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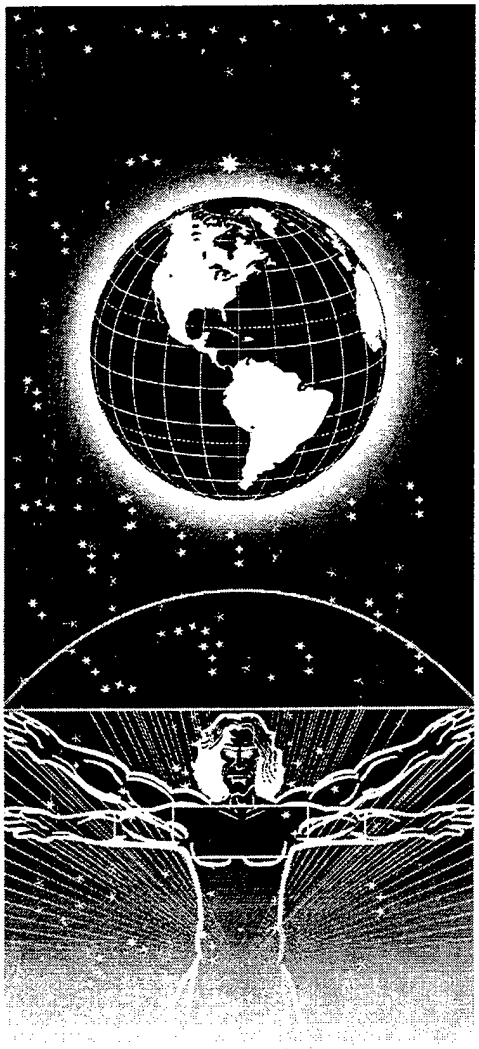

UNITED STATES AIR FORCE ARMSTRONG LABORATORY

OCCUPATIONAL RISK FROM CHROMIUM

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The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

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U.S. Navy (Navy) operations require the use of chrome (Cr) compounds in its various defense program activities. However, certain forms of Cr have been shown to cause acute and chronic toxicity. A reduction in the OSHA PEL from 0.5 mg/m^3 to 0.0005 mg/m^3 has been proposed. Accordingly, the Navy and the Department of Defense (DoD) are concerned over the potential for any adverse affect occurring among the exposed personnel. Currently available chrome toxicity information were reviewed and assessed in this report. Existing epidemiological data and pharmacokinetic models suggest that cancer potency may vary with solubility and form of hexavalent chrome. A new analytical method, ID 215, is now available that identifies hexavalent Cr at the proposed levels. Personal samples analyzed using this method were obtained from the Navy Occupational Exposure Database and evaluated. Estimated potential risk to Naval personnel from hexavalent chrome exposure, assuming no personal protective equipment, were in the 10^{-4} range for the majority of the processes monitored. The highest risks calculated were in the 10^{-2} to 10^{-3} range for abrasive blasting using mineral spirits and sand. Several operations, however, would require the use of respiratory protection and, therefore, risk would be expected to be appreciably less. In general, exposure levels analyzed using ID-215 method were generally one order of magnitude below current standards.

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LIST OF ACRONYMS AND ABBREVIATIONS

AAS	Atomic Absorption Spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
ASTDR	Agency for Toxic Substances and Disease Registry
ASTM	American Standard Testing Method
BW	Body Weight
CAPD	Continuous Ambulatory Peritoneal Dialysis
Carc	Carcinogenic
CFR	Code of Federal Regulation
CPF	Cancer Potency Factor
Cr	Chromium
Cr III	Trivalent Chromium
Cr VI	Hexavalent Chromium
DOD	Department of Defense
ED	Exposure Duration
EF	Exposure Frequency
GM	Geometric Mean
GSD	Geometric Standard Deviation
HPLC	High Performance Liquid Chromatography
HW	Hazardous Waste
IARC	International Agency for Research on Cancer
ICAP	Inductively Coupled Plasma Analysis
IDLH	Immediately Dangerous to Life and Health
IH	Industrial Hygienist
IR	Inhalation Rate
IRIS	Integrated Risk Information System
JHU	Johns Hopkins University
K-S	Kolgomorov-Smirnov Test
LADD	Lifetime average daily dose
LOAEL	Lowest Observable Adverse Effect Level
MA	Metal Arc
MAK	Federal Republic of Germany Maximum Concentration Values in the Workplace
MIG	Metal Inert Gas
MMA	Manual Metal Arc
NAS	National Academy of Science
NEHC	Navy Environmental Health Center
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No Observable Adverse Effect Level
NOED	Navy Occupational Exposure Database
NTP	National Toxicology Program
ORNL	Oak Ridge National Laboratory
OSHA	Occupational Safety and Health Act

PBPK	Physiologically Based Pharmacokinetic Model
PEL	Permissible Exposure Limit
PF	Protection Factor
PPE	Personal Protective Equipment
REL	Recommended Exposure Limit
RF	Respirable Fraction
SMAW	Shielded Metal Arc Welding
SMR	Standardized Mortality Ratio
TA	Tungsten Arc
TLV	Threshold Limit Value
TWA	Time Weighted Average
UCL	Upper Confidence Limit
UTL	Upper Tolerance Limit

OCCUPATIONAL RISK FROM CHROMIUM

1.0 INTRODUCTION

US Navy (Navy) operations require the use of chrome compounds in its various defense program activities. However, certain forms of Cr have been shown to cause acute and chronic toxicity. Accordingly, the Navy and the Department of Defense (DoD) are concerned over the potential for any adverse health effect occurring among exposed personnel. It is appropriate for the Navy to review and assess the chrome toxicology database and prepare an assessment of the potential hazard for adverse human health effects associated with chrome exposures. This report is intended to provide a review and assessment of currently available chrome toxicity information. The report will also include an estimate of the potential risk to Naval personnel from association with chrome exposure.

1.1 Petition and Docket Concerns

The Navy identified its original concerns over pending changes to the risk assessment for hexavalent chromium in its 24 Oct 95 report by the Navy/Industry Task Group (1995) In this report Navy processes and systems which lead to potential worker exposures were annotated and the potential for both technical and economic impacts that may result from changes in OSHA standards were noted. The report specifically investigated the "Petition Requesting a Reduced Tolerance for hexavalent chromium (Cr VI) through an Emergency Temporary Standard of the Occupational Safety and Health Act" dated July 19, 1993 and written by the Public Citizen's Health Research Group and the Oil, Chemical and Atomic Workers International Union. The grounds cited for this request were:

a. "exposure to hexavalent chromium presents a grave danger of lung cancer to employees", and

b. "the requested emergency temporary standard is necessary to protect workers from these grave health risks."

The Navy impact report identified a potential reduction in the OSHA Permissible Exposure Limit (PEL) for Cr VI from the present ceiling level of 100 $\mu g/m^3$ as chromates to an 8-hour TWA of between 0.5 $\mu g/m^3$ and 5.0 $\mu g/m^3$. The Navy/Industry Task Group estimated that if the Cr VI PEL is decreased to 0.5 $\mu g/m^3$, nearly 18,000 workers and 5 major processes will be affected. This represents 17 Navy facilities, 5 private shipbuilders (Navy contractors) and small marine business. One-third of these workers are exposed to welding fumes. The Navy estimates that significantly fewer workers (3,200) are likely to be affected if the Cr VI PEL is established at 5 $\mu g/m^3$ and less (800) affected at a PEL of 10 $\mu g/m^3$.

Concerns over the occupational exposure regulation of hexavalent chrome compounds identified in the OSHA Docket are primarily associated with the inhalation of hexavalent chrome and the carcinogenicity effects seen by this exposure route at levels lower than are currently

recommended by OSHA. Many of the epidemiological studies and industrial hygiene exposures are cited in this report.

1.2 Status of Regulatory Guidance

The Occupational Safety and Health Administration (OSHA) currently regulates hexavalent chromium compounds by a ceiling limit (peak concentration allowable in a workday) of 0.1 mg/m^3 as chromate (CrO_3).

To ensure worker health, Naval facilities also use the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) for 8 hour exposure limits. See Tables 1-1 and 1-2 for current standards published by OSHA and ACGIH. It should be noted that the ACGIH recommends lower standards for certain hexavalent chrome compounds based upon epidemiological data and synergistic effects of the compounds (e.g., Strontium chromate). The ACGIH criteria also suggests varying risk due to the form and bioavailability of chromium compounds.

The National Institute of Occupational Safety and Health (NIOSH) recommends lower standards for hexavalent chrome and compounds. NIOSH publishes Recommended Exposure Levels (RELs) based on documented health effects and toxicity of the compound. Tables 1-1 and 1-2 indicate the levels that NIOSH recommends for exposure to chrome and chrome compounds. The NIOSH levels are not mandatory and are not used as compliance standards by Department of Defense (DoD) Industrial Hygienists (IH). However, the Navy IHs may consider the proposed NIOSH levels and the carcinogenicity classifications from other agencies (see Table 1-3) in making a professional judgment regarding recommendations for medical surveillance for workers.

Occupational health standards are typically driven lower by OSHA when NIOSH recommends lower standards with substantial evidence of risk and the ability to monitor/analyze at recommended levels. Currently, OSHA is working on a method to analyze for hexavalent chrome in air at around 0.0005 mg/m^3. This new analytical method, ID-215, supersedes OSHA analytical method ID-103 which only analyzed to the 0.1 mg/m^3 ceiling limit. It should be noted that most OSHA standards have changed when an analytical method was present to support the analysis of industrial hygiene samples to comply with the standards. When ID-215 becomes a final method, OSHA will be in the position to support a reduction of the hexavalent chrome standards to the proposed 0.5 $\mu g/m^3$.

Table 1-1: Current Recommended Occupational Exposure Standards for Chrome

Regulation	**Chromium and compounds as Cr: Cr metal & Cr(II) & Cr III**	**Cr VI water-soluble compounds**	**Cr VI insoluble compounds**
OSHA PELs	0.5 mg/m^3 [Cr(II & III)] 1.0 mg/m^3 [metal]	0.1 mg/m^3 (as CrO_3) Transitional Limit	

Regulation	Chromium and compounds as Cr: Cr metal & Cr(II) & Cr III	Cr VI water-soluble compounds	Cr VI insoluble compounds
OSHA Ceiling		0.1 mg/m^3 (as CrO_3)	0.1 mg/m^3 (as CrO_3)
ACGIH TLVs	0.5 mg/m^3 [Cr metal & Cr(II & III)]	0.05 mg/m^3	0.01 mg/m^3
NIOSH IDLH		30 mg/m^3 (CrO_3)	
NIOSH RELs	0.5 mg/m^3 [Cr metal & Cr(II & (III)]	0.001 mg/m^3/10 hr Carc 0.025 for non-carc	0.001 mg/m^3/10 hr Carc 0.025 for non-carc
NIOSH Ceiling			0.05 mg/m^3 for carcinogenic (insoluble)

Notes: mg/m^3 = milligrams per cubic meter of air
PEL = Permissible Exposure Limit (8 Hour Time-Weighted Average)
Ceiling = Concentration that should not be exceeded during any part of the working exposure.
ACGIH = American Conference of Governmental Industrial Hygienists
TLV = Threshold Limit Value (8 Hour Average)
IDLH = Immediately Dangerous to Life and Health
NIOSH = National Institute for Occupational Safety and Health
REL = Recommended Exposure Limit
Carc = Carcinogenic
* = synonym for chromic acid or chromates

Table 1-2: Current ACGIH TLVs for Hexavalent Chrome by Specific Compound – All Values Expressed as mg/m^3

Compound	ACGIH TLVs
calcium chromate	0.001 as Cr
chromium trioxide*	0.05 as Cr
lead chromate	0.05 as Pb; 0.012 as Cr
lithium chromate	NA
potassium chromate	NA
potassium dichromate	NA
strontium chromate	0.0005 as Cr
zinc chromate	0.01 as Cr

Notes: mg/m^3 = milligrams per cubic meter of air
PEL = Permissible Exposure Limit (8 Hour Average)
ACGIH = American Conference of Governmental Industrial Hygienists
TLV = Threshold Limit Value (8 Hour Average)
Carc = Carcinogenic
NA = Not Available
* = synonym for chromic acid or chromates

TABLE 1-3: Carcinogenicity of Chrome and Chrome Compounds

	NIOSH	MAK	IARC	NTP	TLV
Cr III as Cr		A2	3		A4
Cr metal			3		A4
Cr VI soluble	X	A2	1	1	A1
Cr VI insoluble	X		1	1	A1
Calcium Chromate	X	A2	1	1	A2
Lead Chromate	X	B	1		A2
Strontium Chromate	X	A2	1	1	A2
Zinc Chromate	X	A1	1	1	A1

Notes: MAK = Federal Republic of Germany Maximum Concentration Values in the Workplace
A1: Capable of inducing malignant tumors as shown by experience with humans
A2: Unmistakably carcinogenic in animal experimentation only
B: Justifiably suspected of having carcinogenic potential
ARC = International Agency for Research on Cancer
1: Carcinogenic to Humans, sufficient evidence of carcinogenicity
3: Not classifiable as to carcinogenicity to humans
NTP = National Toxicology Program
1: Known to be carcinogenic, sufficient evidence from human studies
TLV = ACGIH Cancer Category
A1: Confirmed human carcinogen
A2: Suspected human carcinogen, carcinogenic in animals
A4: Not classifiable as a human carcinogen
NIOSH X = Carcinogen defined with no further categorization

1.3 Requirements

The Navy/DoD are required to protect worker health and safety as well as minimize pollution during their missions. Their policies on hexavalent chrome occupational exposures are not only driven by regulatory risk but by cost impact, technical feasibility, and mission impairment. It is important to note the potential pervasiveness of the hexavalent chrome issue.

The Navy and DoD use a combination of the mission impairment, pervasiveness, regulatory risk, cost driver implications and the technology availability to determine where resources should be allocated and policies set (Fredrickson, 1996) for risk reduction. The reduction of the hexavalent Cr standard to an 8-hour PEL of 0.5 $\mu g/m^3$ would impact the mission of the Navy and DoD due to an increased need for worker protection and monitoring. Real reductions in health risks to Navy workers must accompany the lowering of the PELs. It would be an extremely pervasive issue due to the fact that hexavalent chromium is formed during several processes, such as welding and thermal cutting metal, where the base material does not contain Cr VI. Currently, it is very difficult to engineer chromium out of base materials (various steels) and the welding filler materials as they have gone through testing for performance for the weapon system they support. The reduction in the standard level would

create a larger regulatory risk from OSHA inspections, a larger cost for monitoring and protecting workers and, finally, a technology impact in the form of technical order changes and specification changes. Many technologies to replace hexavalent chromium in the work environment have not been developed.

The Navy is working on technologies to relieve some of the impact from the reduction in the hexavalent chrome standard as both pollution prevention and occupational safety and health initiatives. Ventilation for welding processes are being tested with the intent to reduce occupational Cr VI exposures (Paulson, 1996). Chromic acid anodizing has been replaced with boric acid anodizing on aircraft parts for both the Navy and the Air Force (Fredrickson, 1996). Chrome paints and primers are being researched for most weapons systems in an effort to reduce exposures and waste streams associated with these products (Fredrickson, 1996). For the most part, the Navy has made Cr VI reduction a goal and an unwritten priority.

1.3.1 Schedule Drivers

The petition to OSHA is driving the schedule to reduce hexavalent chrome occupational exposures. The Navy must comply with federal OSHA law. With the anticipated publication of the John Hopkins report (Gibb, 1996)(Gibb *et al.*, 1996), there will be increased pressure for OSHA to publish a revised standard. The OSHA is expected to draft a report early in 1997.

1.3.2 Policy and Agreements

Currently, the Navy and DoD do not have an official policy on the hexavalent chrome occupational exposure scenario (Paulson, 1996). The DoD does, however, have an active program to minimize the use of hexavalent chrome in the manufacture, maintenance and disposal of weapons systems. The DoD also looks for engineering controls to minimize airborne exposures to hexavalent chrome in the workplace environment and for substitute processes and products which would not jeopardized the performance of the products that typically contain Cr VI.

The Navy uses the draft ID-215 analytical method to aid field evaluation of hexavalent Cr exposures and remains in contact with OSHA regarding problems or issues regarding this analytical method (Bishop, 1996). The Navy has been active in this agreement since January 1, 1995. The Navy also agrees to aid in the minimization of Cr VI processes in the manufacturing of Navy weapons systems in an effort to reduce exposures to Navy personnel during the maintenance of those systems (Fredrickson, 1996).

1.4 Introduction to Sources and Processes

The sources and processes which generate an occupational exposure to hexavalent chrome in the Navy and DoD are mainly those that create an inhalation exposure and involve the maintenance of weapons systems such as aircraft, ships, tanks and helicopters. Hexavalent

chrome exposures can also occur through the ingestion route (eating with chromium contaminated hands) or the dermal contact route (touching chromic acid). Most hexavalent chrome exposures occur while the chrome is in some airborne form (e.g. welding fume, chromic acid mist, chrome paint dust). Often, the particle size and form determines the toxicity of the chrome to the worker. Other interferences may include the workers smoking habits. This will be discussed in greater detail in the exposure section. The potential sources of occupational exposure to hexavalent chrome in the Navy and DoD include:

Structure repair
Paint removal, sanding
Construction
Structure fabrication/repair
Metal cleaning
Mechanical/grinding/sanding etc.
Abrasive blast
Barrel finishing
Acid cleaning
Degreasing
Chemical paint stripping
Open tank electroplating
Painting
Spray painting
Dip coating
Wipe coating
Spray coating
Metal machining, milling
Welding
Hot work
Electric arc spraying
Flame spraying
Plasma cutting/arc cutting etc.
Plastics/rubber potting
Woodworking, cutting
Electronics repair
Graphic Arts, photo equipment
Packaging
HW/sewer treatment
Equipment repair

The commercial processes which are impacted by the Navy and DoD are those that manufacture parts for weapons systems or the weapons systems themselves. Many of the commercial processes are identical to the DoD processes. The automobile industry and the chromium mining industries have unique exposure scenarios. As identified in the Navy/Industry Task Group report, more sampling of the processes which generate a hexavalent chrome exposure need to be evaluated. Commercial industrial processes which may generate an occupational exposure to hexavalent chrome are the same as those listed above with the following additional processes:

Mining and Chromium processing
Automobile exhausts
Cement producing
Leather tanning
Textile manufacturing
Photocopying and maintenance (chromium in some inks, papers, paints)

The impact to the DoD from the change to the chrome standard is significant. The DoD acquires, maintains and disposes of weapons systems, communications equipment, services equipment and medical supplies. These materials may all include hexavalent chrome due to the corrosion resistance and pigmentation qualities of the element. Total removal of chrome from DoD products is unlikely; however, the DoD must protect its workers and the public at a realistic risk level.

2.0 CHEMICAL/PHYSICAL CHARACTERISTICS OF CHROME

Chromium (Cr) is a steel gray metal which is so named due to the various bright colors associated with its different compounds. Chromium is strong and hard, brittle, lustrous and resists corrosion. Chrome is used primarily in the metallurgical, refractory and chemical process industries. Steel alloys, stainless steel, cast iron, non-ferrous alloys, chrome-magnesite, chrome-brick, paint pigment, metal plating and wood treatment production use chrome as an integral part of their production (EPA, 1990). An industrial demand exists for chromium compounds due to the oxidation-reduction behavior of the various valence forms. Historically, any spent chromium compound was discharged to the environment as waste. Although emission controls have recently reduced levels of airborne chrome, steel companies remain a major contributing source of chrome emissions to airborne levels and large amounts of chromium wastes in various forms from industrial processes are discharged to the environment (Nriagu and Pacyna, 1988).

Chromium occurs naturally in various earth crust materials. Average chrome concentrations in the continental crust have been reported to be 125 mg/kg with a range that varies from 80-200 mg/kg (NAS, 1974). Concentrations in soil are 10-150 mg/kg and average 40 mg/kg (ATSDR, 1993). Geologic materials such as granite, limestone, sandstone and basalt contain chrome levels that range from 20-1800 mg/kg while serpentine materials can raise chrome levels to 125,000 mg/kg or higher (Bowen 1979).

2.1 Physical-Chemical Characterization of Chromium (Valence, Complexes, Forms)

Chromium is found in nature as ores only in the combined oxidation states, but not in the zero valence state (IARC 1980). Of the three common valence states of chromium, only Cr III occurs naturally; both Cr VI and Cr(0) are produced through industrial processes (ATSDR, 1993). There are many different complexes and forms of chromium compounds. All forms vary in their chemical and physical properties. Among the Cr III compounds are: Cr III acetate & monohydrate, Cr III nitrate, Cr III chloride, ferrochromite, Cr III phosphate, Cr III sulfate, and sodium chromite. Hexavalent chromium compounds include: ammonium dichromate, calcium chromate, chromium oxide, Cr VI trioxide, lead chromate, potassium chromate, potassium dichromate, sodium chromate, sodium dichromate/dihydrate, strontium chromate, and zinc chromate to name a few. Other than the specific compounds that OSHA regulates as chromates/chromic acid, chromium compounds are regulated as Cr II and Cr III by the Occupational Safety and Health Administration (OSHA) (29 CFR 1910.1000). For the purposes of this exposure assessment, our evaluation is limited to hexavalent chromium compounds.

Although the physical distinction between "soluble" and "insoluble" is arbitrary and has been subject to criticism, the two Cr VI forms appear to belong to different health hazard categories (Zatka, 1985). For example, the National Institute for Occupational Safety and Health (NIOSH) differentiates between two forms of hexavalent chromium in airborne contaminants; the water soluble alkali metal and ammonium chromates, considered toxic but not carcinogenic, and the water insoluble chromates, believed to be carcinogenic (Zatka, 1985).

Hexavalent chromium rarely occurs in nature apart from anthropogenic sources because it is readily reduced in the presence of oxidizable organic matter; however, hexavalent chromium compounds that occur most commonly in the form of chromate and dichromate are stable in natural waters because of the low concentration of reducing matter (EPA 1984). With the exception of a few compounds, hexavalent chromium exists as oxo species that are strong oxidizing agents. The oxidizing potential of chromate ions depends on the pH of the media. These ions are much more powerful oxidizing agents in acid solutions than in basic solutions (ORNL/EPA 1978).

Chromium is a d-block transitional element and, because of its various valence states, has many industrial uses. Chrome exists in several oxidation states that range between -2 to +6. In the environment, the trivalent (Cr^{+3}) and the hexavalent (Cr^{+6}) oxidation states are prevalent due to the pH and chemical redox potentials in the environmental system (Mertz, 1969). Although there are many species, this report will deal with the most common species, Cr III and Cr VI. Table 2-1 below describes the most common chrome compounds and their oxidation states.

Table 2-1-COMMON CHROME SPECIES AND VALENCE

DIVALENT Chrome (Cr^{+2})	Solubility in Water
Chromous chloride ($CrCl_3$)	Soluble
Chromous sulfate ($CrSO_4$)	Soluble
TRIVALENT CR (Cr^{+3})	
Chromic oxide (Cr_2O_3)	Practically insoluble
Chromic Hydroxide ($Cr(OH)_3$)	Insoluble
Chromic sulfate ($Cr_2[SO_4]_3$)	Practically insoluble
Chromite ore ($FeO\text{-}Cr_2O_3$)	Practically insoluble
HEXAVALENT Chrome (Cr^{+6})	
Chromium trioxide (CrO_3) + $H_2O \leftrightarrow H_2CrO_4$	Very soluble
Chromic acid (H_2CrO_4)	Very soluble
Chromic acid Anhydrides	
Sodium chromate (Na_2CrO_4)	Soluble
Lead Chromate ($PbCrO_4$)	Insoluble
Strontium Chromate ($SrCrO_4$)	Insoluble
Zinc Chromate ($ZnCrO_4$)	Insoluble
Potassium chromate ($K_2\ CrO_4$)	Soluble
Dichromates	
Sodium dichromate ($Na_2Cr_2O_7$)	Very soluble
Potassium dichromate ($K_2Cr_2O_7$)	Very soluble
Ammonium dichromate ($(NH_4)2Cr_2O_7$)	Very soluble

Trivalent chromium compounds are the more stable form of chrome, readily forms complexes and thus its chemistry is more complex than Cr VI (Cary, 1982; NAS,1974). Except for chrome acetate, chrome nitrate and chrome chloride, most trivalent chrome salts are generally insoluble in aqueous solvent. Cr III has less of an affinity for oxygen so it tends to

forms complexes more readily. At the concentrations found in the environment, Cr III most readily forms complexes with hydroxyl ion (OH^{-1}) forming $Cr(OH)^{+2}$, $Cr(OH)_3^0$ and $Cr(OH)_4$ (Cary, 1982). Citric and fulvic acids present in the soil can readily complex with Cr III and will prevent precipitation at pH values of up to 7.5.

Hexavalent chrome is a very strong oxidizing agent and generally exists as an oxygenated species that is soluble but that is pH dependent. The result is that Cr VI compounds tend to be more soluble in water At pH=0, H_2CrO_4 is the dominant species. At pH levels above 0 and up to 5.9, Cr exists mainly as $HCrO4^{-1}$. At pH above 6.0, the dominant species is CrO_4^{-2}. In the general environment, a pH of 0 is not likely, thus the latter two species normally will be present.

At high concentrations (greater than 520 mg/L, 0.01 M) Chrome exists as a dimer whereas at lower pH values (more acid) the dichromate ion $(Cr_2O_7)^{-2}$ is the prevalent form. However, in water the pH is usually neutral, thus the $(CrO_4)^{-2}$ species dominates (Beas and Mesmer, 1977). In soil with a low clay content the pH is neutral to alkaline and Cr VI will be mobile under these conditions and can find its way into drinking water sources (Neiboer and Jusys, 1988).

The majority of the Chrome background particulate is the Cr III species with minor amounts (less than 10%) of Cr VI. However, due to its redox and pH dependency, those values will vary. Windblown dust and volcanic materials appear to be major contributors of Cr to background levels in the air and may deposit tons of chrome per year. Studies of background air samples in remote areas such as Greenland, Antarctica and the Arctic indicate the presence of $5.0x10^{-6}$ to $1.2x10^{-3}$ $\mu g/m^3$. In urban areas, chromium content of air samples average 0.015 to 0.03 $\mu g/m^3$, with higher levels over industrial facilities (Nriagu and Pacyna, 1988). In its Quantitative Risk Assessment OSHA used analytical data to estimate Cr VI as 40% of total chrome in chromate production plants (ICF Kaiser, 1995).

Cr VI is usually released into the environment from industrial waste and there are a number of possible fates, including pollution of soil and surface water and leaching into groundwater. In the groundwater, Cr can remain stable and, in turn, can be taken up by plants or animals or can be adsorbed/precipitated onto soil colloids or organic matter. Due to the redox potential, a portion of the Cr VI will be reduced to the Cr III form by inorganic electron donors, such as Fe^{+2}, Mn^{+2}, and S^{-2}, or via biological processes involving organic matter. Following this conversion, Cr^{+3} can be expected to precipitate as an oxide or hydroxide or to form complexes with various other ligands. This fraction includes a vast majority of global Cr reserves. Soluble Cr^{+3} complexes, such as those formed with citrate, undergo oxidation when they come in contact with manganese dioxide, thus reforming hexavalent Cr in trace amounts. Hexavalent compounds (mainly the Cr VI chromates and dichromates) are mobile in soil/water systems and can be toxic to a variety of terrestrial and aquatic organisms. Hexavalent chrome compounds are more toxic than trivalent Cr compounds, largely because they are strong oxidizers and highly soluble. Trivalent Cr compounds tend to form relatively inert precipitates at near-neutral pH and are generally considered to be the most stable form in equilibrium within most soil/water systems (Bartlett 1991).

Freshwater Cr concentrations generally contain 1.0 μg/L (range 0.1-6.0 μg /L), while sea water averages 0.3 μg/L (range 0.2μg/L to 50 μg/L) (Bowen, 1979). Chrome concentrations in

the Mississippi River have been reported as high as 84.0 μg/L. Chrome levels in the Eastern U.S. waters are generally higher than in the Western U.S. (NAS, 1974). The significance of the water solubility for the carcinogenic potency of the chromates has not been clarified by animal studies (Langard, 1989) and the toxicity of Chrome has been relegated to the Cr VI species.

Chrome is known to be an essential component of animal nutrition and functions mainly in the metabolism of glucose, in fat and protein metabolism. It acts primarily by mediating insulin activity (Anderson, 1981). While shown to be nonessential for plants, it is nevertheless required by some microbes, possibly as a cofactor for specific enzyme systems. Bacteria with plasmid-conferred resistance to Cr VI toxicity have been isolated from water, soil and sediments, and the resistance mechanisms somewhat characterized. One of the chief mechanisms to ward off toxicity is the ability for bioreduction of toxic Cr VI to the relatively nontoxic Cr III. This was shown to occur directly by enzymatic processes at the cell membrane, and indirectly with microbially produced H_2S acting as the reducing agent (Losi *et al.*, 1994).

2.2 Chemical Analysis

Chrome is very sensitive to the redox potential so that any chemical analysis of Cr species requires very careful technique for sampling methodology and for storage, as well as for extraction, isolation and the actual analysis. There are several methods that can be used for analysis of chrome depending upon the matrix sampled. The major methods for total and Cr VI and their detection limits are listed (Table 2.2).

TABLE 2-2-MAJOR METHODS FOR TOTAL AND Cr VI

Method	Species Detected	Approx. Detection Limit (μ⊇/L)
Flame atomic absorption spectrometry	Total Cr	500 [a]
Graphite furnace atomic absorption spectrometry	Total Cr	1[a]
Inductively coupled plasma optical emission spectrometry	Total Cr	6-10 [a]
Inductively coupled plasma mass spectrometry	Total Cr	0.5[a]
Colorimetric (Diphenycarbizide)	Cr VI	50[b]
High performance liquid chromatography (single column ion chromatography)	Cr VI	92[c]

[a] Varies with instrument
[b, c] Gochfeld, 1991

Atomic Absorption Spectrometry (AAS) and Inductively Coupled Plasma Analysis (ICAP) are frequently used for analysis of total chrome while colorimetry and high performance liquid chromatography (HPLC) are generally the methods chosen for quantifying Cr VI levels. The

difference between total chrome and Cr VI is assumed to be Cr III and in each case a matrix spike assists in correctly identifying levels and any interfering substances.

2.3 Sampling Methods

Current industrial hygiene (IH) practices for the sampling and analysis of hexavalent chrome are driven by which analytical method the IH chooses to use. The IH can analyze by the OSHA ID-103 analytical method, draft OSHA ID-215 method, the NIOSH 7600 or the NIOSH 7604 method depending upon the level of detection desired, the laboratory availability and affordability. Since January 1, 1995, the Navy Environmental Health Center (NEHC) has recommended that field IHs use the draft OSHA ID-215 method of analysis. Although the issue of oxidation of Cr III to Cr VI still exists, the ID-215 method seems to correct concerns of the past and does analyze for hexavalent chromium in the most accurate and precise way available today.

2.4 Speciation Chemistry

Table 2-3 identifies the means of speciating chromium compounds during analysis of occupational exposures. They are the NIOSH 7600 and 7604 methods, the OSHA ID-103 and the draft ID-215 methods. Another speciation method is the ASTM D 5281-92 "Standard Test Method for Collection and Analysis of Hexavalent Chromium in Ambient, Workplace, or Indoor Atmospheres". This method does speciate for hexavalent chromium; however, it is an impinger collection method which is extremely difficult to use in field sample collection.

Knowledge of the valance state and compound solubility for chrome exposures is important. It is desirable to have analytical procedures which are capable of distinguishing between soluble and insoluble chrome.

The investigation of Zatka, 1985 confirmed that Cr III is partially oxidized to Cr VI in hot alkaline solutions. The amount of Cr VI produced in hot solutions was very small, though analytically significant, and remained unchanged even when a large excess of Cr III salt was used. The equations signifying this are:

$$Cr^{3+} + 3\ OH^- \leftrightarrow Cr\ (OH)_3$$

$$Cr(OH)_3 + OH^- \leftrightarrow [Cr(OH)_4]^-$$

$$[Cr(OH)_4]^- + \text{heat} \rightarrow CrO(OH) + H_2O + OH^-$$

Therefore, digestion of samples in the laboratory must be done with this reaction in mind. Also, welding fumes are reported to degrade, affecting the accuracy of the monitoring of these fumes (Zatka, 1985). It is believed that the "aging" phenomenon of the fume aerosols may be of wet-chemical nature and may be explained by a secondary air oxidation of leached Cr III rather than by primary redox reactions within the fume solids (Thomsen and Stern, 1981).

2.5 Collection Effectiveness

The NIOSH and OSHA analytical methods require that an air sample be collected using a 37 millimeter diameter polyvinyl chloride (PVC) filter (5 micron pore size) contained in a polystyrene cassette. A calibrated sampling pump is used to draw the air sample through the cassette and collect any particulate or mist.

Table 2-3: Recommended Industrial Hygiene Sampling and Analysis Procedures for Hexavalent Chrome

Analytical Method	**OSHA ID-103**	**Draft OSHA ID-215**	**NIOSH 7600**	**NIOSH 7604**
Matrix	Air	Air	Air	Air
Detection Limit: Qualitative Quantitative	0.006 mg/m^3 0.019 mg/m^3 as CrO_3 (30 L sample)	6.24 x 10^{-3} µg/m^3 2.18 x 10^{-2} µg/m^3 as Cr VI (960 L)	0.5 µg/sample	0.5 µg/sample
Recommended Sampling Rate	2.0 L/min	2.0 L/min	to 4.0 L/min	to 4.0 L/min
Recommended Sample Air Volume	Range 30-960 L (to meet ceiling limit)	2.0 L/min for 480 min	Min: 8 L mg/m^3) Max: 400 L	Min: 100 L mg/m^3) Max: 1000 L
Sampling Collection Device	diameter PVC filter (5 µm pore size) in polystyrene cassette	diameter PVC filter (5 µm pore size) in polystyrene cassette	diameter PVC filter (5 µm pore size) in polystyrene cassette	diameter PVC filter (5 µm pore size) in polystyrene cassette
Analytical Procedure: Extraction (E) Dilution (D) Analytical Device (A)	aqueous solution of carbonate/ bicarbonate buffer, (D), (A) differential pulse polarography	aqueous solution 10% sodium carbonate & 2% sodium bicarbonate, (A) ion chromatograph with postcolumn UV-vis detector at 540 nm	aqueous solution 0.5 N sulfuric acid (soluble forms) or 2% sodium hydroxide - 3% sodium carbonate (insoluble forms), (D), (A) visible absorption spectrophotometry (540 nm) Analyte: CrO_4^{2-} diphenylcarbazide complex	mL aqueous solution of 2% sodium hydroxide - 3% sodium carbonate (insoluble forms), (D), (A) ion chromatograph y, conductivity detection Analyte: chromate ion

Notes: µg/m^3 = micrograms of contaminant per cubic meter of air
L/min = liters per minute of air
PVC = polyvinyl chloride
um = microns
nm = nanometers wavelength
mL = milliliters

Most commercial industry and DoD IH sampling is done according to NIOSH 7600 (this method is specific for Cr VI) or a modified version (NIOSH 7300) analyzing with an inductively coupled plasma detector with a mass spectrometer detector attached. This method requires that the industrial hygienist stochiometrically convert from total chrome to hexavalent chrome, which leads to a greater possibility of error.

It is interesting to note that Thomsen, 1981 reported that the Cr VI contents found in the same welding fume aerosol depended on the sampling method. Fume specimen collected in water-filled impingers showed higher Cr VI levels than were found in the same fume simultaneously collected on a filter (Zatka, 1985). The fume was shown to undergo a distinct aging process in which the maximum Cr VI content was reached within 20 seconds and then began to fall (Zatka, 1985). Within a few minutes, it reached a steady value equal to the Cr VI content in the filter specimen (Zatka, 1985). Interestingly enough, only fumes generated by metal inert gas (MIG) welding showed the aging phenomena (Zatka, 1985). No Cr VI evolution was observed in manual metal arc (MMA) welding fumes suggesting that not all fume aerosols were subject to aging (Zatka, 1985). Therefore, in light of the sampling collection effectiveness one must assume a level of uncertainty for welding monitoring.

2.6 Uncertainties in Sample Collection and Analysis

There are various uncertainties associated with the sample collection and analysis. Uncertainties are introduced during the sampling phase of Cr VI occupational exposure assessments. Each process varies day to day in an occupational environment. While samples are collected, an industrial hygienist must rely on the workers knowledge of the process for a complete evaluation.

Uncertainties are also introduced by the analysis of the hexavalent chrome samples. The NIOSH 7600 method (visible absorption) publishes an accuracy of $\pm$ 18.58% and a coefficient of variation of 0.084. The NIOSH 7604 method (ion chromatography) publishes an accuracy of $\pm$ 13.0% and a coefficient of variation of 0.066. The OSHA ID-103 publishes an overall error range of $\pm$ 2.7% to $\pm$ 8.7% and a precision of 0.1 to 0.6 mg/m^3 as CrO_3. The OSHA ID-215 draft uv-vis method publishes an overall error of $\pm$ 12.9% and a precision of 0.11 to 0.41 $\mu g/m^3$.

3.0 EXPOSURE ASSESSEMENT

3.1 Description of Exposure Scenarios

Contaminate sources of hexavalent chromium vary according to process. In general, particulate hexavalent chromium is generated during a physical process such as metal working (sanding, grinding), painting with chromate pigments and depainting. Fumes of hexavalent chromium are evident in processes which involve heating such as welding on stainless steel. Mists are produced during processes which involve the soluble forms of hexavalent chromium such as plating and painting. All contaminate sources of hexavalent chromium are present within DoD processes investigated by this report.

Historically, occupational exposure to chromium occurs mainly from stainless steel production and welding, chromate production, chrome plating, ferrochrome alloys, chrome pigment, wood treatment and tanning industries. For most occupations, the exposure is due to both Cr III and Cr VI states present as soluble and insoluble fractions. However, exceptions are the plating industry where the exposures are primarily due to soluble Cr VI and the pigment industry handling (e.g., painting and depainting) where exposure is due to insoluble Cr VI. The typical concentration ranges ($\mu g/m^3$) of airborne Cr VI to which workers in these industries were exposed during an average 5 to 20 years of employment were: stainless steel welding, 50 to 400; chrome plating, 5 to 25; ferrochrome alloys, 10 to 140; and chrome pigment, 60 to 600 (ATSDR, 1993). Because of better emission control measures, occupational airborne chromium concentrations have declined significantly during the past decades (Stern, 1983). Additionally, some toner powders used in copying machines contain inhalable chromium. Therefore, those maintaining or discarding of these toner cartridges may also be at risk for occupational exposures to chromium. It is estimated that 175,000 persons in the United States may be occupationally exposed to Cr VI (IARC 1980).

3.2 Documented Pathways of Exposure, Numbers and Type of Receptors

In the occupational environment, Cr VI is released into the air through a physical (e.g., sanding, blasting) or a chemical breakdown (e.g., acid etching, heating) of substrate. Hexavalent chromium can be released in the form of particulates, fumes and mists. Hexavalent chromium is first released into the air and then either breathed, ingested or dermally contacted by a human receptor. These pathways of exposure must be evaluated according to their effects on the body. The form and particle size distribution of released chrome is a function of the industrial process. Hewett (1995) reported on particle size distribution of fumes from welding processes. Bonde and Christenson (1991) described the ratio of total chrome and Cr VI from various welding processes alone with measures of uptake

At the cellular level, ingestion uptake is mediated by the transport of chromium across membranes. Cr VI is actively transported but Cr III has a much lower uptake. In general, trivalent chromium enters at extremely high concentrations around the cell. In contrast, hexavalent chromium exists as an oxy-anion (CrO_4^{-2}) that readily enters the cell by an anion transport system (Coogan *et al.*, 1991). Once inside the cell, hexavalent chromium is reduced

ultimately to the trivalent form with intermediate oxidation states (e.g., Cr^{+5}) produced during reduction (De Flora and Wetterhahn, 1989). It is theorized that radicals formed during the reductive process, as well as trivalent chromium and other intermediates formed, are ultimately responsible for the intracellular effects of hexavalent chromium (Cohen *et al.*, 1992). Owen (1990) indicated a five-fold ratio of Cr VI over Cr III by oral absorption and a 2.5-fold ratio for inhalation absorption.

During inhalation exposures to hexavalent chromium, completed exposure pathways occur for all paint removal processes, metal cleaning processes, abrasive blasting processes, painting processes, coating and plating processes, welding and cutting processes, packaging, hazardous waste/sewer treatment, woodworking, electronics repair, flight line operations and plastics processes. The main route of exposure as mentioned earlier is the inhalation of hexavalent chromium in the dust, mist or fume form. The inhalation exposure pathway has been documented through industrial hygiene air sampling as mentioned and analyzed in later sections of this report.

There are two other potential pathways of exposure with hexavalent chrome containing materials. These are ingestion and dermal contact. In the Navy occupational setting, ingestion of contaminants occurs by personnel touching dust or other matter and then eating, drinking, smoking or touching their lips without proper handwashing techniques.

3.3 Factors Breaking Pathways

The inhalation pathway of exposure in an occupational setting is typically broken through the use of some type of pollutant control device. Engineering pollution control devices are usually present in the form of industrial ventilation systems such as the push-pull ventilation systems on open tank plating devices, paint booth ventilation system used during painting and depainting, and sanders with High Efficiency Particulate filters on them to remove the dusts, fumes or mists. The DoD employs many types of engineering controls for their hexavalent chromium processes.

Personal protective equipment (PPE) is another effective means to break the exposure pathway of hexavalent chromium in an occupational environment. PPE is usually recommend for those areas where monitoring has shown an unacceptable exposure to hexavalent chromium. In the DoD, PPE is recommended for any dermal contact pathway, for any ingestion pathway and for inhalation pathways where exposures have been monitored above one-half of the OSHA permissible exposure limit. PPE is not as effective in controlling exposures as engineering controls because it involves "user compliance" in the wear of the control. Some types of PPE recommended for hexavalent chromium exposure scenarios are gloves, protective suits, half-face respirators (10 times protection over no protection), full-face respirators (50 times protection over no protection) and supplied air respirators. The gloves and suits are recommended to break the ingestion and dermal contact exposure pathway. Respirators aide in the reduction of inhalation exposures.

Other ways to break exposure pathways are the use of administrative controls such as shortened work periods or flexible time for hexavalent chromium workers. Usually, administrative controls are not used in the DoD due to the large cost of management

associated with them. However, in the event that engineering controls or PPE are not appropriate or available, administrative controls are a good option to break the pathway of exposure. The ingestion and dermal contact routes of exposure are broken by personnel using proper handwashing and housekeeping techniques.

3.4 Summary of Existing Navy/DoD/Other Exposure Databases

The data used for the determination of risk came from the Navy Occupational Exposure Database (NOED). The NOED contains air sample results conducted by the Bureau of Medicine and Surgery field industrial hygienists and analyzed by the Navy Consolidated Industrial Hygiene Laboratories. Air sampling data is presented in the database either by individual concentrations or by time weighted averages for an 8-hour work day. The Navy's assessment of worker exposure is based on homogenous exposure groups. That is, the workers are grouped by the expectation of having the same exposure profiles or distributions. This is usually determined by the process or the task (the operation). Therefore, exposure assessments are based on the best determined refinement of the elements of a unique homogeneous exposure group description. For example, if a welder is performing shielded metal arc welding (SMAW), his exposure assessment is grouped for statistical treatment in the operation code for SMAW.

3.4.1 Statistical Evaluation of Data

Three types of statistical evaluation of the Naval data were performed: calculations of the Cox Upper Confidence Limits (UCLs), the 95th % upper tolerance limit (UTLs), and the arithmetic means. The UCL calculations are referenced in Table 3-1 (Rappaport and Selvin, 1987). This method determines the geometric mean from a lognormal distribution. It then computes the 95% UCL for the distributions. Only the data from six processes in Table 3-1 were able to fit to this stringent statistical evaluation. A 95% UCL was determined for those six processes.

To better determine risk, the upper tolerance limits (UTLs) were calculated in Table 3-2. This data used the geometric mean without testing for normality with the Kolgomorov-Smirnov test. This forced the data to be considered normal for those processes having greater than 5 sample points. The data in Table 3-2 shows that all nine processes were evaluated using the UTLs calculated. The hypothetical risks in Table 3-2 were calculated using the geometric mean.

Lastly, simple arithmetic means were calculated on each set of sampling data per process. These mean concentration values are shown in Table 3-3 and 3-4. Risks are then calculated based upon the arithmetic mean per process for excess cancer risks by inhalation of hexavalent chromium. This was done because, in most processes, the Navy does not have data speciated for Cr VI using the OSHA ID-215 method in statistical proportions (greater than 5 samples). Therefore, most of their processes cannot be characterized. Table 3-4 displays risks calculated using the arithmetic mean divided by a protection factor of 50 to represent full-face respirator. Processes in which less than five samples were collected were not included in Table 3-3 and 3-4. Among the processes with less than five samples; abrasive blasting with

mineral spirits, abrasive blasting with sand, metal cleaning, and spray painting with compressed air had a sample which exceeded the current PEL. However, based on one to three samples, one cannot conclude that these processes consistently exceed the OSHA PEL and would be hazardous on a long-term basis. In addition, PPE would likely be worn during most of these processes.

Table 3-1 Cox UCL Calculations

Concentration Term by COX UCL: Samples from Jan 95 to Nov 96 (ID-215)										
Operation	Stressor	TWA Sample Range (mg/m^3)	GM	GSD	K-S	95th %tile	PN%	MLE	Cox UCL	Hypo-thesis Test P%
Abrasive Blast	Mineral Grit, Ins Cr	0.00072 - 0.16	0.00706	5.248	A	0.108	41.7	0.02	0.136	81
Abrasive Blast	Insoluble Cr VI	0.00009 - 0.022	0.00155	14.726	A	0.1295	24.5	0.05	1770	50
Metal Clng, Sanding	Insoluble Cr VI	0.00004 - 0.78	0.00062	9.51	R					
Open Tank Plating	Insoluble Cr VI	0.00004 - 0.00022	0.00012	2.11	A	0.0004	<0.1	0.0002	0.0006	75
Spray Pnt, Comp Air	Insoluble Cr VI	0.00001 - 0.33	0.00437	8.548	A	0.149	34.8	0.0436	0.208	99
Welding, Shield MA	Insoluble Cr VI	0.00003 - 0.0082	0.0004	7.535	A	0.0111	5.6	0.0031	0.158	12
Welding, Gas MA	Insoluble Cr VI	0.00002 - 0.0075	0.0001	11.435	R					
Welding, Gas TA	Insoluble Cr VI	0.00002 - 0.012	0.0001	7.653	R					
Oxygen Cutting	Insoluble Cr VI	0.00002 - 0.0020	0.00011	7.431	A	0.0031	1.3	0.0008	0.385	13

Notes:

MA = Metal Arc
TA = Tungsten Arc
TWA = Time Weighted Average (8 hour)
GM = Geometric Mean
GSD = Geometric Standard Deviation
K-S = Kolgomorov-Smirnov Test for Normality
95%tile = 95% of samples are below this value
R = Rejected
A = Accepted

Table 3-2 Risk Calculations for Forced UTL Calculations (Geometric Mean)

Operation	Stressor	TWA Sample Range (mg/m^3)	GM	GSD	UTL	LADD Lt Work	LADD Heavy Work	Risk Light Work	Risk Heavy Work
Abrasive Blast	Mineral Grit, Ins Cr	0.00072 - 0.156	0.00706	5.248	0.659	7.03E-05	2.11E-04	2.88E-03	8.64E-03
Abrasive Blast	Insoluble Cr VI	0.00009 - 0.220	0.00155	14.7	1.00E+06	1.54E-05	4.63E-05	6.32E-04	1.90E-03
Metal Clng, Sanding	Insoluble Cr VI	0.00004 - 0.781	0.00062	9.51	0.146	6.17E-06	1.85E-05	2.53E-04	7.59E-04
Open Tank Plating	Insoluble Cr VI	0.00004 - 0.00022	0.00012	2.11	0.0361	1.19E-06	3.58E-06	4.90E-05	1.47E-04
Spray Pnt, Comp Air	Insoluble Cr VI	0.00004 - 0.327	0.00437	8.55	0.597	4.35E-05	1.34E-04	1.78E-03	5.35E-03
Welding, Shield MA	Insoluble Cr VI	0.00003 - 0.00823	0.0004	7.54	1.9	3.98E-06	1.19E-05	1.63E-04	4.90E-04
Welding, Gas MA	Insoluble Cr VI	0.00002 - 0.0075	0.0001	11.4	27.6	9.95E-07	2.98E-06	4.08E-05	1.22E-04
Welding, Gas TA	Insoluble Cr VI	0.00002 - 0.0122	0.0001	7.65	0.0961	9.95E-07	2.99E-06	4.08E-05	1.22E-04
Oxygen Cutting	Insoluble Cr VI	0.00002 - 0.00201	0.00011	7.43	524.0	1.09E-06	3.28E-06	4.49E-05	1.35E-04

Notes: MA = Metal Arc
TA = Tungsten Arc
TWA = Time Weighted Average (8 hour)
GM = Geometric Mean
GSD = Geometric Standard Deviation
K-S = Kolgomorov-Smirnov Test for Normality
95%tile = 95% of samples are below this value
R = Rejected
A = Accepted
LADD = Lifetime average daily dose = GM * Respirable Fraction * Inhalation Rate * Exposure Frequency * Exposure Duration / Body Weight
Risk = Excess lifetime cancer risk

Table 3-3 Risk Summary Table (Using Arithmetic Mean per Process)

Process Description	Concentration (mg/m3)	LADD Lt. Work	LADD Heavy work	Risk Light Work	Risk Heavy Work
Abr blast, mineral grit	0.096	9.55E-04	2.87E-03	1.15E-02	3.44E-02
Abr blast, organics	0.0647	6.44E-04	1.93E-03	7.73E-03	2.32E-02
Metal clng mech, sand	0.0523	5.21E-04	1.56E-03	6.25E-03	1.87E-02
Open tank electroplating	0.000728	7.25E-06	2.17E-05	8.70E-05	2.61E-04
Spray paint, comp air	0.216	2.15E-03	6.46E-03	2.58E-02	7.75E-02
Shielded metal arc weld	0.00373	3.71E-05	1.11E-04	4.46E-04	1.34E-03
Gas metal arc welding	0.00489	4.86E-05	1.46E-04	5.84E-04	1.75E-03
Gas tungsten arc weld	0.00326	3.25E-05	9.74E-05	3.90E-04	1.17E-03
Oxygen cutting	0.00194	1.93E-05	5.799E-05	2.32E-04	6.95E-04

Table 3-4 Risk Summary Table for Arithmetic Mean Considering Respiratory Protection

Process Description	Concentration (mg/m3)[a]	LADD Light Work	LADD Heavy Work	Risk Light Work	Risk Heavy Work
Abr blast, mineral grit	0.00192	1.91E-05	5.73E-05	2.29E-04	6.88E-04
Abr blast, organics	0.00129	1.29E-05	3.86E-05	1.55E-04	4.64E-04
Metal clng mech, sand	0.00105	1.04E-05	3.12E-05	1.25E-04	3.75E-04
Open tank electroplating	1.457E-05	1.45E-07	4.35E-07	1.74E-06	5.22E-06
Spray paint, comp air	0.00433	4.31E-05	1.29E-04	5.17E-04	1.55E-03
Shielded metal arc weld	7.465E-05	7.43E-07	2.23E-06	8.91E-06	2.67E-05
Gas metal arc welding	9.776E-05	9.73E-07	2.92E-06	1.17E-05	3.50E-05
Gas tungsten arc weld	6.526E-05	6.49E-07	1.95E-06	7.79E-06	2.34E-05
Oxygen cutting	0.0000388	3.86E-07	1.16E-06	4.63E-06	1.39E-05

[a] Concentration represent the arithmetic mean divided by a protection factor of 50 (full-face respirator).

3.4.2 Documentation of Exposure Factors and Methods Used in Risk Assessment (Duration & Frequencies, Intake Rates, Weights, Uptake Assumptions)

Currently there are only exposure values available to evaluate airborne monitoring data for carcinogenic risk to workers. There are no values available to evaluate cancer risks to workers by the oral route of exposure or dermal contact, nor to evaluate the oral exposures for non-cancer effects. The Navy does not have data on oral exposures from eating, drinking or smoking. These pathways are not easy to monitor in an occupational setting. Therefore, only the inhalation exposure pathway was monitored for carcinogenic risk to workers.

The excess inhalation cancer risks were calculated using the equation for estimating inhalation uptake or lifetime average daily dose (LADD) (Paustenbach, 1991). The following assumptions were made: That the fraction of Cr VI which was respirable (RF) was 0.23, the inhalation rate (IR) was 10 meters cubed per day for light work and 30 meters cubed per day for heavy work, the exposure frequency (EF) was 250 days per year at 8 hours per day or 53% of a year, the exposure duration (ED), was the fraction of a lifetime or 40 of 70 years for an occupational exposure. The body weight (BW) was assumed to be 70 kilograms for the average working male. The Navy is 85% male. The concentrations used were arithmetic means of the exposure data in Table 3-3 and the geometric mean of the exposure data in Table 3-2. The equations used were:

LADD (mg/kg/day) = (Concentration x RF x IR x EF x ED)/BW

Risk was calculated using the EPA cancer potency factor (CPF) of 41 (mg/kd-day)$^{-1}$ for inhalation of hexavalent chromium (IRIS, 1995) at the following equation:

Risk (unitless probability) = CPF (mg/kg-day)$^{-1}$ x LADD (mg/kg/day)

where: CPF of Cr VI = 41 (mg/kg-day)$^{-1}$

As you can see from the Tables, the risks for the geometric mean are higher than acceptable under the older toxicity information for hexavalent chromium for both abrasive blasting and spray painting without PPE. For the arithmetic mean risk calculations, the following processes indicate an increase cancer risk assuming total bioavailability of chrome based upon the toxicity data for hexavalent chromium:

Abrasive blasting with mineral spirit
Abrasive blasting with sand
Abrasive blasting with organics
Metal cleaning, grinding
Metal cleaning, sanding
Metal cleaning, NEC
Spray painting with compressed air

The calculations in Tables 3-2 and 3-3 do not take into account the use of respiratory protection which is recommended for processes where exposures are monitored at one-half the OSHA permissible exposure limit (PEL). The Navy is quite conservative in their PPE recommendations, however, we must also remember that OSHA only requires compliance with the ceiling limit for hexavalent chromium. The hypothetical lifetime risk calculated on the majority of these processes were in the 10^{-4} range, acceptable for industrial exposure. The highest risks calculated was in the 10^{-2} to 10^{-3} range for abrasive blasting using mineral spirits and sand. These are processes, however, where PPE (including respiratory protection) are worn.

Table 3-4 presents risks calculated using the arithmetic mean of the process monitoring data using a blanket respiratory and a protection factor of 50. Risks were all calculated according to the above equation yet the mean concentration was divided by a factor of 50 considering full face respiratory protection. The hypothetical risks were all well within acceptable

limits, ranging from 10^{-4} to 10^{-7}. Later in this report we will evaluate the proposed change in the toxicity of hexavalent chromium and that impact to the occupational risks in the Navy from using compounds containing hexavalent chromium.

3.5 Medical Monitoring

Currently the Navy has an extensive medical monitoring program for hexavalent chromium workers. The matrix of compounds involved in the program include:

Chromic acid
Chromite ore processing
Zinc chromate
Sodium dichromate
Chromium (VI) water soluble
Chromium (VI) water insoluble
Lead chromate
Tert-butyl chromate
Sodium chromate
Potassium chromate
Chromium phosphate
Chromium carbonyl
Zinc chromate hydroxide
Chromium oxide
Strontium chromate
Calcium chromate
Barium chromate
Zinc potassium chromate
Zinc yellow

The medical surveillance of employees who use these compounds includes the following tests:

Medical History
Work History
Family History
Laboratory tests:
- Hematology
- Serum Chemistry
- Urinalysis
- Radiology
- Spirometry

Physical Examination:
- Special attention to: kidney, mucous membranes, nasal mucosa, respiratory system, skin

Most of the medical surveillance occurs at initial employment, annually thereafter, and at termination of work. The only tests listed above not completed annually are the radiology

(chest x-ray) and a portion of the liver profile. The Navy currently has no centralized mechanism for collecting information on medical surveillance examinations. The workers placed in medical monitoring programs is based on specific local exposure assessments.

3.6 Compare Exposures to Commercial Levels

In general, Navy exposures to hexavalent chromium appear to be considerably less than those in the private sector. This is largely because the Navy operations mainly include the maintenance of ships, aircraft and ground equipment. In the private sector, many corporations are involved with the manufacture of hexavalent chromium containing parts, compounds or materials. There are a number of commercial studies on the effects of welders (van der Wal, 1985, 1986, 1990, Moulin *et al.,* 1993, Matczak *et al.*, 1993, Karlsen *et al.,* 1994, Wilson *et al.*, 1991, Dryson *et al.*, 1991, Becker, 1985) and platers (Lindberg *et al.,* 1985) which were mentioned in this report and others. None of these studies used the OSHA ID-215 method for analyzing hexavalent chromium. Therefore, it is difficult to make a direct comparison between the data. However, the values were observed to at least make a guess at the typical commercial values or hexavalent chromium during welding and plating.

Welding processes, as in the Wilson, 1981 study, observed mean concentrations around the maintenance shop of 0.001 mg/m^3 of Cr VI. In the same study, personnel were monitored at a mean concentration of 0.002 mg/m^3. These values were monitored on stainless steel welding in confined spaces at a petrochemical plant. Again, a direct correlation cannot be made with our Navy data, however, it is comforting to note that Navy welding processes were monitored using the OSHA ID-215 method at an order of magnitude lower. This is basically due to the reduction in the detection limit of the ID-215 method. It is important to note that the ID-215 method does not differentiate between soluble and insoluble Cr VI.

For plating processes (Lindberg *et al.*, 1985), it is necessary to note documented additional exposures to nickel, zinc, copper, tin and cadmium. As in welding on stainless steel, there is a potential for synergistic effects from multiple heavy metal contaminants. In the Lindberg study for hard chrome platers, average Cr VI concentrations in mg/m^3 ranged from 0.02 for manual plating to 0.0025 for automatic plating. Navy open tank processes ranged from 0.0001 to 0.001 mg/m^3. These values again cannot be directly compared but they give you a good indication that Navy processes are again lower than commercial processes in the exposure to hexavalent chromium.

A search of the NIOSH database abstracts on Health Hazard Evaluation Reports was performed to assess the relative level of exposure for processes similar to those found in the DOD. Reports from 1974 through 1995 were included. The NIOSH surveys were performed to assess process health effects and the effectiveness of control technologies, not as research projects. Documentation on methods and materials is limited in some cases. Table 3-5 identifies the process, whether or not documented exposures exceeded the current chrome OSHA PEL or NIOSH REL and provides comments where ranges of exposure were documented.

Significant variability in the exposure levels can be noted. There was no information in the abstracts or the reports reviewed to assess process characterization variables to correlate

the potential of over exposure to a process capacity. The reports on control technologies infer there is existing technology available to control exposure to acceptable levels with the current recommended OSHA PEL. No information was located on the cost of these control strategies.

Welding and painting routinely exceeded the current OSHA PEL standards, although at times a total chrome analysis was used to estimate Cr VI levels. The highest exposure levels recorded were for shipbuilding. Subjectively, these data suggest significant investment in control equipment will be needed for DOD processes. They also suggest the technology should be available for control in most instances. These studies were not in enough depth to draw a conclusion on the cost of control. In one study, Tinker AFB aircraft repair operations, down draft tables, PPE, HEPA vacuums and added air monitoring was required to achieve compliance with current standards for cleaning operations in their jet engine nozzle shop

Table 3-5 NIOSH Surveys of Commercial Processes with Chrome Exposures (1974-1995)

NIOSH Survey Area - Process Description	Exceed PEL	Exceed REL	Comments
Welding, manufacturing	-	-	0.003 to 0.01 mg/m^3 Total Cr
Welding, manufacturing		+	0.001 - 0.01 mg/m^3 Total Cr
Aircraft Maintenance, grinding	+		0.002 - 33 mg/m^3 Total Cr
Casting, dip tank		-	
Auto Body, spray paint		-	
Manufacture, spray paint		-	
Tank car repair, welding		-	
Auto Body, spray paint		-	
Electroplate		-	
Auto body, painting		-	
Aircraft, painting	+		$SrCrO_4$
Cabinet Finishing	+		
Refinery, maintenance, welding		+	
Manufacturing, painting		+	
Manufacturing, welding		-	
Manufacturing, painting		-	
Auto body, painting			0.010 -0.200 mg/m^3 Total Cr
Manufacturing, spray painter	+		Zinc Chromate
Transportation maintenance	+		
Manufacturing, plating		-	
Manufacturing, welding		-	
Manufacturing, welding		-	
Manufacturing, painting		-	
Manufacturing, welding		-	
Manufacturing, welding		-	0.0011 - 0.0152 mg/m^3 Cr VI
Pigment mixing		-	
Aircraft, maintenance, plating	-		
Manufacturing, refractory	-		

NIOSH Survey Area - Process Description	Exceed PEL	Exceed REL	Comments
Aircraft maintenance, plating	-		
Manufacturing, welding		+	
Maintenance, welding		+	0.002 - 0.001 mg/m^3 Cr VI
Manufacturing, spray painting		-	<0.0004 mg/m^3 Cr VI
Manufacturing, painting		-	
Manufacturing, plating		-	
Manufacturing, dye testing		-	
Manufacturing, spray painting		+	<0.023 mg/m^3 Cr VI
Manufacturing, painting	-		
Forestry, painting		-	
Manufacturing, welding	-		
Manufacturing, torch braze	-		
Aircraft maintenance, dip braze	-		
Ordnance maintenance, braze	-		
Manufacturing, welding	-		
Manufacturing, painting	-		
Manufacturing, plating	-		
Manufacturing, plating	-		
Manufacturing, plating	-		
Aircraft maintenance, plating	-		
Manufacturing, plating	-		
Aircraft maintenance, plating	-		
Manufacturing, plating	-		
Aircraft maintenance, plating	-		
Manufacturing, circuit boards	-		
Manufacturing, plating	-		mean 0.004 mg/m^3 Cr VI
Transportation, painting	-		
Foundry, welding		+	
Manufacturing, refractory	-		
Manufacturing, plating	-		
Manufacturing, automotive	-		
Maintenance, welding	-		
Manufacturing, tractors	-		
Manufacturing, chemical	-		
Manufacturing, welding	-		
Manufacturing, electronics	-		
Manufacturing, painting	-		
Maintenance, welding	-		
Maintenance, welding	+		
Maintenance, welding	+		
Maintenance, welding	+		
Maintenance, welding	+		0.003 - 0.426 mg/m^3 Cr VI
Refining, maintenance		+	
Maintenance, welding	-		

NIOSH Survey Area - Process Description	Exceed PEL	Exceed REL	Comments
Manufacturing, welding	+		Avg 0.19 mg/m^3 Cr VI
Maintenance, painting	+		2.4 mg/m^3 Cr VI
Transportation, painting	+		> 0.1 mg/m^3 Cr VI
Manufacturing, welding	-		
Manufacturing, electronics		+	0.0 - 0.011 mg/m^3 Cr VI
Shipbuilding, welding	+		< 4.9 mg/m^3 Cr VI
Manufacturing, plating		+	0.001 - 0.014 mg/m^3 Cr VI
Manufacturing, plating	-		
Manufacturing, plating		+	
Manufacturing, plating		-	
Manufacturing, plating	-		
Maintenance, welding		+	
Maintenance, welding		+	0.01 -2.3 mg/m^3 Total Cr
Maintenance, welding	+		0.65 - 1.0 mg/m^3 Total Cr
Maintenance, welding	-		
Transportation, painting	-		
Manufacturing, welding	-		
Manufacturing, painting	-		
Manufacturing, welding	+		
Manufacturing, plating		-	0.003 - 0.006 mg/m^3 Cr VI
Manufacturing, plating	-		
Manufacturing, welding	-	-	
Manufacturing, painting	-		
Manufacturing, welding		-	Avg 0.006 mg/m^3 Cr VI
Manufacturing, plating	-		0.0004 - 0.0113 mg/m^3 Cr VI
Manufacturing, plating	-		

+ = exceeded current OSHA PEL or NIOSH REL
- = did not exceed current OSHA PEL or NIOSH REL

3.7 Recommendations

To better assess occupational exposures to hexavalent chromium in the Navy, it would be advantageous to:

A. Continue using ID-215 and gather as much airborne sampling data as possible for all Navy processes. Sufficient data does not exist to determine 95% statistical confidence limits in most areas.
B. Continue to incorporate as many material substitutions for hexavalent chromium as possible in pollution prevention and occupational health risk reduction efforts.
C. In the interim, continue the conservative approach of recommending respiratory protection to workers performing hexavalent chromium processes. The use of proper PPE, engineering controls and administrative controls cannot be stressed

enough to show Navy compliance with a potential change in the hexavalent chromium standard.

D. From process characteristics attempt to document the source of Cr VI to assess its solubility characteristics.

4.0 HUMAN HEALTH EFFECTS

4.1. General Discussion

OpTech (1996a) summarizes the adverse effects reported for chromium exposure. Toxicity of chromium has been reviewed by ATSDR, 1993; Burrows, 1983; EPA, 1984; Fan and Harding-Barlow, 1987; and IARC, 1980. For noncarcinogenic effects, the adverse symptoms included contact dermatitis (ATSDR, 1993; IARC, 1980; Maloof, 1955), contact hyper-sensitivity (IARC, 1980; Polak *et al.*, 1973), nasal septum ulceration or perforation (Cavazzani and Viola, 1970; Gomes, 1972; IARC, 1980; Kleinfeld and Russo, 1965; Lieberman, 1941; Sassi, 1956), chronic obstructive airway disease (Davies *et al.*, 1991), coughing, nasal irritation, sneezing, rhinorrhea, and nosebleeds (Gomes, 1972). Coughing, wheezing, dyspnea (Langard *et al.*, 1980), duodenal ulcers (Lucas and Kramkowski, 1975; Sassi, 1956), chronic ulcers (IARC, 1980; Maloof, 1955), gastritis, stomach cramps, indigestion (Lucas and Kramkowski, 1975), dizziness, headaches, weakness (Lieberman, 1941), oligospermia (Haneke, 1973 as cited in Bonde, 1993), reduced semen quality (Mortensen, 1988), and difficulties in conception (Rachootin and Olsen, 1983) were also reported. EPA (1990) reported that Cr VI is highly irritating to the nasal mucosa and airways and can induce morphological changes.

4.2. Genotoxicity

A higher incidence of chromosomal aberrations after exposure to chromium has been reported (Bigaliev *et al.*, 1978; Deng *et al.*, 1988; Elias *et al.*, 1989; IARC, 1980). Cr VI compounds caused mutations and allied effects in a wide range of prokaryotic and eukaryotic systems, both *in vitro* and *in vivo*, whereas Cr III compounds were not active in similar test systems; Cr III was active only at extremely high cytotoxic concentrations (National Institute of Public Health and Environmental Protection, 1990). Therefore, it was concluded that Cr VI is mutagenic and Cr III is not mutagenic (National Institute of Public Health and Environmental Protection, 1990).

4.3. Carcinogenicity

Chromium was reported to be carcinogenic to humans in certain chromium industries (ATSDR, April 1993; Guillemin and Berode, 1978; IARC, 1973, 1980; Silverstein *et al.*, 1981; Sjogren *et al.*, 1987; Sorahan *et al.*, 1987). In epidemiological studies, an association was found between occupational exposure to chromium compounds and mortality from lung cancer, especially in the chromate-producing industry (Baetjer, 1950a, 1950b; Bidstrup and Case, 1956; Gafafer, 1953; Hayes *et al.*, 1979; Machle and Gregorius, 1948; Mancuso, 1975; Mancuso and Hueper, 1951; National Institute of Public Health and Environmental Protection, 1990; Taylor, 1966). An increased frequency of chromosomal aberrations has been observed in workers exposed to Cr VI compounds. On the basis of these studies, IARC (1980) concluded that there is sufficient evidence of respiratory carcinogenicity in humans occupationally exposed during chromate production (National Institute of Public Health and Environmental Protection, 1990). On the basis of the available data (including the evaluation by IARC), it was concluded that Cr VI is

carcinogenic to humans (National Institute of Public Health and Environmental Protection, 1990). EPA (1988) concluded that hexavalent chromium compounds are human carcinogens, classified as weight-of-evidence Group A (based on chromate production workers and animal data which indicate that inhaled hexavalent chromium compounds are carcinogenic).

4.4 Pivotal Human Exposure Studies Used by Criteria Setting Organizations

4.4.1. Cancer Effects

There are a number of key studies that criteria-setting organizations used as a basis for developing criteria and/or standards for chromium in air. NIOSH (1975) cited the following references for cancer effects: Bourne *et al.*, 1951; Bourne and Ruskin, 1950; Bourne and Street, 1950; Bourne and Wunderle, 1950; Bourne and Yee, 1950; Gafafer, 1953; Gross and Kolsch, 1943; Hueper, 1958; Langard and Norseth, 1975; Laskin, 1968; Laskin 1972; Machle and Gregorius, 1948; Mancuso, 1951; Mancuso and Hueper, 1951; Nettesheim *et al.*, 1971; NIOSH (1973); Urone *et al.*, 1950; Urone and Anders, 1950; and Watanabe and Fukuchi, 1975.

ACGIH (1996) cited the following studies for cancer effects: ATSDR (1993); HSE (1989); IARC (1990); IPCS (1988); Jones (1990); Langard (1989, 1990); Lees (1991); Mancuso (1975); and Norseth (1986).

Basically, the studies suggested that chromium produces cancer in humans. EPA selected the Mancuso data for developing the cancer unit risk factor (EPA,1988).

4.4.2. Noncancer Effects

There are a number of key studies used by NIOSH (1975) for setting criteria. These include the following: Bloomfield and Blum, 1928; Gafafer, 1953; Gomes, 1972; Gresh, 1944; Kleinfeld and Russo, 1965; NIOSH, 1973; and Zvaifler, 1944. Basically, these studies report perforated or ulcerated septum, inflamed mucosa, "chrome holes" in the nose (Bloomfield and Blum, 1928; Kleinfeld and Rosso, 1965), lacrimation, nasal itching and soreness, and epistaxis (Kleinfeld and Rosso, 1965).

ACGIH (1996) cited the following studies: Henderson *et al.* (1979), who reported enzymatic and cytologic changes in lung tissue in lab animals given chromium and Johansson *et al.* (1980; 1986a, 1986b, 1987), who reported changes in alveolar macrophages and phagocytic activity with chromium administration to lab animals.

4.5 Critical Reviews of Pivotal Studies

4.5.1. Study Uncertainties

Uncertainties exist in these studies regarding (1) sampling methods and procedures, (2) analytical methods, (3) measurements, and (4) methods for analyzing data. Numerous methods have been used to measure chromium in different media, but only recently have accurate methods been developed to measure this analytically troublesome element (EPA, 1984). In general, chromium is an extremely difficult element on which to obtain reliable data (Burrows, 1983). Moreover, most of the accurate methods measure elemental chromium; but relatively few provide usable information on the oxidation states for trace amounts (EPA, I984). Sampling and analytical methods have been reviewed by the EPA (1984); analytical methods have also been reviewed by IARC (1980).

Current epidemiological evidence suggests that hexavalent chromium is the primary agent causing chromium carcinogenesis, and only a few are cited for the sake of brevity (Mancuso, 1975; Hayes, 1979, Langard, 1980; Hayes *et al.*, 1989;). The most recent among this group is by Hayes (1989), who conducted a study of mortality among 1,879 male workers employed in a New Jersey chromium pigment factory. The study was conducted with a follow-up from 1940 to 1982. Vital statistics from 1,737 (92%) of the eligible cohort members was determined. For all malignant neoplasms, 101 deaths were observed while 108.8 were expected, SMR = 93 (standardized mortality ratio; n. s.). For the entire study group, no significant excess was observed for respiratory cancer or cancer at other sites. However, the total number of years of employment and the total number of years of exposure to chromate dusts were both statistically significantly ($p<0.05$, for trend) associated with an increased risk for lung cancer. The excess risk for lung cancer associated with duration of exposure to chromate dusts was, however, only clearly apparent for subjects followed for 30 years or more after initial employment. For this group, the SMR's were 81, 139, 201, and 321 for the subjects with 0 years, less than 1 year, 1-9 years, and 10+ years of exposure to chromate dusts (p less than .01, for trend), respectively. The risk for digestive cancer was only weakly associated with exposure to chromate dusts (Hayes *et al.*, 1989).

In another study chromium concentrations in the air were measured in seven different workroom environments, where exposure to water soluble hexavalent or trivalent compounds was expected. Urinary excretion of chromium was measured before and after the same arbitrarily chosen working day. End-of-shift urinary chromium and its increase above pre-exposure levels were closely related to the concentration of water soluble Cr VI in the air. The values corresponding to 50 micrograms/m^3 in the air, which is the current threshold limit value in most countries, were 29.8 and 12.2 micrograms/g of creatinine, respectively. Urinary chromium in workers exposed to water insoluble chromates or to water soluble Cr III sulfate was definitely higher than that observed in subjects not occupationally exposed to chromium compounds, but cannot be recommended as a short-term exposure test evaluating job-related hazard (Mutti, 1984).

Workers producing chromate pigments and chromate pigment spray painters and those in the chrome plating industry appear to have a higher risk of respiratory cancer. Several

studies indicate that workers in the chromium alloy welding and ferro-chromium alloy producing industries also have an excess risk for respiratory cancer.

The epidemiological investigations of chronic exposure to Cr VI or to Cr VI and Cr III, by various authors report a higher incidence of respiratory (lung) cancer among humans associated with employment in these various chrome industries (Mancuso, 1975; Langard *et al.*, 1975; Langard and Norseth, 1989; Sheffet *et al.*, 1982; Hayes *et al.*, 1979; Langard, 1990; ATSDR, 1992). Although these cases cite the incidence of lung cancers among workers, a review of such studies suggests that the reports may be faulty and incomplete. Bianchi and Levis (1987) suggest that exposure to Cr VI may only seem to be of significance for cancer in humans. A review indicates that conclusions were made without evaluation of possible concomitant exposures and personal lifestyles. These were not considered or generally unknown, and the conclusions appear to extend beyond what the data suggests.

Langard (1990) recently conducted a review of the epidemiological studies that were published relative to lung cancers and chrome exposures. They were reviewed with reference to carcinogenic potency, significance of solubility and valence state. In such instances however, consideration of smoking and lifestyle as confounding factors are neglected or impossible to ascertain and determine their impact. The support for causality, establishing a chrome exposure to lung cancer appears frequently to be lacking.

For example, studies cited in Japan by Ohsaki *et al.*, (1978), reported 14 cases of lung cancer among 133 (aged 27-64) males exposed for between 10 and 36 years to either chromium trioxide, sodium or potassium dichromate, and/or water soluble trivalent compounds. Smoking was confirmed among twelve (12) of the fourteen (14) lung cancer cases; only one was confirmed as a non-smoker. No other information on the last case is presented. These data suggest that more of the lung cancer cases were associated with smoking but this association was not evaluated for possible tumor causality.

Zorber (1979) reported 11 out of 17 cases of lung cancers associated with chrome alkali production. Three (3) of eleven (11) were exposed only to Cr III and neither Cr VI exposures nor smoking histories were known or considered in the etiology. Twenty (20) other cases of lung cancer were reported by Abe *et al.* (1982). Fifteen (15) of the twenty were confirmed to be heavy smokers. Tsuneta (1982) reported twenty five (25) male lung cancers in chromate factory workers. The incidence was calculated to be 16 times higher than in the general population. Further examination indicated that 20 of the 25 were smokers, while only four were non smokers. Authors report cases of individuals who died of respiratory illness and they cite work exposure to various chromates. However, other variables that may be at play in initiating the disease are not examined nor are they considered in conclusions relating to the disease or to death. Most important is the fact that smoking was heavily implicated in the lung cancer cases.

The major difference between 20 noncancer and 60 lung cancer patients, irrespective of the histological type, was a decreased ability to activate cyclophosphamide in the latter group. This altered responsiveness was considered to be due to the high prevalence of smokers among the lung cancer patients. The significant decrease in cyclophosphamide activation was observed in other groups of smokers. Thus, individual smoking habits were associated with a stimulation of detoxifying mechanisms which is in agreement with the results of a previous study with human alveolar macrophages and must be considered an important factor in the

resulting lung cancers that have been previously associated with chrome exposures (F. L. Petrilli *et al.*, 1986, J. Clin. Invest., 77:1917-1924, 1986, in ATSDR, 1993). It was significant in the case of sodium dichromate exposures. Such an effect was further enhanced by considering only individuals smoking during the last 24 h before collecting lung specimens (DeFlora *et al.*, 1984, 1987). The possibility exists that smoking could have caused the lung cancers, in which case the incidence is far different, or the smoking may have reduced the ability of lung tissue to metabolize the mutagens and to remove the active agent, without possible incidence. This is a confounding variable that casts suspicion on the epidemiology studies and their conclusions.

It is highly likely that concomitant exposures to other materials will have different effects. The plating and welding industries are well known for the possible concomitant exposures to other chemical species (degreasing organics as well as inorganics). Gonzalez *et al.*, (1995) has shown that concomitant exposures of Cr VI to other metals may significantly alter the metabolism of the individual metal species and the ultimate effect. They showed that simultaneous exposure of chrome and arsenic can alter the metabolism and excretion of chrome and arsenic metabolites. Gonzalez *et al.* (1995) studied the effect of administered Dichromate ion on the methylation process of arsenic (As) exposure in Wistar rats. After oral administration of various concentrations of As V and Cr VI, arsenic metabolites (inorganic, methylarsonic acid [MMA] and dimethylarsinic acid [DMA] were separated by cation-exchange chromatography and measured by atomic absorption spectrophotometry. Administration of high doses of As produced enzymatic saturation and non-enzymatic depletion, with decreases in DMA levels. The presence of the dichromate ion supported arsenate methylation and it favored reduction of As V to As III. The Cr VI produced a significant decrease in the total As excreted (Gonzalez *et al.*, 1995). Altering the mechanism(s) affects metabolism and causal factors initiating mammalian toxicity are very important elements that are unavailable and add to the uncertainty of possible conclusions.

4.6 Recent Studies

The ongoing John Hopkins University (JHU) study supports earlier conclusions that chromium (VI) is carcinogenic (OpTech, October 1996a); however, the JHU study is reportedly stronger than many previous studies because it minimized confounding effects (such as smoking), used better collection and analytical methods, and collected more samples for better accuracy. The JHU study measured Cr VI, whereas most previous studies reported carcinogenic effects for total chromium. The JHU study also is better than previous studies because personal samplers were used for 20 to 30 percent of the data (Gibb, EPA, personal communication, October 1996). Personal samplers clipped to the collars of the workers collected samples in the worker's breathing zone. Most of the previously cited reports that indicate adverse effects used other methods of sampling, such as impingers, which measure the chromium concentration for an area. In addition, the JHU study collected 200,000 measurements over the entire length of the study. Overall, the JHU data is reportedly more accurate and is more reflective of the actual dose of Cr VI to which the workers were exposed throughout their employment; it supports the conclusion that the Cr VI is carcinogenic to humans at lower doses than previously reported.

4.6.1 Chrome (III and VI) LOAELs

Based upon a maximum of 49 years exposure to a mixture of Cr VI and Cr III, the lowest adverse effect level (LOAEL) which produced a lung cancer effect was 0.04mg/m^3 (Langard *et al.*, 1980). In the study showing a maximum exposure of 29 years to Cr VI ($PbCrO^4$ or $ZnCrO^4$), the LOAEL was 0.1 mg/m^3 (Sheffet *et al.*, 1982). Langard and Norseth (1975) indicate that for humans exposed to Cr VI ($PbCrO^4$ or $ZnCrO^4$) for a maximum of 19 years, the LOAEL was 0.5 mg/M^3. For a study showing a maximum exposure of 7 years, the LOAEL producing a lung cancer was 0.5 mg/m^3 (Mancuso, 1975). Table 4-1 shows the calculated LOAELs that may be a minimum level to cause lung cancer, based upon Cr VI and/or Cr VI/III occupational exposures.

Table 4-1. Cancer LOAELs and Duration of Exposure.

Duration of Occup. Exposure	Chrome Species	LOAEL mg/m3	Reference
1-49 years	Chrome VI	0.04	Langard, 1980.
1 mo.-29 years	Chrome VI	0.1	Sheffet *et al.*, 1982.
4-19 years	Chrome VI	0.5	Langard & Norseth, 1975.
1-7 years	Chrome VI and III	0.5	Mancuso, 1975.
90 d.- 5 years	Chrome VI and III	0.4	Hayes *et al.*, 1979.

4.6.2. Noncancer Endpoints

No current studies of noncancer effects are available for comparison with past research cited by criteria-setting agencies. The same comments that applied to the cancer effects listed above probably apply to noncancer effects because much better measurement, sampling, and analysis methods are available today.

4.6.3 Chrome (VI) NOAELs:

Toxic responses in the animal studies correlate well with human responses to chrome exposures, in that the respiratory tract and local dermal toxicity were frequently evident in human studies. In humans, exposures of 0.002 to 0.01 mg/m^3 Cr VI were sufficient to cause nasal mucosal atrophy or ulceration, a mild decrease in lung function, epistaxis and rhinorrhea. Based upon these studies of acute effects and exposure levels, and an uncertainty factor of 10 for possible variability or sensitivity, a no adverse effect level (NOAEL) for inhalation exposures was calculated to be 0.001 mg/m^3 (ATSDR, 1992).

NOAELs were also calculated from studies in which animals were exposed to Cr VI levels of:

a.) 0.2mg/m^3, no gastric, renal, or hematological toxicity were expected, and

b.) 0.1mg/m^3 no hepatotoxic effects were expected.

An acceptable exposure value of 0.001 mg/m^3 would be typical using uncertainty safety factors of 10 for extrapolation from animals to humans and 10 for the use of possible variability in toxicity.

5.0 TOXICOKINETICS

5.1 Physiological Based Pharmacokinetic Models (PBPK)

5.1.1. Existing PBPK Models and Target Organs

A physiologically based Pharmacokinetic (PBPK) model of chromium disposition in the rat was developed (O'Flaherty and Radike, 1991; O'Flaherty, 1993a, 1995a; 1996). Absorption, distribution, and excretion of chromium were superimposed on a general physiological model of rat growth and development. The general structure of the model is similar to that of a model of lead kinetics in rats (O'Flaherty, 1991a, 1991b, 1991c, 1993b, 1996). As with lead, when chromium is exchanged between plasma and the bone surfaces in contact with plasma, chromium can become incorporated into actively mineralizing bone, although with much lower efficiency than is observed with lead. Both exchange between plasma and bone surfaces and incorporation into actively mineralizing bone were included in the model. The long residence times of bone-seeking elements required that bone turnover and metabolism be incorporated into physiologically based models for these elements (O'Flaherty, 1995a). The following three mechanisms were potentially important in the overall interchange of bone-seeking elements between blood and bone: (1) rapid exchange at bone/blood interfaces, (2) trapping or incorporation with forming bone and loss with resorting bone, and (3) slow exchange throughout the total bone volume (O'Flaherty, 1995a).

The model considers both Cr VI and Cr III, administered either orally or by inhalation (O'Flaherty and Radike, 1991). It incorporates reduction of Cr VI to Cr III in all tissues including the lung and the GI tract but does not incorporate Cr VI reduction to Cr III in bone. The model takes into account different absorption and reduction rates in the lung and GI tract and different efficiencies of transfer of Cr III and Cr VI into tissues including erythrocytes, where Cr VI is reduced to Cr III and retained for an extended period of time (O'Flaherty, 1993a).

Parallel absorption and disposition schemes for Cr VI and Cr III were linked in the model by reduction processes occurring throughout the body, including the lung and GI tract (O'Flaherty, 1996). Examination of a number of data sets from studies in which chromium salts were administered to rats intravenously, orally, or by intratracheal instillation established that intravenous administration, on the one hand, and oral and intratracheal administration on the other hand, resulted in different disposition patterns (O'Flaherty, 1996). The model was calibrated on the basis of published oral and intratracheal kinetic studies in rats given soluble Cr III and Cr VI salts. In the most complete of these studies, chromium concentrations were monitored in individual tissues for 42 days following intratracheal administration of a soluble Cr VI salt. Urinary excretion delay was included in the model to fit excretion data from two other intratracheal studies. Model predictions of blood chromium concentrations were compared with the results of a published kinetic study in which rats were administered a soluble Cr VI salt by inhalation (O'Flaherty, 1996).

Concerning the researcher's assessment of the completeness and effectiveness of her model for predicting tissue concentration, O'Flaherty (1996) reported that "the behavior of the model in several specific respects strongly suggests that it reflects physiologic behavior with

reasonable fidelity." Further, O'Flaherty (1996) indicated that the model accounts for most of the major features of Cr VI and Cr III kinetics in the rat, including reduction of Cr VI to Cr III. It performs reasonably well in simulation of a rat inhalation exposure and can also predict tissue concentrations following chronic exposure.

Another model was developed by Thomann *et al.* (1994) for Cr VI using oral ingestion in the rat. In Thomann *et al.* (1994), rats were exposed to 100 ppm Cr VI in their drinking water for 6 weeks, followed by a 140-day period of depuration. Tissue concentrations of chromium at the end of the 6-week exposure period were greatest in the bone, spleen, and kidney with lower concentrations present in the liver and blood. The overall kinetics of chromium depuration from the tissues were relatively slow, especially for the largest compartment, which included bone. A three-compartment model was developed to fit the data.

Thomann *et al.* (1994) reported that the model "provides a reasonable representation of the data. The depuration of the three compartments is reproduced, as is the limited data taken during the uptake phase. The principal location of the chromium mass in the storage compartment is captured, as is the behavior of the liver-kidney-spleen compartment."

In another model, Lim *et al.* (1983) studied the distribution and kinetics of intravenous ^{51}Cr in six human subjects using a whole-body counter and plasma counting. Principal concentrations were found in the liver, spleen, soft tissue, and bone. The data were fit to a model consisting of a plasma pool in equilibrium with three different compartments.

Lim *et al.* (1983) reported that the functional model did not describe the complete kinetics of Cr III in individual organs, but that it adequately described the kinetics in the functional compartments. Lim *et al.* also reported that the model adequately describes the kinetics of ^{51}Cr administered as $CrCl_3$ and that it should be useful in assessing the metabolism of Cr III, its nutritional requirement by humans, and its importance in disease processes such as diabetes.

Borguet *et al.* (1996) used the model developed by Lim *et al.* (1983) for healthy people and adapted it to the specific situation of the continuous ambulatory peritoneal dialysis (CAPD) patient. For this purpose, three CAPD patients were submitted to an acute ^{51}Cr-labeled dialysis dwell of 6 hours. Borguet *et al.* (1996) also reported that the experimental pharmacokinetic data were in close agreement with the values predicted by the modified functional model for Cr III kinetics and metabolism. According to this model, the effect of long-term CAPD treatment (10 years) should result in an accumulation of chromium with a factor of 100 over normal values in those organs, especially liver and spleen, known to have a slow exchange of chromium with the central plasma compartment. They reported that this predicted and dramatic increase was in close agreement with the chromium concentrations found in liver tissue of three patients who died after a variable time on CAPD.

In summary, the four models summarized herewith generally predict tissue concentrations for the laboratory rat and have been applied to patients in clinical settings.

5.1.2 Parameters Used in PBPK Models

Parameters for chromium in the rat were reported by O'Flaherty (1996) and O'Flaherty and Radike (1991). Parameters included values for absorption, distribution, excretion, and reduction of Cr VI to Cr III for all tissues except bone and lag time for excretion of urine. Thomann *et al.*, 1994 also reported these parameters for their model. Thomann administered 100 ppm Cr VI to rats in the drinking water for the modeling study.

5.1.3 Validity of the PBPK Models

As reported by O'Flaherty (1996), who published the partial validation of a physiologically based model of Cr VI and Cr III kinetics in the rat, the model for chromium accounted for most of the major features of Cr VI and Cr III kinetics in the rat, including reduction of Cr VI to Cr III. It performed reasonably well in a simulation of rat inhalation exposure and could also predict tissue concentrations following chronic exposure.

Two important uncertainties relating to the kinetic behavior of chromium were identified. First, only limited information regarding the fractional absorption of chromium from environmental sources is available. Since even soluble salts of Cr III and Cr VI were not particularly well absorbed, either from the lung or from the GI tract, O'Flaherty (1996) suggested that bioaccessibility of chromium to absorption processes was the most important single characteristic for determining the potential absorption and toxicity of a chromium source. The availability or absorbability of chromium from environmental sources is unknown for all but a few chemically defined salts. Second, little is known about the importance of bone as a reservoir and continuing source of internal exposure to chromium. The mechanism(s) by which chromium is incorporated into bone and the dependence of bone chromium uptake on age and physiologic status are important features of any complete model of chromium kinetics.

To determine how good the model was at predicting the tissue concentration, O'Flaherty (1996) compared the observed and predicted tissue concentrations of Cr VI and Cr III after administering chromium in the drinking water to rats for 1 year starting at age 34 days. Simulated tissue concentrations were compared to observed tissue concentrations using the data of MacKenzie *et al.* (1958). Tissue concentrations were reported for bone, kidney, and liver. O'Flaherty (1996) reported that the model performed only moderately well in simulating one-year oral exposures of rats to Cr III and Cr VI. She further suggested that the MacKenzie *et al.* (1958) tissue concentration data in Table 4 (Attachment A) supported a dose-dependent kinetic linearity on chronic exposure, particularly for liver and kidney, which is not taken into account by the model.

The percent difference (which equals observed tissue concentration/predicted tissue concentration x 100) was calculated from MacKenzie *et al.* (1958) data for each organ. For liver, the percent difference varied from 20.0 to 82.6 and the predicted liver concentration was always higher than the observed value. The model performed best at predicting bone chromium because the percent difference varied only from 0.7 to 3.9. The biggest differences were observed for the kidney, where the percent difference varied from 2.0 to 90.6. The fact that

there are differences between predicted and observed tissue concentrations suggests that other undetermined factors are responsible for these differences and should be taken into consideration in the model.

The model of Gargas and Andersen (1988, as cited in Yang, 1992) showed modeled and actual tissue concentrations coinciding exactly and there was an exact fit with the modeled concentration superimposed over the actual concentration. Before making the correction for suicide inhibition, the modeled tissue concentrations were always greater than the experimental (actual) tissue concentrations. Similar to the concentrations described in the model of Gargas and Andersen (1988, as cited in Yang, 1992), modeled liver concentrations were always higher than the observed tissue concentrations by 10.0 to 82.6%, using the O'Flaherty (1996) model and the MacKenzie *et al.* (1958) data for chromium ingested in the drinking water. For chromium, reductive metabolism of Cr VI by biological reductants (including glutathione, cysteine, ascorbate, hydrogen peroxide, and flavoenzymes) and the formation of radicals have been reported in the literature (Sugiyama, 1991) (see OpTech, 1996a, for further details of this reductive metabolic process). The unique metabolism of chromium in cells may help explain differences between simulated and actual chromium tissue concentrations reported by O'Flaherty (1996). If chromium metabolism were more accurately incorporated into the model, it might better reflect the actual tissue concentration.

That there is room for refinements in the O'Flaherty (1996) model for chromium is further supported by the fact that simulated tissue concentrations in the liver are, with the exception of one data point, greater than actual tissue concentrations when the model is used to predict the Weber (1983) tissue data. Weber administered one dose of soluble ^{51}Cr VI salt intratracheally and measured the chromium in lung, plasma, whole blood, liver, kidney, GI tract and contents, other tissues, and the residual carcass for a period of 42 days after administration. All the data points for the simulation except one are greater than monitored liver concentrations (O'Flaherty, 1996). Refinements in obtaining actual monitored data for tissue metabolism of chromium may help to optimize the fit. For other tissues monitored by Weber (1983), the model performs reasonably well when predicting tissue concentrations.

O'Flaherty (1996) used data from other researchers (Bragt and van Dura, 1983; Edel and Sabbioni, 1985; Langard *et al.*, 1978) in her model. Without making "corrections" for chromium metabolism, similar to those mentioned above, O'Flaherty reported that her model predicted the actual tissue concentrations with reasonable fidelity, although there were some differences indicating that some, as yet, unknown factors may be incorporated into the model.

For the Thomann *et al.* (1994) model, the simulation has a good approximation of the actual compartment concentrations of chromium for bone and carcass as well as for liver, kidney, and spleen. Although the compartment and modeled concentrations are not exactly superimposable, the two closely approximate one another. Generally speaking, the actual compartment concentrations exceed the simulated concentrations for each of the tissues. However, for blood, the simulated dose of chromium and the observed data do not approximate one another very well. Most of the actual data points for the blood greatly exceed the simulated data and are clustered between 40 and 75 days. The actual data points do not extend out to 200 days as do the simulation data points for the other tissues. This suggests that other factors are involved that have not been taken into consideration in developing the model. It has been suggested that more data points be obtained for the blood for a longer length of time.

In summary, the PBPK models proposed by Thomann *et al.* (1994) and O'Flaherty (1996) predict the actual compartment chromium concentrations reasonably well using either the oral or inhalation routes of exposure in the rat; however, there is room for refinement in both models.

5.2 Absorption

5.2.1. Tissue Distribution and Absorption Rates by Route of Exposure

Absorption and clearance from the lung was determined by many factors (O'Flaherty, 1993a; O'Flaherty and Radike, 1991). For a more comprehensive review of pulmonary absorption and clearance, see O'Flaherty and Radike, 1991. The range of half-lives reported for clearance of chromium from the lung (Bragt and van Dura, 1983 and Weber, 1983, as cited in O'Flaherty, 1993a) suggested that chromium was present in the lung in different states from which it was cleared at different rates. That lung-to-GI tract transfer was important was shown by Langard *et al.* (1978), who observed rapid increases in fecal chromium during 6-hour inhalation exposures of rats to dusts of a moderately soluble Cr VI salt. Bragt and van Dura (1983) showed that the amount of chromium appearing in the feces increased sharply as the solubility of the Cr VI salt decreased.

Regarding Cr III and Cr VI, Edel and Sabbioni (1985, as cited in O'Flaherty and Radike, 1991) demonstrated that chromium was much more efficiently absorbed in rat lung from a soluble Cr VI salt than it was from a soluble Cr III salt. At least some of the Cr VI reaching the systemic circulation from the lung persists as Cr VI until it reaches red cells (O'Flaherty and Radike, 1991). When a Cr III salt and a Cr VI salt were given intratracheally and the distribution of chromium between plasma and red cells was measured 24 hours later (Edel and Sabbioni, 1985, as cited in O'Flaherty and Radike, 1991), 15% of the blood chromium was found in the red cells after Cr III administration, but 61% was found after Cr VI administration. Thus, a significant fraction of the absorbed Cr VI had become associated with the red cells as Cr VI before it could be reduced to Cr III.

The kinetics of clearance of chromium salts from the lung suggested that systemic absorption is a rapid process that may be complete within an hour after a single intratracheal dose (Bragt and Van Dura, 1983, as cited in O'Flaherty and Radike, 1991).

Particle size distribution of a chromium-containing aerosol is also a critical factor, since it determines localization of the chromium within the lung; unfortunately, little is known about this distribution (O'Flaherty and Radike, 1991).

No data is currently available on dermal absorption and tissue distribution. Cr III and Cr VI are absorbed to different extents from soluble salts in the GI tract of rats (O'Flaherty and Radike, 1991). By comparing concentrations of radioactive Cr in the blood 4 to 10 days after intravenous or oral administration of hexaaquochromium trichloride $[Cr(H_20)_6)Cl_3]$, Mertz *et al.* (1965, as cited in O'Flaherty and Radike, 1991) judged that 2 to 3% of the oral dose had been absorbed.

MacKenzie *et al.* (1959, as cited in O'Flaherty and Radike, 1991) monitored radiolabel in blood, tissues, urine, and feces of adult rats given single doses of Cr VI as Na_2CrO_4 by stomach tube. The amount of chromium excreted in the urine by day 14 was greater when the rats had been fasted prior to chromium administration (6%) than when they had not (3%). Comparison of average levels of radiolabel in blood, erythrocytes, and plasma after administration of Cr VI or Cr III demonstrated that Cr III was absorbed approximately one-tenth as well as Cr VI and was absorbed less efficiently in nonfasted rats than it was in fasted rats. Thomann *et al.* (1994) reported that between 1 and 11% was absorbed in the body after rats drank 100 ppm Cr VI in the drinking water; percentages varied depending on the compartment and the number of weeks after exposure.

Hopkins (1965, as cited in O'Flaherty and Radike, 1991) and Mertz *et al.* (1964, as cited in O'Flaherty and Radike, 1991) studied the distribution of Cr III administered intravenously as $^{51}CrCl_3$. Hopkins monitored adult and weanling rats for up to 4 days following chromium administration. He found that the spleen and kidney continued to accumulate chromium over the 4-day observation period and that the liver, testis, and epididymis lost chromium slowly. In contrast to the findings of Hopkins, MacKenzie *et al.* consistently reported slow loss of chromium from liver, kidney and spleen (MacKenzie *et al.*, 1959; Bragt and van Dura, 1983; Edel and Sabbioni, 1985). A relatively large fraction of chromium is taken up by the bone marrow in rabbits (Kraintz and Talmage, 1952, as cited in O'Flaherty and Radike, 1991) and rats (Bragt and van Dura, 1983). This general distribution suggested that chromium was trapped by the reticuloendothelial system (Kraintz and Talmage, 1952). Kidney, spleen, and bone marrow and, to a lesser extent, liver, were cleared of their chromium more slowly than were other tissues.

Witmer (1991, as cited in O'Flaherty and Radike, 1991) reported that bone is a significant repository for chromium after oral or intraperitoneal administration of chromate salts to rats. Weber (1983) found that after administration of a radiolabeled chromate salt by intratracheal intubation, the radiolabel was found to be located primarily in the epiphyseal region of the long bones. The distribution of radiolabel was reported to be similar to that seen after administration of bone-seeking tracers. Kraintz and Talmage (1952) also noted localization of radiolabel in the epiphyses of long bones after intravenous administration of $^{51}CrCl_3$ to rabbits.

Hopkins (1965, as cited in O'Flaherty and Radike, 1991) observed that the bone of young growing rats tended to concentrate chromium with time (7% increasing to 12% of the dose) after an intravenous injection of $^{51}CrCl_3$, while the bone of mature rats acquired less label initially (4% of the dose), and the amount of chromium in mature bone did not increase with time. These observations suggested that incorporation of chromium into bone is associated with growth of new bone (O'Flaherty and Radike, 1991). It was inferred that rapid surface exchange of blood and bone chromium accounted for approximately 4% of the dose, while the additional incorporation of chromium into bone of growing rats was due to bone growth (O'Flaherty and Radike, 1991).

In the Thomann *et al.* (1994) study, in which 100 ppm Cr VI was administered to rats in the drinking water for up to 12 weeks, it was reported that total chromium concentrations were greatest in the kidney, followed by the spleen, liver, and blood. In all organs except for blood, chromium concentrations increased with length of exposure, indicating that the rate of absorption exceeded the rate of excretion in these tissues. In another experiment where the rats were exposed for up to 20 weeks, highest concentrations were seen in the bone, spleen,

and kidney with lower concentrations present in the blood, liver, and remaining carcass. After a 42-day exposure period, the carcass and bone accounted for the most significant portion of the body burden mass of chromium over time. It was also indicated that different tissues showed different dynamic behaviors. The liver showed a biphasic loss while the other tissues, such as the spleen, kidney, and bone, did not. The blood concentration declined below detection at about 35 days after depuration. Thus, it appeared that under chronic dosing conditions, chromium accumulated in a long-term storage site which slowly released chromium to the well-perfused tissues, i.e., the liver, kidney, and spleen (Thomann *et al.*, 1994).

5.2.2. Elimination and Excretion Rates

Approximately 21 to 22% of an intravenous dose of a soluble salt of either Cr III or Cr VI is excreted in the urine in the 24 hours following administration, irrespective of its oxidation state (O'Flaherty, 1993a; O'Flaherty and Radike, 1991). Not all chromium is excreted in the urine. Studies by Cikrt and Bencko (1979) and Cavalleri *et al.* (1985) (both cited in O'Flaherty, 1993a) demonstrated that 2 to 3.5% of an intravenous dose of Cr VI is excreted in the bile, whereas less than 1% of an intravenous dose of Cr III is excreted in the bile. Larger fractions are excreted in the feces, demonstrating that there is significant transfer of chromium from the intestine to the intestinal tract contents. If the gastrointestinal and biliary excretion data of Cikrt and Bencko (1979) are combined with the urinary excretion data of MacKenzie *et al.* (1959) to estimate fractional absorption from the GI tract, the calculation suggests approximately 17% absorption of soluble Cr VI and 6 to 7% absorption of soluble Cr III by fasted rats (O'Flaherty, 1993a). For the Thomann *et al.* (1994) model developed using rats that ingested Cr VI in the drinking water, loss via the feces was assumed to be small because after oral exposure ceased, the main excretion was considered to occur via the urine.

5.2.3 Valence Conversion Dynamics

Enzymatic and nonenzymatic reduction of Cr VI to Cr III occurs in virtually all tissues and body fluids, including saliva, gastric juice, and alveolar fluids (Petrilli and DeFlora, 1988, as referenced in O'Flaherty and Radike, 1991). Cavalleri *et al.* (1985) reported that no appreciable reduction of Cr VI occurs in rat bile. The model also does not include reduction of Cr VI to Cr III in bone (O'Flaherty and Radike, 1991). In rat whole blood and plasma *in vivo*, the half-life of intravenous Cr VI is less than 1 minute (Cavalleri *et al.*, 1985).

5.2.4 Influences on Metabolism, Excretion, and Elimination

Several factors influence the metabolism, excretion, and elimination of Cr VI and Cr III. Results of studies in which rats were injected with ^{51}Cr in various chemical forms indicated that the behavior of the radiochromium varied as a function of chemical form prior to injection, the solvent used, and the route of administration (Visek *et al.*, 1953). The isotope was given in the trivalent state as chloride and chromite in solutions buffered by acetate and citrate. Hexavalent chromium was given as a solution of sodium chromate. Doses were administered by the

intravenous, oral, intraperitoneal, or intratracheal routes. Trivalent ^{51}Cr differed in its physiological behavior from the hexavalent form because the former is bound by plasma proteins and the latter by erythrocytes (Visek *et al.*, 1953). The trivalent chromium showed increased excretion and decreased absorption by the reticuloendothelial system. Researchers explained this on the basis of the colloidal nature of the chromite, the protein binding of the chromic chloride, and the complexing action of the buffers.

In addition, Visek *et al.* (1953) reported species differences between rats and rabbits regarding the behavior of chromium. Kraintz and Talmage (1952, as cited in Visek *et al.*, 1953) observed a species difference between rats and rabbits in the behavior of ^{51}Cr buffered with acetate. In this study, rats showed the highest concentration of ^{51}Cr in the bone at 24 hours, whereas rabbits showed the highest concentration in the spleen. Visek *et al.* (1953) also reported that in rats, the organ of maximum absorption following intravenous injection of acetate buffered $^{51}CrCl_3$ was the bone.

6.0 BIOCHEMICAL MECHANISMS

Although the physical distinction between "soluble" and "insoluble" is arbitrary and has been subject to criticism, the two Cr VI forms appear to belong to different health hazard categories (Zatka, 1985). For example, the National Institute for Occupational Safety and Health (NIOSH) differentiates between two forms of hexavalent chromium in airborne contaminants; the water soluble alkali metal and ammonium chromates, considered toxic but not carcinogenic and the water insoluble chromates, believed to be carcinogenic (Zatka, 1985). Hexavalent chromium rarely occurs in nature apart from anthropogenic sources because it is readily reduced in the presence of oxidizable organic matter; however, hexavalent chromium compounds that occur most commonly in the form of chromate and dichromate are stable in natural waters because of the low concentration of reducing matter (EPA 1984). With the exception of a few compounds, hexavalent chromium exists as oxo-species that are strong oxidizing agents. The oxidizing potential of chromate ions depends on the pH of the media. These ions are much more powerful oxidizing agents in acid solutions than in basic solutions (ORNL/EPA 1978).

With the exception of acetate and nitrate salts, the trivalent chromium compounds are generally insoluble in water. In most biological systems, chromium is present in the trivalent form (Anderson 1981). The physical or chemical forms and the mode by which Cr III compounds are incorporated into biological systems are poorly characterized. Inorganic Cr III compounds display little or no *in vitro* insulin-potentiating activity, but upon chelation with certain organic compounds, acquire significant insulin-potentiating activity. Although the structure is not known, GTF, an insulin-potentiating factor present in normal humans, was identified as a chromium complex of nicotinic acid. A biologically active form of chromium, isolated from brewer's yeast, was found to contain Cr III, nicotinic acid, and possibly the amino acids glycine, cysteine, and glutamic acid (Anderson 1981).

In aqueous solutions, Cr III forms a hexaaquo complex $[Cr(H_2)_6]^{3+}$ of reasonable stability. In alkaline solutions or when heated, the hexaaquo Cr III readily undergoes the following polymerization through the formation of hydroxy- or oxo-bridged compounds (EPA 1984).

$$Cr(NO_3)_3 \rightarrow [Cr(H_2O)_6]^{3+} \rightarrow \text{heat or } OH^- \quad [Cr(OH)(H_2O)_5]^{2+} \text{ heat and standing}$$

$$[(H_2O)_5\text{-}Cr\text{-}O\text{-}Cr(H_2O)_5]^{4+} \leftarrow [(H_2O)_4\ Cr \begin{matrix} OH \\ \\ OH \end{matrix} Cr(H_2O)_4]^{4+}$$

Such ions may cross-link protein fibers and may play an important part in the chemistry of tanning (EPA 1984). Hexaaquo Cr III complex does not exist in biological systems because it undergoes olation and polymerization. Once the Cr III compounds undergo olation and polymerization, they are rendered biologically inactive. Only chelated Cr III compounds that remain in solution are bioavailable (Hertel 1986). Some organic and inorganic ligands present in physiological systems can keep Cr III in solution by preventing the olation and polymerization process through chelation, thereby allowing Cr III to perform its physiological functions (Anderson 1981).

7.0 DATA GAPS & RECOMMENDATIONS

This section discusses the major assumptions of the exposure assessment, the uncertainty associated with each, and how this uncertainty is expected to affect the cancer risk. Also included are the sampling methods and procedures, analytical methods, and measurements and methods for analyzing data.

7.1 Monitoring Data

Monitored data may or may not be reflective of chromium levels to which Navy personnel are exposed. For instance, if workers wear respiratory protection, then the monitored data is not reflective of the actual chromium concentration to which they have been exposed. In this case, there should be no cancer risk since there was no chromium exposure. If personnel do not wear respiratory protection, then the monitored data is reflective of the actual chromium concentration to which they have been exposed, which may increase cancer risk. Current quantitative risk assessments have been based on partial personal monitoring (ICF Kaiser, 1995) using a mixture of speciation chemistry and assumptions. Epidemiological studies with more complete monitoring data suffer from too short a follow-up period on the exposed population (Pastides *et al.*, 1994). Gochfeld and Witmer (1991) identified speciation of valence state and solubility along with interconversion as problem areas requiring added research. Speciation may be of particular importance in processes not related to chromate production. Currently, quantitative risk levels are based on production plant exposures, generally in older facilities, and not on welding or chromate painting processes. Better speciation of soluble and insoluble Cr VI in these later processes is needed.

In this assessment, occupational cancer risk calculations were performed for military personnel who used respiratory protection and those who did not. All Cr VI exposures were assumed to have equal cancer relative risk factors regardless of the bioavailability of the Cr VI by route of exposure.

Chromium is a difficult element on which to obtain reliable data. Only recently have reliable methods been used to measure Cr VI in different media. The ID-2I5 method used in this assessment to measure Cr VI is difficult to implement in the laboratory. The problem of interconversion of air samples on PVC cassettes or extraction and digestion from matrices has not been resolved (Gochfeld, 1991).

7.2 Uncertainties in Toxicology Studies

There is no carcinogen potency factor (CPF) or q* currently available to quantitate dermal chromium cancer effects, but there are dermal effects from chromium. Animal studies for chrome toxicity have been equivocal. Inhalation studies have not induced significantly increased tumors in laboratory animals but Cr VI has been shown carcinogenic by injection, intrabroncial, intrapleural or intratracheal implantation. Calcium chromate has been the only consistent agent but other metal chromates have demonstrated tumors (EPA, 1988). Non-

cancer toxicity retains some uncertainty (ATSDR, 1993). Bioavailability and kinetic distribution uncertainty and intercellular mechanisms require added research (Gochfeld, 1991). Chromium exposures have been associated with occupational asthma related to soluble Cr III (Park *et al.*, 1994) and renal function from soluble Cr VI (Wedeen and Qian, 1991 and Wang *et al.*, 1994). Dose response assessments for these non-cancer effects retain some uncertainty.

7.3 Uncertainties in CPF

The following are uncertainties in the Mancuso (1975) study and the CPF (or q*) value used to calculate LADD:

A. Total chromium rather than Cr VI was used to estimate CPF;
B. Smoking habits of workers were not taken into account when calculating CPF;
C. Monitored data taken near the end of the Mancuso study was used to estimate exposures throughout the entire study;
D. The number of cancers (61%) used to calculate the CPF in his study were too high (personal communication, R. Ratney, Mabbitt & Associates)

Ratney reported that these factors "cast suspicion on the study." He indicated that Mancuso (1975) may have seen lung cancers that really weren't there, that perhaps people who died of cancer were not included in the database, or that subjects of the study may have left the company ("were lost to followup").

The Hayes cohort was found to be consistent with Mancuso for respiratory cancers (ICF Kaiser, 1995). Both studies were base on chromate production facilities. Chromates have been reported as respiratory cancer risks for both soluble and insoluble forms of Cr VI but the Sjogern cohort of welders failed to demonstrate statistically significant increases in cancer rates, although the observed deaths were 5 when 2 were expected in the 110$\mu g/m^3$ exposure group (ICF Kaiser, 1995). Cancer potency for insoluble Cr VI and other chrome compounds is uncertain. A reliable inhalation carcinogenesis model for Cr VI remains to be developed (Gochfeld, 1991).

7.4 Recommendations:

Due to the performance of chromium compounds and the difficulty to develop effective engineering emission controls, it is likely that chromium exposures will continue to be a risk management problem for the military. Effective speciation monitoring is recommended on various military processes involving chromium to identify potentially high risk processes and to aid in the assessment of the validity of a single Cr VI cancer risk factor for all Cr VI compounds. The Navy has implement such a system for chrome valence speciation but improved information on process parameters and compounds involved may be useful.

The role of bioavailability in pulmonary cancer risk factor for chromium VI compounds seems to require added research. Existing epidemiology and PBPK models suggest the cancer

potency may vary with solubility and form of Cr VI. Uptake and distribution of compounds generated in critical military processes may be important factors in risk management decisions.

The JHU epidemiology study has not yet been published but information released suggests they are addressing some of the uncertainties in the current quantitative risk assessments. Follow-up of other epidemiology studies is continuing and may give better insight into processes other than chromate production. Quantitative dose response assessments from these studies, along with information on the exposure profiles on these processes, may be important to compliance and risk management actions. A critical review of this study is recommended to include assessment of chrome speciation used in the dose response determination.

Certain stainless-steel welders (Bonde, 1990) had very high chromium residuals in seminal fluids. Due to concerns over reproductive risks, this observation may suggest added research as to cause and effect.

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