medical surveillance in construction or shipyards be triggered by exposure to Cr(VI) above the PEL for 30 days or more per year, as proposed for general industry? OSHA seeks comments as to whether or not the proposed triggers are appropriate for offering medical surveillance and whether there are additional triggers that should be included.**

All workers with potential exposure to Cr(VI) at or above the proposed OSHA action level should be provided the opportunity to participate in a medical surveillance program at no expense to the employee [NIOSH 1988a]. NIOSH suggests an action level trigger (as opposed to a PEL trigger) because there is significant risk of lung cancer at the proposed PEL, and an exposure concentration has not been identified below which respiratory or dermal adverse health effects of occupational Cr(VI) exposure do not occur. Additionally, NIOSH suggests there should be no eligibility criteria for participation in a medical surveillance program, such as length of employment, health status, or type of industry in which employed.

The goal of a medical surveillance program is secondary prevention of adverse health effects from occupational exposure to Cr(VI). Through the medical surveillance program, the occurrence of adverse health effects can be identified at the earliest possible time and interventions at both the workplace and individual level can be initiated. NIOSH suggests that shifting the responsibility for diagnosis of signs and symptoms of exposure to workers would be a departure from long-established public health practice.

Since no safe level of exposure for skin sensitization has been established, all workers with potential exposure to portland cement should be monitored for adverse effects from dermal exposure. OSHA may want to consider a medical surveillance trigger for workers with dermal exposure. For example, the construction industry standard for methylenedianiline (29 CFR 1926.60 (n)(1)(i)(B) requires a medical surveillance program for workers “who are subject to dermal exposure to MDA for 15 or more days per year.”

Regarding the frequency of medical surveillance, each worker should receive initial and periodic medical examinations. Medical examinations should be conducted by a licensed physician or other qualified, licensed health care professional. The initial examination should include a physical examination, with particular emphasis on the upper and lower respiratory system and skin, occupational history, respiratory symptom questionnaire, spirometric testing, and chest radiographs (see further discussion below

on spirometry and radiographs). The initial (baseline) examination should be performed as soon as possible after assignment to a job with potential exposure to Cr(VI). OSHA may want to consider a time frequency of within three months of assignment for a spirometric test and within 3 to 6 months for a chest X-ray.

The onset of upper airway symptoms is often reported in the first few months of exposure to Cr(VI). Therefore, NIOSH suggests a thorough medical evaluation of the upper respiratory tract be conducted every six months for the first two years of employment and annually thereafter, unless adverse health effects warrant more frequent monitoring.

Annual medical examinations should include a physical examination with emphasis on the upper and lower respiratory system and skin, respiratory symptom update questionnaire, occupational history update questionnaire, and spirometry. OSHA may want to consider a requirement for annual spirometry for the first three years and every two to three years thereafter, or as indicated by current medical recommendations and the scientific literature. Based on the findings from these examinations, more frequent and detailed medical examinations and/or testing may also be necessary. Interpretation of annual lung function changes within an individual worker are specified and updated by professional organizations such as the American Thoracic Society (ATS) and the American College of Occupational and Environmental Medicine (ACOEM) [ATS 1995; ACOEM 2004].

The value of periodic chest radiographs in a medical surveillance program should be evaluated by a qualified health care professional based on current medical recommendations and scientific literature, in consultation with the worker, to assess whether the benefits of testing warrant the additional exposure to radiation. Radiographs are not sensitive indicators of airflow obstruction, and although lung cancer is often first detected on chest radiographs, the utility of either routine radiographic or tomographic lung images in early detection of cancer remains a topic of scientific inquiry. If the qualified health care professional deems periodic chest radiographs useful, the timing and frequency of the radiographic examinations should take into account the observed latency and natural history of occupational lung cancer associated with Cr(VI) [Luippold et al. 2003; Langard 1990], as well as symptoms of other relevant findings.

Medical examinations provide an opportunity to inform the worker of potential respiratory and dermal risks of occupational Cr(VI) exposure, including signs and symptoms of adverse health effects and information to avoid exposure. At this time, workers may also be instructed to report adverse health effects to their supervisor. OSHA may want to consider developing guidance for health care professionals who are responsible for the provision of these examinations. Such guidance could be provided through a nonmandatory appendix to this rulemaking or in a separate guidance document.

***60*. OSHA has not included certain biological tests (e.g., blood or urine monitoring, skin patch testing for sensitization, expiratory flow measurements for airway restriction) as a part of the medical evaluations required to be provided to**

employees offered medical surveillance under the proposed standard. OSHA has preliminarily determined that the general application of these tests is of uncertain value as an early indicator of potential Cr(VI)-related health effects. However, the proposed standard does allow for the provision of any tests (which could include urine or blood tests) that are deemed necessary by the physician or other licensed health care professional. Are there any tests (e.g., urine tests, blood tests, skin patch tests, airway flow measurements, or others) that should be included under the proposed standard's medical surveillance provisions? If there are any that should be included, explain the rationale for their inclusion, including the benefit to worker health they might provide, their utility and ease of use in an occupational health surveillance program, and associated costs.

NIOSH agrees with OSHA that urine and blood tests are of uncertain value as early indicators of potential Cr(VI)-related health effects. However, spirometry may be a useful test in the detection of airflow obstruction and may identify early signs of airway disease due to Cr(VI) exposure.

Interpretation of spirometry has been standardized and, thus, is a practical and useful test for medical surveillance [ATS 1995]. When used to monitor a worker's lung function, the ATS recommends annual spirometry. Early detection of adverse health effects associated with occupational Cr(VI) exposure such as airflow obstruction allows for counseling of workers on the potential risk of remaining in the workplace, provides the opportunity for more intensive medical evaluation and treatment if necessary, and allows assessment of workplace interventions to minimize the progression of disease and risk of long-term adverse health effects.

Including a baseline chest radiograph in the initial examination of each worker in the medical surveillance program would provide an important point of reference for the evaluation of any abnormalities that may be detected on subsequent chest radiographs performed either as part of the medical surveillance program or for clinical evaluation.

***61*. OSHA has not included requirements for medical removal protection (MRP) in the proposed standard. OSHA has made a preliminary determination that there are few instances where temporary worker removal and MRP will be useful. The Agency seeks comment as to whether the final Cr(VI) standard should include provisions for the temporary removal and extension of MRP benefits to employees with certain Cr(VI) related health conditions. In particular, what endpoints should be considered for temporary removal and for what maximum amount of time should MRP benefits be extended?**

NIOSH agrees with OSHA that there are few instances where temporary worker removal and MRP will be useful for workers exposed to Cr(VI). However, one instance that may be appropriate for temporary worker removal with MRP is the occurrence of adverse dermal effects, such as skin erosions and ulcers, mucosal perforations, and dermatitis. Temporary worker removal from Cr(VI) exposure for these effects would provide necessary time for adequate diagnosis, especially whether the etiology of dermatitis is irritant or allergic; appropriate treatment; and follow-up. This time can also

be used for worker education regarding the proper use of personal protective equipment and appropriate work practices to avoid recurrence of adverse dermal effects. Simultaneously, the work environment can be reevaluated for controls that may help to prevent future cases.

Workers with adverse dermal effects who are removed from Cr(VI) exposure and receive appropriate treatment and follow-up should recover within six to eight weeks. Workers diagnosed with allergic dermatitis may still be able to return to work as long as adequate protective measures, such as personal protective equipment and work practices, are in place to prevent re-exposure. Thus, 60 days would be an appropriate maximum amount of time for the extension of MRP benefits.

***62*. OSHA has proposed that employers provide hazard information to employees in accordance with the Agency's Hazard Communication standard (29 CFR 1910.1200), and has also proposed additional requirements regarding signs, labels, and additional training specific to work with Cr(VI). Should OSHA include these additional requirements in the final rule, or are the requirements of the Hazard Communication standard sufficient?**

NIOSH supports the OSHA proposals in paragraph (l) *Communication of chromium (VI) hazards to employees* regarding signs, labels, and additional training specific to work with Cr(VI). As noted in the response to question 27, the additional training required, including the health hazards associated with Cr(VI) exposure, measures employees can take to protect themselves, and the proper use of personal protective equipment are important for addressing dermal hazards. Although the general requirements of the Hazard Communication standard are useful for all workplace hazards, Cr(VI)-specific requirements provide focused and enhanced protection of workers from Cr(VI) exposure. Cr(VI) levels reported in cements are as low as 2 ppm and are associated with allergic skin reactions [CSTEE 2002].

Incorporating hazard communication messages and dermal training provisions in the final rule also increases the likelihood that the appropriate mix of task-specific information will be transmitted to workers. For example, mentioning that employees should not rinse their hands in tool rinse buckets, or describing how to remove both gloves without exposing bare skin are important for worker health but are less likely to be included in a portland cement material safety data sheet. OSHA can provide an important tool for small construction employers by putting such information in an appendix or guidance material. See “A Safety and Health Practitioner’s Guide to Skin Protection [CPWR 1999a]
http://www.cdc.gov/elcosh/docs/d0400/d000458/d000458.html

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Appendix B.

Comments to DOL

Post-Hearing Comments of the
National Institute for Occupational Safety and Health
on the
Occupational Safety and Health Administration
Proposed Rule
Occupational Exposure to Hexavalent Chromium

29 CFR Parts 1910, 1915, 1917, 1918, and 1926
Docket No. H054A

Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

March 21, 2005

These post-hearing comments are submitted by the National Institute for

Occupational Safety and Health (NIOSH) in response to requests for information or clarification made on February 2, 2005, at the Occupational Safety and Health Administration (OSHA) informal public hearing on hexavalent chromium (Cr(VI)).

1. Additional published Cr(VI) studies

NIOSH included the citations for several recent Cr(VI)-related publications in its January 2005 testimony on the OSHA proposed rule on occupational exposure to Cr(VI). NIOSH scientists have also participated in the publication of the following Cr(VI)-related publications since 2002 (enclosed):

The following studies review the molecular mechanisms of Cr(VI) carcinogenesis:

- Chiu A, Katz AJ, Beaubier J, Chiu N, Shi X [2004]. Genetic and cellular mechanisms in chromium and nickel carcinogenesis considering epidemiologic findings. Mol Cell Biochem 255:181–194.

- Ding M, Shi X [2002]. Molecular mechanisms of Cr(VI)-induced carcinogenesis. Mol Cell Biochem 234-235:293–300.

- Harris GK, Shi X [2003]. Signaling by carcinogenic metals and metal-induced reactive oxygen species. Mutat Res 533:183–200.

- Leonard SS, Bower JJ, Shi X [2004]. Metal-induced toxicity, carcinogenesis, mechanisms and cellular responses. Mol Cell Biochem 255:3–10.

- Leonard SS, Harris GK, Shi X [2004]. Metal-induced oxidative stress and signal transduction. Free Radic Biol Med 37:1921–1942.

The following molecular studies demonstrate the ability of lead chromate to generate reactive oxygen species and cause DNA strand breakage:

- Leonard SS, Roberts JR, Antonini JM, Castranova V, Shi X [2004]. PbCrO4 mediates cellular responses via reactive oxygen species. Mol Cell Biochem 255:171–179.

- Leonard SS, Vallyathan V, Castranova V, Shi X [2002]. Generation of reactive oxygen species in the enzymatic reduction of PbCrO4 and related DNA damage. Mol Cell Biochem 234-235:309–315.

- Wang S, Leonard SS, Ye J, Gao N, Wang L, Shi X [2004]. Role of reactive oxygen species and Cr(VI) in Ras-mediated signal transduction. Mol Cell Biochem 255:119–127.

The following studies review the pulmonary effects of welding fumes:

- Antonini JM. Health effects of welding [2003]. Crit Rev Toxicol 33:61–103.

- Antonini JM, Lewis AB, Roberts JR, Whaley DA [2003]. Pulmonary effects of welding fumes: review of worker and experimental animal studies. Am J Ind Med 43:350–360.

- Antonini JM, Taylor MD, Zimmer AT, Roberts JR [2004]. Pulmonary responses to welding fumes: role of metal constituents. J Toxicol Environ Health A 67(3):233–249.

The following publications report lung injury in rats caused by exposure to welding fumes:

- Antonini JM, Taylor MD, Millecchia L, Bebout AR, Roberts JR [2004]. Suppression in lung defense responses after bacterial infection in rats pretreated with different welding fumes. Toxicol Appl Pharmacol 222:206–218.

- Taylor MD, Roberts JR, Leonard SS, Shi X, Antonini JM [2003]. Effects of welding fumes of differing composition and solubility on free radical production and acute lung injury and inflammation in rats. Toxicol Sci 75:181–191.

2. Issue of paper tape (RAC sampler) exposure data in the Baltimore cohort

Dr. Deborah Proctor of Exponent proposed that the information in Fig. 1 *CrO_3 exposures over time for selected jobs; chromium production workers, USA,* from Gibb et al. [2000], suggests that exposures for the period 1965–1979 based on the paper-tape RAC sampler were systematically lower than exposures reported prior to 1965 or after 1979. If RAC sampler data underestimated true exposure levels, perhaps as a consequence of Cr(VI) reduction on the paper tape, risk assessments based on these data could overestimate the risk from Cr(VI).

However, examination of Fig. 1 does not support the inference that the reported exposures were systematically lower during 1965-1979. Fig. 1 shows that the observed variance in the annual average exposures is much lower during the period of RAC-based sampling. This follows from the large numbers of samples taken using the RAC system, compared to before or after that period, so that random variation in annual averages was considerably diminished. From Fig. 1, there was a consistent decline in exposure levels for two of the three jobs reported in the years immediately preceding RAC deployment (1960–1965) and roughly constant median exposure after 1965 until the end of the study. Conclusions are limited by the display of only three jobs and the absence of more

detailed descriptive statistics on exposures over time, but Fig. 1 does not reveal a systematic lowering of exposure during 1965–1979.

3. Epidemiological review of lung cancer risk in the color pigment industry

It has been argued that the risks in color-pigment workers are much less than those in the chromate production facilities where risk assessments were performed. It is not possible to perform a comparable risk assessment for the color pigment workers because of inadequate exposure history and low statistical power; however, a range-finding estimate of excess lifetime risk can be calculated from the Hayes cohort [1989] as follows. The overall lung cancer SMR found by Hayes was 1.16 (95% CI: 83-158); in those with no exposure it was 0.92, and in those with any duration in chromate dust-exposed jobs, SMR = obs/exp=24/16.74 = 1.43 (observed and expected by subtraction from Tables I and III [Hayes, 1989]). The overall relative risk based on the exposed vs. unexposed was approximately 1.43/0.92 = 1.56, giving an excess risk of 0.56. The average duration of employment appeared to be in the range of 5 to 10 years, so that the excess risk per year of exposure was in the range of 0.56/10 to 0.56/5, or 0.056 to 0.11 per year. Using a table of theoretical excess lifetime risk for lung cancer (Table 1, substituting “yr” for “mg-yr/m^3” and “1” for “mg /m^3“), these estimated excess risks correspond to lifetime excess risks for working in the New Jersey plant of approximately 110 to 200 per thousand. This is somewhat below that estimated from the Baltimore cohort for work at the current PEL but still a substantial excess, and comparable to the excess risk predicted from the Baltimore cohort for a lifetime exposure at the average level experienced in the Baltimore plant (43 µg/m^3 CrO_3): about 120 per thousand. Average exposure in the Baltimore plant was calculated from mean cumulative exposure divided by mean duration of employment [Park et al. 2004]. The above estimates for color-pigment workers are presented here strictly as range-finding estimates, and the confidence limits for the estimates from the Hayes et al. [1989] study are wide, meaning that the estimates are uncertain and therefore not useful for a quantitative risk assessment. (Table 1 was constructed using a standard life-table procedure that has been used by NIOSH in several published studies [Park et al. 2004; Park et al. 2002; Rice et al. 2001].)

Table 1. Theoretical Excess Lifetime Risks for Lung Cancer Mortality by Observed Excess Rate Ratio and Exposure Level[1]

	Excess Rate Ratio per mg-yr/m^3							
	.01	.02	.05	.10	.20	.50	1.00	1.44
SMR	1.01	1.02	1.05	1.10	1.20	1.50	2.00	2.44
Carcinogen Concentration								
Mg/m^3								
0.001	0.0000	0.0000	0.0001	0.0002	0.0004	**0.0011**	**0.0022**	**0.0031**
0.002	0.0000	0.0001	0.0002	0.0004	0.0009	**0.0022**	**0.0043**	**0.0063**
0.005	0.0001	0.0002	0.0005	**0.0011**	**0.0022**	**0.0054**	**0.0108**	**0.0155**
0.010	0.0002	0.0004	**0.0011**	**0.0022**	**0.0043**	**0.0108**	**0.0214**	**0.0307**
0.020	0.0004	0.0009	**0.0022**	**0.0043**	**0.0086**	**0.0214**	**0.0422**	**0.0601**
0.050	**0.0011**	**0.0022**	**0.0054**	**0.0108**	**0.0214**	**0.0524**	**0.1009**	**0.1410**
0.100	**0.0022**	**0.0043**	**0.0108**	**0.0214**	**0.0422**	**0.1009**	**0.1877**	**0.2550**[2]
0.200	**0.0043**	**0.0086**	**0.0214**	**0.0422**	**0.0819**	**0.1877**	**0.3272**	**0.4212**
0.500	**0.0108**	**0.0214**	**0.0524**	**0.1009**	**0.1877**	**0.3830**	**0.5698**	**0.6581**
1.000	**0.0214**	**0.0422**	**0.1009**	**0.1877**	**0.3272**	**0.5698**	**0.7194**	**0.7678**
2.000	**0.0422**	**0.0819**	**0.1877**	**0.3272**	**0.5101**	**0.7194**	**0.7965**	**0.8192**

1. Calculated using life-table algorithm described in Park et al. [2004]; Park et al. [2002]; Rice et al. [2001].
2. From Baltimore cohort [Park et al. 2004]

4. Epidemiological review of lung cancer risk in the aerospace industry

The experience of potentially chromate-exposed workers in the aerospace industry is examined in the Alexander et al. [1996] and Boice et al. [1999] studies. In both studies, it is unclear if chromate dusts generated in parts fabrication (e.g., cutting, drilling, deburring, grinding) were adequately characterized and these process areas appropriately classified in terms of exposure to chromate. If a comprehensive retrospective exposure assessment was not feasible, perhaps more powerful analyses could have been achieved using multivariate approaches analyzing duration in process areas without requiring detailed exposure assessments for each process. The published analyses were limited to univariate approaches.

For the color pigment workers, it is possible to perform a range-finding,

approximate estimate of excess lifetime risk from chromate exposures in the Boice [1999] cohort. Among painters, the overall SMR was 1.11; in process areas where chromate exposures were presumably small (assembly, fabrication) the SMR was 0.92. The relative risk – exposed vs. unexposed – for painters was approximately 1.11/0.92 = 1.21, for an excess risk of 0.21. The average exposure level reported for chromate-exposed workers was 15 $\mu g/m^3$ as CrO_3 [Marano et al. 2000] and the average duration spent in painting appeared to be on the order of 10 years; therefore the excess risk per mg-yr/m^3 was 0.21/(10×.015) = 1.4, which is close to the excess risk from the Baltimore cohort (1.44) [Park et al. 2004]. Using Table 1, *Theoretical Excess Lifetime Risks for Lung Cancer Mortality by Observed Excess Rate Ratio and Exposure Level* (above), this estimated excess risk corresponds to lifetime risks – at the average exposure level reported for chromate-exposed workers at this plant – of approximately 45 per thousand which is below the estimate for the Baltimore cohort but still a substantial excess. The true background lung cancer rate may have corresponded to an SMR below 0.92 due to the healthy worker effect and possible chromate exposures in the assembly/fabrication areas, suggesting a true excess lifetime risk higher than the range-finding estimate of 45/1000. Boice et al. [1999] did not publish the confidence intervals of the SMR; however, including a healthy worker adjustment and using a Poisson approximation, the 95% confidence interval around the published SMR of 1.21 is estimated at 0.84-1.58.

5. Epidemiological review of lung cancer risk in welding

The relation between excess lung cancer mortality and employment duration in stainless steel welding has been noted to be inconsistent in some studies [Simonato et al. 1991; Gerin et al. 1993]. Several factors may impact the interpretation of these studies and are consistent with an underlying risk associated with duration. These factors include the healthy worker survivor effect and variations across multi-employer worksites. The healthy worker survivor effect is a form of confounding in which workers with long employment durations systematically diverge from the overall worker population on risk factors for mortality. For example, because smoking is a risk factor for disease, disability and death, long duration workers would tend to have a lower smoking prevalence, and hence lower expected rates of diseases that are smoking related, like lung cancer. Not taking this into account among welders might result in long duration welders appearing to have diminished excess risk when, in fact, excess risk continues to increase with time.

In addition, a consideration in multi-employer studies is that conditions might vary widely across employers, including those involved not only in stainless steel, but also mild steel welding activities. Worker career duration decisions may depend in part on working conditions, such that jobs with high exposures are held, on average, for less duration than jobs with lower exposures. In the absence of detailed individual exposure histories, this pattern of employment could result in

long duration welding employment appearing to have lower risk than some shorter duration employment when it does not.

6. Further investigation of exposure-response in the Baltimore cohort

In response to interest in the question of a threshold for the Cr(VI) exposure response, NIOSH investigated non-linear features of the exposure response, including threshold, dose rate effects, and other attributes in the Baltimore cohort. Variations in the construction of the cumulative exposure metric were investigated corresponding to cumulative exposure thresholds, exposure intensity thresholds, variable dose-rate effects, and a declining burden of accumulated future risk. The ability to identify these non-linearities, however, was limited by the available exposure history which was constructed from annual average exposure levels assigned to job titles. The best fitting models had no threshold for exposure intensity and the study had sufficient power to rule out thresholds as large as 30 $\mu g/m^3$ CrO_3 (15.6 $\mu g/m^3$ Cr(VI), likelihood ratio test). For cumulative exposure, slightly better fitting models were observed for thresholds of 0.05 - 0.5 mg-yr/m^3 (as CrO_3), but were not statistically significant. In the best-fitting model, cumulative exposure thresholds as large as 0.4 mg-yr/m^3 CrO_3 were excluded (upper 95% confidence limit, likelihood ratio test). The current Cr(VI) standard permits lifetime cumulative exposures up to 4.5 mg-yr/m^3 CrO_3. Departure from linearity of the dose rate effect was negative, corresponding to intensity raised to the 0.8 power, but was not statistically significant. Models with declining risk burdens based on half-lives ranging from 0.1 to 40 years fit less well than assuming a constant burden. Examination of non-linear features of the hexavalent chromium - lung cancer response supports the use of the traditional (lagged) cumulative exposure paradigm: no threshold, linearity in intensity, and constant increment in risk following an exposure.

7. The role of chest radiography in medical surveillance for workers exposed to hexavalent chromium above the action level

The initial chest radiograph is recommended as a component of the worker's baseline evaluation, with a goal of documenting any pre-existing abnormalities in the tissues susceptible to health effects resulting from occupational exposure to Cr(VI). As such, an initial chest radiograph provides an important point of reference for the evaluation of any abnormalities that may be detected on subsequent chest radiographs performed either as part of the medical surveillance program or for clinical evaluation and serves to assure the worker and the employer that any abnormalities detected at baseline are not the result of exposure to Cr(VI). NIOSH believes the chest radiograph serves this function only during the initial/baseline examination, and cannot serve this purpose for individuals who have been exposed to Cr(VI) for more than 6 months. The role of periodic chest radiographic imaging for detection of lung cancer is discussed in the testimony submitted by NIOSH.

8. Response to concerns raised regarding dose-rate effects of Cr(VI)

In comments to the OSHA docket submitted by Elementis Chromium LP (Ex. 38-216-1), Dr. Joel Barnhart uses the results of the Steinhoff et al. [1986] rat study to support the idea that Cr(VI) is not likely to be carcinogenic to humans at current occupational exposures. For reasons described below, NIOSH disagrees with Dr. Barnhart's analysis and supports OSHA's view that the Steinhoff et al. [1986] rat study found a dose-rate effect in rats under the specified experimental conditions, that this effect may have implications for human exposure, and that the data are insufficient to use in a human risk assessment for Cr(VI).

Steinhoff et al. [1986] exposed rats to the same total dose of Cr(VI) by either a once-per-week or five-times-per week treatment for 30 months. No increased incidence of lung tumors was observed in animals dosed five times weekly. However, in animals dosed once per week, the tumor incidences were 0/80, 0/80, 1/80 and 14/80 in the control, 0.05, 0.25 and 1.25 mg/kg exposure groups, respectively. This increase in tumors in the 1.25 mg/kg group was statistically significant.

This study clearly demonstrates that, within the constraints of the experimental design, a dose-rate effect was observed. This may be an important consideration for humans exposed to high levels of Cr(VI). However, quantitative extrapolation of that information to the human exposure scenario is difficult.

Dr. Barnhart's statement that larger particles are delivered to the lung tissue by intratracheal instillation than would be delivered if the particles had to traverse the nasal passages, where filtering would occur, is correct. However, in comparing this to human studies, one large unknown from the epidemiological investigations is the distribution of particle sizes to which workers were exposed. If there was a significant fraction of larger particles in the workers' exposures, the actual dose of Cr(VI) that reached the deep lung would be lower than the total dose of Cr(VI) estimated in the risk assessment. Therefore, it is difficult to directly compare the potency of Cr(VI) across species.

In addition, although Cr(VI) is a lung carcinogen in rats and humans, there is evidence that it is not simply a direct-acting genotoxin. Intracellularly, Cr(VI) compounds undergo a complex metabolic reduction pathway that produces a variety of reactive forms of chromium, free radicals, and reactive oxygen species. These reactive intermediates and products of Cr(VI) intracellular reduction are believed to be responsible for the genotoxicity and mutagenicity of Cr(VI) compounds [Ding and Shi 2002; Leonard et al. 2002]. These reduction processes may be enzymatic and the rates may vary across species. Therefore, Dr. Barnhart's belief that all lung cells (regardless of species) are equivalent targets, may not be accurate.

NIOSH agrees with the Elementis comment that irritation may be important in the

observed dose-rate effect and that irritation may exacerbate the carcinogenic process for Cr(VI). However, other factors need to be considered in the absence of clear data indicating the mechanism of action. For example, short-term saturation of the extracellular reduction capacity, or other mechanistic considerations may be the critical factor. No experimental data were collected in the Steinhoff et al. [1986] study to tease out competing hypotheses. In addition, NIOSH has found no studies demonstrating the time course of irritation in rats and the doses of repeated instillations causing a prolonged irritation response that may exacerbate carcinogenicity. Because of this uncertainty regarding the mechanism of the dose-rate effect, it is speculative to make a quantitative extrapolation to human exposures.

In a separate investigation, Glaser et al. [1986] exposed rats to 100 μg/m^3 for 22 hours per day and, after 18 months exposure, observed a marginally increased tumor response. The daily dose, as calculated by Dr. Barnhart, was only 75.5 μg/kg. This is below the daily dose experienced by the divided-dose (5X/week) group of Steinhoff et al. [1986] which had no increase in tumor response. The dose in the Glaser study was administered over 22 hours, unlike the intratracheal installation, which was administered over a very short time span. Although there is a question of statistical reliability because of the small sample size in the Glaser study, this study does not support dose-rate as the most important factor in carcinogenesis.

The comment by Dr. Barnhart that the exposure-response analyses of employees in the Baltimore [Park et al. 2004] or Painesville [Crump et al. 2004] cohorts should exclude the workers who were exposed to relatively high concentrations of Cr(VI) is addressed in NIOSH's oral testimony and elsewhere in these post-hearing comments. Briefly, NIOSH tested for the effect of dose-rate (intensity) of exposure in the calculation of cumulative exposure used in modeling exposure response, and found that the best fitting model is linear with no dose-rate effect.

For these reasons, NIOSH agrees with OSHA's assessment of the dose-rate effect observed in the Steinhoff et al. [1986] study: it indicates that high doses of Cr(VI) should be avoided, but provides no evidence for a quantitative extrapolation of such dose-rate effects in humans.

9. Dr. Lurie of Public Citizen asked NIOSH if a SECAL would be an option for hexavalent chromium because the technologic and economic feasibility analysis presented by OSHA indicated only a minority of industries could not meet a PEL lower than proposed.

Determining the appropriateness of using a special engineering control air limit (SECAL) requires more than noting that most industries could meet a lower PEL. The published risk assessments referenced in the preamble clearly establish a large excess risk of lung cancer for exposure to Cr(VI) over a working lifetime at

the proposed PEL, and reducing the PEL would provide additional protection for workers. Based on the data in Tables IX-1 and IX-3 of the preamble, industries employing approximately 48% of the affected workers would be able to use engineering controls to reduce exposures below the proposed PEL of 1 μg/m^3 with no increase in the use of respiratory protection. However, by adopting a SECAL, many additional workers would be required to routinely wear respiratory protection. NIOSH acknowledges the difficulties in administering effective respiratory protection programs. For three industry/application groups – electroplating, welding, and painting -- a substantial number of workers would have to use respiratory protection to meet a reduced PEL. These industry/application groups employ approximately 52% of the affected workers.

Given the large increase in the number of workers that would be required to wear respiratory protection, particularly in small businesses, it may be useful to weigh the impact against the value of reducing exposure to a known carcinogen.

10. Ms. Kate McMahon of the Chrome Coalition asked if non-stainless steel was being produced on one of the two days of a NIOSH site visit conducted in 1990 at a specialty steel production facility. Ms. McMahon stated that operation of the AOD furnace would be indicative of stainless steel production.

The health hazard evaluation (HHE) report was identified as HETA 89–364–2202, and it documents that operation of the argon-oxygen decarburization (AOD) vessel is associated with production of stainless steel [NIOSH 1989]. The report documents that the AOD vessel was not operating on March 20, 1990, but was operating on March 21. The chromium content of the stainless steel ranged from 11% to 18%. The air sampling worksheets in the HHE file indicate the date for each sample collected for hexavalent chromium reported in Table 6 of the HHE report. That information is provided below.

Results of air samples collected on March 20, 1990, when the AOD was *not* in operation (by job description or area, with measured concentrations of Cr[VI] in air reported in :g/m^3):

1st Helper, Furnace #4 -- 0.31
1st Helper, Furnace #3 -- 0.47
Senior Melter -- 0.57
Floor Crane -- 0.43
Utility Man -- 0.40

Results of air samples collected on March 21, 1990, when AOD *was* in operation (by job description or area, with measured concentrations of Cr[VI] in air reported in :g/m^3):

2nd Helper, Furnace #2 -- 1.15
3rd Helper, Furnace #2 -- 1.94
AO Helper -- 0.59
Ladle Crane -- 1.23
Maintenance -- 0.54
Laborer (Cleaning) -- 0.58

General area sample, SW Corner -- 1.92

For this same HHE, Ms. Elisabeth Torsnor of Outo Kumpu in her testimony stated that the data are not representative of the population, and that none of the samples actually lasted 8 hours. In the report, the NIOSH investigators determined, based on the number of "heats" processed in the melt shop each day, that the work load during the two days of exposure monitoring was representative of typical production rates for this facility. The workers monitored were representative of their job titles and are anticipated to have performed tasks expected of the job title. The samples collected, although not for a full 8 hours, are acceptable because they included at least 75% of the exposed period and were representative of the workers' exposures that day [NIOSH 1977].

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