HEALTH ASSESSMENT FOR CHROMIUM

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1. EXECUTIVE SUMMARY

Chromium is a substance that can exist as several different chemical species. The trivalent form (Cr(III)) and the hexavalent form (Cr(VI)) are believed to be the biologically active species, but their health impacts are not identical, in part because Cr(VI) readily penetrates biological membranes while Cr(III) generally does not. Cr(III) is an essential trace element while Cr(VI) compounds are associated with cancer induction.

Exposure to chromium in occupational settings has resulted in nasal septum perforation, respiratory irritation, and skin reactions. However, at current ambient chromium levels, no acute or noncarcinogenic chronic adverse health effects, with the possible exception of adverse reproductive effects, are expected to occur. Chromium has demonstrated adverse reproductive effects, including teratogenesis in animals. However, experimental data are inadequate to assess potential human reproductive risks from ambient exposures

Genotoxicity tests, animal cancer bioassays, and epidemiologic studies provide evidence for a carcinogenic response to chromium exposure. All short-term assays reported show that Cr(VI) compounds possess genotoxic capabilities, while tests of Cr(III) compounds are generally negative or generate positive results at much higher doses than those used in Cr(VI) tests. Animal studies show similar findings with respect to cancer as the outcome, i.e., the evidence for the carcinogenicity of Cr(III) is weak, but several hexavalent chromium compounds have demonstrated statistically significant increases in cancer incidence rates. No direct inhalation animal studies have resulted in statistically significant increases in tumor incidence. Rather, the evidence from animal studies supports carcinogenesis at the site of contact. Several epidemiologic studies have shown a strong high association between chromium exposure in the workplace and respiratory cancer. However, these studies were not designed, nor in general did their authors attempt, to systematically identify noncarcinogenic adverse health effects or link the increased cancer mortality to a specific form of chromium.

In reviewing the health information on chromium, the International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence to demonstrate the carcinogenicity of chromium in both animals and humans. The Department of Health Services (DHS) concurs with these findings and believes, at this time, that there are inadequate data to confirm or refute the carcinogenic potential of trivalent chromium. In addition, the DHS has not found compelling evidence demonstrating the existence of a threshold with respect to chromium carcinogenesis.

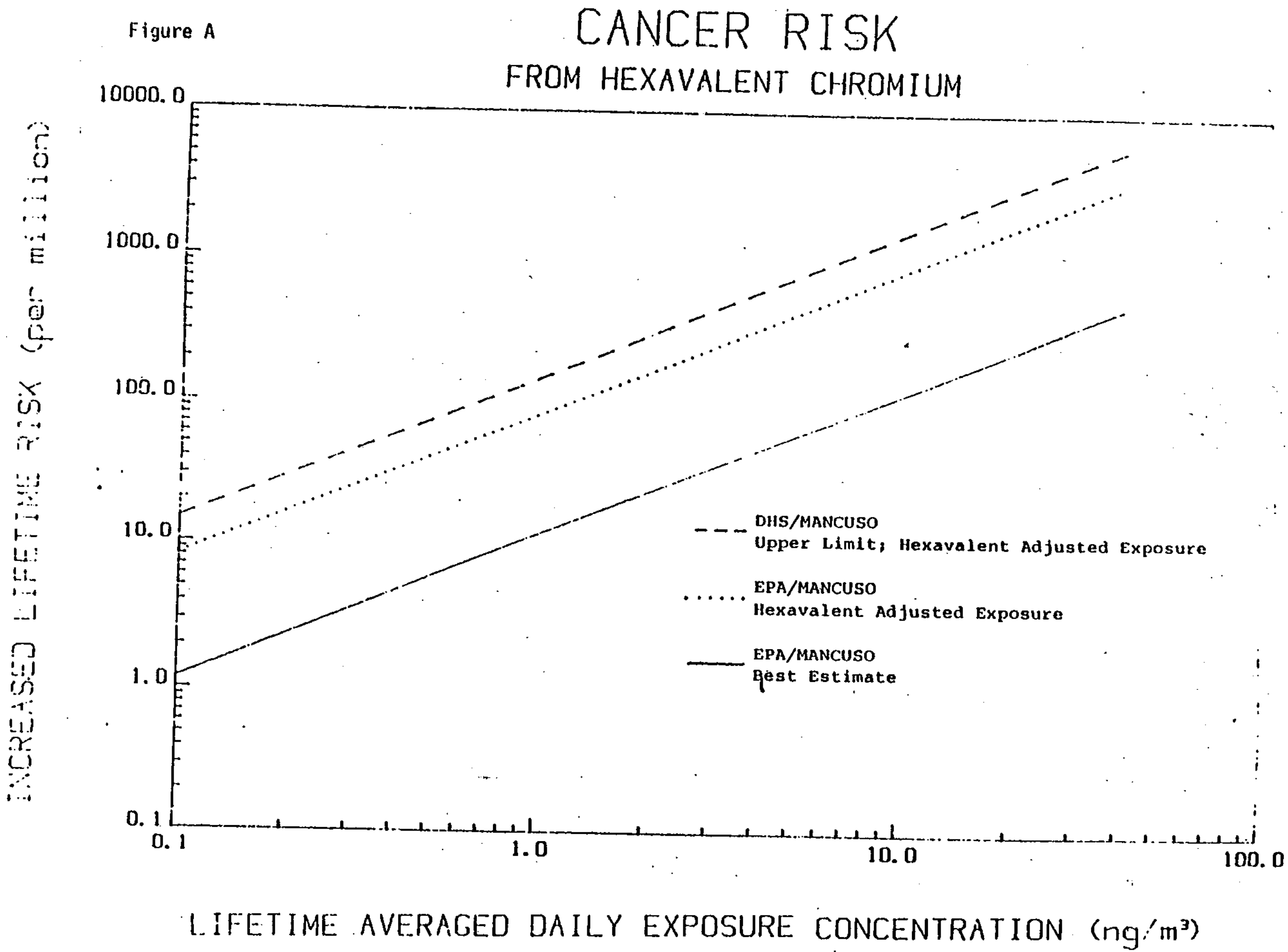
The staff of DHS recommends adopting the risk assessment performed by the Environmental Protection Agency (EPA), in which a linear nonthreshold model was applied to the epidemiologic study (Mancuso, 1975) judged to be most methodologically sound and to contain the best exposure data to derive dose-response curves for hexavalent chromium. Data from animal studies were judged to be inadequate for quantitative risk assessment by the staff of DHS.

One of the strengths of the DHS risk assessment is its reliance on human airborne exposures, which obviates uncertainty related to extrapolation between species and from noninhalation routes of exposure. In addition, the use of a linear nonthreshold extrapolation model yields risk estimates that are public health protective. Conversely, there are limitations in the epidemiologic data which create uncertainty in the risk assessment. Uncertainty enters the risk assessment by virtue of extrapolating from high occupational exposure levels to low ambient levels, the reliance on imprecise historical exposure levels as the basis for estimating potency, the lack of data differentiating between chromium oxidation states and compound specificity, and the lack of control for potential confounding factors (e.g., cigarette smoking).

However, making certain assumptions, it is possible to describe dose-response curves for hexavalent chromium. Based on the results derived from application of the linear nonthreshold model and the Mancuso data, the staff of <u>DHS recommends that the Air Resources Board consider the increased lifetime carcinogenic risk from a continuous lifetime exposure to hexavalent chromium as falling in the range of 12 to 146 cancer cases per nanogram hexavalent chromium per cubic meter of air per million people exposed (12-146 cancers/ng/m^3/million)</u>. This range is illustrated in Figure A, where the solid line represents the curve based on the EPA assessment using total chromium as the exposure, the dotted line is based on the EPA assessment adjusting for the hexavalent chromium fraction of the exposure, and the dashed line was generated by taking the upper limit of the 95% confidence interval for carcinogenic risk due to chromium and adjusting for the hexavalent fraction of the workplace exposure. There are not, however, sufficient data from this or other epidemiologic studies to estimate the risk of specific hexavalent compounds for airborne exposures.

The risk model and potency estimates can be applied to populations living near point source emitters of hexavalent chromium as well as to the general population. In estimating risks to populations around such "hot spots", however, it should be noted that while the excess theoretical cancer risk among individuals most heavily exposed can be considerable (e.g., .006), the number of people so exposed may be relatively low (e.g., a few thousand people) and therefore the actual number of additional estimated cancer cases will also be relatively low.

Figure A



CANCER RISK
FROM HEXAVALENT CHROMIUM
10000.0
1000.0
100.0
10.0
1.0
0.1
INCREASED LIFETIME RISK (per million)
DHS/MANCUSO
Upper Limit; Hexavalent Adjusted Exposure
EPA/MANCUSO
Hexavalent Adjusted Exposure
EPA/MANCUSO
Best Estimate
0.1
1.0
10.0
100.0
LIFETIME AVERAGED DAILY EXPOSURE CONCENTRATION (ng/m³)

This document presents an evaluation of the health effects resulting from exposure to chromium compounds. The purpose of this undertaking was to determine if exposure to chromium at current ambient levels is likely to produce adverse effects on human health. To achieve this objective, data on the chemistry, toxicology, and epidemiology of chromium were reviewed by the staff of the California Department of Health Services. Salient features of this review are presented and a quantitive risk assessment based on the carcinogenicity of hexavalent chromium is provided.

2. CHEMISTRY

The chemistry of chromium has been reviewed elsewhere (EPA, 1984; Hayes, 1980) and only the relevant chemical properties of this substance will be briefly summarized here, relying on the above secondary sources. The issues of principal chemical concern regarding chromium compounds' toxicity are oxidation state and solubility. It is important to bear in mind that the physical and molecular characteristics of the interaction of chromium compounds with biological systems are not well known. Thus, mechanisms of toxicity are uncertain.

Chromium is a transition element (subgroup VI B of the periodic table) with an atomic weight of 52.01. The most common oxidation states are 0,+2,+3 and +6, although it can occur in all oxidation states from -2 to +6. Trivalent (Cr(III)) and hexavalent (Cr(VI)) compounds have been the most extensively studied in biological systems, and with the exception of relatively unstable species, such as Cr(V), are thought to be the only biologically significant forms of chromium.

Cr(III) is the most stable oxidation state, forming coordination complexes that tend to hydrolyze and chelate in liquids. The coordination complexes are exclusively octahedral, with ligands such as water, urea, sulfates, ammonia and organic acids (EPA, 1984). Stable complexes can thus be formed with amino acids, peptides, proteins, nucleic acids and other macromolecules.

Cr(VI) is virtually always bound to oxygen in ions such as chromates (CrO_4^{-2}) and dichromates ($Cr_2O_7^{-2}$). At physiologic pH, the dichromate ion dissociates into the chromate ion. Cr(VI) ions are strong oxidizing agents and are readily reduced to Cr(III) in acid or by organic matter (NAS, 1974). Although chromium is the sixth most abundant element in the earth's crust, Cr(VI) is rarely found in the biosphere because it is so easily oxidized by organic matter (Love, 1983; EPA, 1984).

Certain biological activities of chromium compounds (e.g., carcinogenicity) have been considered to be related to their water solubility. Table 2-1, which lists solubilities of some common chromium compounds, is intended as a reference for subsequent discussions.

Table 2-1. Solubility of Chromium Compounds

Compound	Description of Solubility
Chromite ore (III)*	no information available
Chromium metal (0)	insoluble in water
Barium chromate (VI)	practically insoluble in water (4.4 mg/l at 28°C)
Calcium chromate (VI)	soluble in water (163 g/l at 20°C and 182 g/l at 45°C)
Chromic acetate (III)	soluble in cold water, insoluble in ethanol
Chromic chloride (III)	anhydrous form is insoluble in cold water and slightly soluble in hot water; in its hydrated forms it is very soluble in water (585 g/l) and insoluble in methanol, ethanol, acetone and diethyl ether
Chromic oxide (III)	insoluble in water
Chromic phosphate (III)	slightly soluble in cold water; reacts with most acids and alkali but not with acetic acid
Chromium carbonyl (0)	insoluble in water
Chromium potassium sulfate (III)	soluble in water (243.9 g/l at 25°C)
Chromium sulfate (III)	the heptahydrate is soluble in water (124 g/l at 0°C); the anhydrous salt is slightly soluble in ethanol
Chromium trioxide (VI)	soluble in water (625.3 g/l at 20°C)

Ferrochromium (O)	insoluble in water
Lead chromate (VI)	practically insoluble in water (580 μg/l at 25°C)
Lead chromate oxide (VI)	insoluble in water
Potassium chromate (VI)	soluble in water (629 g/l at 20°C and 792 g/l at 100°C)
Potassium dichromate (VI)	soluble in water (49 g/l at 0°C and 1020 g/l at 100°C)
Sodium chromate (VI)	soluble in water (873 g/l at 30°C)
Sodium dichromate (VI)	soluble in water (2380 g/l at 0°C)
Strontium chromate (VI)	slightly soluble in water (1.2 g/l at 15°C)
Zinc chromate (VI)	soluble in acids and liquid ammonia; insoluble in cold water and acetone; decomposes in hot water
Zinc chromate hydroxide (VI)	slightly soluble in water

*Oxidation state is noted in parentheses adjacent to the name of each substance.

Source: Adapted from IARC, 1980.

3. PHARMACOKINETICS

The absorption, distribution and excretion of chromium compounds have recently been reviewed elsewhere (EPA, 1984). Therefore, relevant issues are only presented in summary form below.

3.1 Absorption

The extent of absorption of chromium compounds via the respiratory tract, gastrointestinal tract or skin depends on the chemical form. In general, Cr(VI) is better absorbed than Cr(III) because of its facility in crossing cell membranes.

Biological membranes have traditionally been considered permeable to Cr(VI), but not Cr(III) (e.g., IARC, 1980). However, with appropriate heterocyclic aromatic ligands, Cr(III) can also enter cells (Warren et al., 1981). The magnitude of a toxic effect resulting from Cr(VI) exposure may depend in part on whether the reduction of Cr(VI) to stable Cr(III) complexes occurs intra- or extracellularly.

3.1.1 Inhalational Deposition and Absorption

Deposition and retention of inhaled chromium depend on the dose, size and solubility of the substance under investigation. Chromium in ambient air has been reported to contain principally respirable particulates, with a mass median diameter of about 1.5 to 1.9 μm (EPA, 1984).

In this size range particles can reach and be deposited in the deep lung (i.e., respiratory bronchioles and alveoli), though a large percentage may be carried out in the exhaled airstream (Langard, 1982). Soluble particulates will be taken up regardless of deposition site; insoluble compounds need to be deposited in the deep lung in order to be taken up (Langard, 1982). Particles deposited on the ciliated bronchial epithelium will be cleared via the mucociliary escalator and swallowed. Clearance of such particles occurs more quickly than those deposited in the alveoli, which will be cleared to some extent by pulmonary macrophages that migrate to the mucociliary escalator or lymph channels.

In a report on the distribution of chromium in the lungs of 35 randomly selected autopsies conducted in a highly industrialized city, Bartsch et al. (1982) found the greatest quantities in interbronchial lymph nodes (reflecting clearance processes), with the remainder distributed over a gradient increasing towards the lung apices, suggesting a relationship to normal breathing. In other words, the asymmetric pulmonary distribution of chromium was due to inhaled chromium, in contrast to the uniform distribution of constitutive elements in the lung, such as potassium, calcium, copper and zinc. Using particle induced x-ray emission analysis, the concentration of chromium averaged 2.85 $\mu g/g$ dry lung tissue (Bartsch et al., (1982). In itself, this number is of little value, since there was no information on the correlation of chromium content with age distribution, smoking habits (chromium is found in cigarette smoke), possible occupational exposures, or concentrations of chromium in the lungs of an "unexposed" population.

There is insufficient information to estimate accurately the percentage of chromium absorption from the lungs (EPA, 1984; Langard, 1982). A few rodent experiments involving exposure to chromium dusts or intratracheal instillation of water-soluble chromium compounds indicate that Cr(VI) compounds are absorbed much more quickly than those containing Cr(III), probably because the latter bind to extracellular macromolecules while the former readily penetrate cell membranes. Langard et al. (1978) reported that after short-term (about 6 hours) exposure to zinc chromate dust (mean concentration was 7.35 mg/m^3, 99% of particles were less than 5 μm in diameter), mean blood concentrations in two rats increased from 0.007 μg/ml to 0.31 μg/ml. After several months of repeated exposures mimicking occupational exposure patterns (6-1/2 hr/day, 5 days/week), mean blood chromium values in 12 rats were about 0.5 μg/ml. Thus, significant absorption of this insoluble chromate occurred relatively quickly: near steady-state values were achieved in a small sample of rats within a few hours' exposure.

Clearance patterns following intratracheal instillation of several water-soluble chromium compounds (sodium chromate (VI), potassium dichromate (VI) and chromic chloride (III)) in guinea pigs were reported by Baetjer et al. (1959). The analytical method could not distinguish Cr(III) from Cr(VI), so that the percentage of Cr(VI) reduced in tissue to Cr(III) could not be ascertained. Ten minutes post-instillation, 15% of the Cr(VI) was retained in the lungs compared to 69% of the Cr(III). At this time 20% of the administered dose of Cr(VI) was found in the blood and 5% in the liver, spleen and kidney. For Cr(III) only 4% was found in the blood and other tissues. The authors assumed that the remainder had been cleared from the lungs up the trachea and swallowed. At 24 hours post-instillation, only 11% of the Cr(VI), while 45% of the Cr(III) remained in the lungs. Another early study cited by EPA (1984) indicates that, at least for intratracheal instillation, a substantial portion of the administered dose (55% of chromic (III) chloride during the first week after exposure) was found in feces, also suggesting substantial tracheal clearance (Visek et al., 1953). (The latter estimate may be too high, since biliary excretion was not investigated.)

3.1.2 Gastrointestinal Absorption

Chromium compounds are poorly absorbed from the gastrointestinal tract of humans and animals, although Cr(VI) is better absorbed than Cr(III). Most studies have traced the fate of orally administered $^{51}Cr\ Cl_3$(III) and $Na_2{}^{51}CrO_4$(VI). Based on fecal analysis or on whole body radioactivity, absorption estimates ranged from less than 0.5% for $CrCl_3$ to about 11% for Na_2CrO_4 in humans and less than 1% to 3% for both salts in rats (EPA, 1984). Others have estimated that up to 3-6% of Cr(VI) may be absorbed by rats (IARC, 1980). Absorption was increased by fasting or duodenal administration (EPA, 1984; Donaldson and Barreras, 1966). The facility with which Cr(VI) crosses cell membranes is not reflected in a significantly higher absorption in the animal experiments, possibly because acid gastric fluids reduce Cr(VI) to Cr(III) (Donaldson and Barreras, 1966) (See Section 3.2). Furthermore, constituents of gastric juices bind Cr(III), inhibiting absorption (Donaldson and Barreras, 1966). In any case, for purposes of the risk assessment in Section 8, gastrointestinal absorption of chromium swallowed after tracheal clearance is not considered to contribute significantly to total chromium absorption.

3.1.3 Dermal Absorption

Dermal absorption of chromium was recently reviewed (Polak, 1983). The principal relevant aspects are that:

(1) Cr(III) binds to skin components, particularly in the epidermis, and thus generally does not penetrate intact skin (but see #(4), below). However, all Cr(III) salts tested penetrate skin stripped of the stratum corneum.

(2) Cr(VI) compounds in aqueous solution readily penetrate intact skin and are systemically absorbed at high concentrations (1%), but do not pass beyond the skin at lower concentrations (0.1 to 0.001%).

(3) Some Cr(III) salts (e.g., $CrCl_3$) penetrate intact skin almost as well as Cr(VI) compounds.

(4) Cr(VI) is reduced to Cr(III) by skin constituents, particularly proteins containing sulfhydryl groups.

(5) Penetration of Cr(VI) increases with increasing pH of the solution, which correlates with decreasing reactivity as an oxidant, and thus a decreasing probability of Cr(VI) being reduced to Cr(III).

Particulate forms of chromium are unlikely to be absorbable percutaneously unless dissolved. Even in the latter situation it is unlikely, in view of the above findings, that either Cr(III) or Cr(VI) would be systemically absorbed in quantities significant enough to consider for purposes of the risk assessment in Section 8.

3.2 Transport and Distribution

Although most studies of chromium transport, distribution and elimination have been conducted in animals, the general model (at least for Cr(III)) has been confirmed in human subjects using intravenously administered $^{51}Cr(III)$, followed by whole-body scintillation scanning and counting and plasma counting (Lim et al., 1983). Cr(III) is transported in the blood bound mainly to transferrin, with uptake by kidney, bone marrow, liver, spleen and soft tissues.

Transferrin is taken up into cells (e.g., reticulocytes) by endocytosis (Light and Morgan, 1982): Cr(III) may thus enter cells bound to this protein, as does iron, the usual occupant of transferrin binding sites. Liver and spleen appear to act as long-term storage depots for chromium, perhaps reflecting patterns of transferrin metabolism. Inhaled Cr(III) would follow a somewhat different distribution pattern, since a large percentage is retained in the lungs (See Section 3.1.1)

The transport and tissue uptake patterns of Cr(VI) are probably similar to those of Cr(III), but, because of different experimental designs, inter-study comparisons are problematic (EPA, 1984). Furthermore, clearance of chromium from whole blood after administration of Cr(VI) is slower than after that of Cr(III), due to facile erythrocytic uptake of the former, followed by intracellular reduction to Cr(III), with binding to erythrocyte proteins, especially hemoglobin. (See Section 3.3, "Metabolism") Unlike Cr(III), Cr(VI) is not significantly bound to plasma proteins (Love, 1983).

3.3 Metabolism

In vitro studies have demonstrated that cell membranes are substantially more permeable to chromate (VI) solutions than to Cr(III), which may result from transport via an anion channel (Kitigawa et al., 1982; Levis et al., 1978). Chromate metabolism has recently been reviewed by Connett and Wetterhahn (1983), whose relevant findings are summarized in the next paragraph.

Absorbed Cr(VI) can react with multiple cellular components, resulting in reduction to Cr(III) by reaction with cellular macromolecules or small molecules, such as cysteine, reduced glutathione, and ascorbic acid. Few purified proteins will reduce chromate at physiologic pH. However, in erythrocytes chromate rapidly oxidizes and binds to hemoglobin; oxidation is potentiated in vitro by the presence of reduced glutathione (Kitigawa et al., 1982). In vitro studies of liver microsome preparations containing cytochrome P-450 and NADPH-dependent cytochrome P-450 reductase indicate that Cr(VI) is reduced, with the formation of a Cr(V) reactive intermediate (Wetterhahn Jennette, 1982; Polnaszek, 1981). There is also substantial Cr(VI) reduction within mitochondria by as-yet-unidentified substances. Reduction of Cr(VI) is not a random process, since most macromolecules and small molecules studied do not appear capable of effecting this process under physiologic conditions (Connett and Wetterhahn, 1983).

Cr(III) resulting from intracellular Cr(VI) reduction is capable of a variety of interactions with cellular constituents, many of which may result in toxicity. Cr(III) can form stable coordination complexes with amino acids and nucleic acids, and can cause intra- and intermolecular cross-linking of proteins and polynucleotides (See Section 5, "Genotoxicity"). Cr(III) may also affect enzyme activity by binding to enzyme protein or to substrate (Levis et al., 1978). About half of intracellular Cr(III) complexes formed are found in the nucleus (Leonard and Lawreys, 1980).

3.4 Elimination

Elimination of chromium was reviewed by EPA (1984) and Langard (1982), from which most of the following summary is adapted.

The major routes of chromium elimination are via the kidneys and gastrointestinal tract (i.e., by biliary excretion). Some is also eliminated in hair, nails, milk and sweat. (Guthrie, 1982,; Leonard and Lawreys, 1980). It is unknown which pathway predominates for the elimination of nutritionally required, ingested trace amounts of Cr(III)(See Section 3.5), since the kinetics of elimination have been studied at higher dose levels.

Clearance from plasma, representing tissue uptake and renal clearance, is rapid, occurring within hours, while elimination from tissues is much slower, with half-times (for Cr(III)) ranging from several days to about 12 months for storage sites (e.g., liver and spleen). Numerous experimental studies in animals indicate that urinary excretion of chromium predominates (>50%), with less than 10% appearing in bile, while a substantial percentage appears to deposit in storage compartments.

Several studies compared elimination of Cr(III) and Cr(VI) administered intravenously, subcutaneously and by gavage. Generally it appears that Cr(VI) is more rapidly excreted than Cr(III) (EPA, 1984). This observation was supported in a recent study examining clearance kinetics of chromium in mice dosed intraperitoneally with

1/6 the LD_{50} of Cr(III) or Cr(VI) (Bryson and Goodall, 1983). After a single intraperitoneal dose of chromium trichloride (Cr(III)) or potassium dichromate (Cr(VI)), mice were serially sacrificed. At 3 days 87% of Cr(III) was retained, while only 31% of Cr(VI) was; at 7 days these numbers were 73% for Cr(III) and 16% for Cr(VI); and after 3 weeks they were 45% and 7.5%, respectively. (Retention sites were not specified since the method of analysis involved whole body acid digestion.) In a treatment regimen consisting of once-weekly doses of the same substances, Cr(III)-treated mice retained about 9 times as much of the administered doses as those treated with Cr(VI) (totalling approximately 70% of the total injected chromium). Analyses of excreta showed that Cr(VI) was eliminated more rapidly in urine and feces than Cr(III).

The differential excretion and retention of Cr(III) and Cr(VI) probably reflect the greater ability of Cr(III) to form complexes with components of biological systems and of Cr(VI) to cross cell membranes. However, in view of the ready biological reduction of Cr(VI) to Cr(III) both intra- and extracellularly, this distinction in the clearance kinetics of the different oxidation states cannot be complete. In any case, it is clear that exposure to chromium in either oxidation state can result in long (years) residence times in human tissues. For example, Tsuneta et al. (1980) reported that the mean concentration of chromium (not speciated) in the upper lobes of lung cancer patients who were former chromate workers was 72 times greater than that in non-exposed control lungs (36.7 μg/g wet weight compared to 0.51μg/g), even many years after the exposures had ended.

3.5 Chromium as an Essential Nutrient

Although chromium has been recognized as an essential nutrient in animals for more than two decades, the precise nutritional biochemistry has yet to be elucidated. Cr(III) was identified as the active component of a glucose tolerance factor found in brewer's yeast, which could correct an induced deficiency state. The latter is characterized by glucose intolerance (measured by an intravenous glucose tolerance test in animals), glycosuria, hypercholesterolemia, decreased longevity, decreased sperm counts and impaired fertility (Mertz, 1969; Anderson and Polansky, 1981).

Guthrie (1982) reviewed 12 clinical studies on chromium supplementation, reporting that both inorganic Cr(III)(usually as chromium chloride) and chromium administered in brewer's yeast extract significantly ameliorated glucose intolerance and hypercholesterolemia and decreased fasting insulin levels in some subjects, including diabetics, asymptomatic hyperglycemic individuals, and healthy controls. Chromium's nutritional role has not been thoroughly delineated, but appears at least to potentiate insulin activity (Mertz, 1975). The biologically active Cr(III) complex, which also includes nicotinic acid and several amino acids, strongly binds insulin (Guthrie, 1982).

Although there are inadequate data to formulate a recommended dietary allowance for chromium, an adequate and safe intake of 50 to 200 μg/day for adults has been suggested (NAS, 1980a). Daily intakes for adults in the U.S. are probably less than 200 μg/day, although it is unclear what percentage of Cr(III) intake would be in biologically active forms (Guthrie, 1982). Gastrointestinal absorption of organically bound chromium (as in food) is higher than for inorganic Cr(III), which, as noted in Section 3.1.2, is poorly absorbed from the gastrointestinal tract (NAS, 1980a). The Safe Drinking Water Committee of National Academy of Sciences has reported estimates of the daily intake of chromium by different routes as:

(a) food: mean 62 μg/day (range 37-130) from "typical self-selected American diets";
(b) drinking water: mean 17 μg/day (range 1-224) assuming consumption of 2 liters/day; and
(c) air: less than 0.5% of dietary intake in areas where ambient chromium concentrations average 0.015 $\mu g/m^3$ and less than 4% in highly polluted areas with an ambient chromium concentration of 0.35 $\mu g/m^3$ (NAS, 1980b).

It should be noted that the estimated average daily chromium intakes from food and water refer to Cr(III) and thus are not relevant to the cancer risk assessment for Cr(VI) in section 8.

4. ACUTE AND CHRONIC TOXICITY

4.1 Acute Toxicity

4.1.1 Animal

Because of its poor gastrointestinal absorption and bioavailability, Cr(III) is considered to be relatively nontoxic when orally administered. Oral LD_{50}s in rats are chromic chloride, 1.9 g/kg; chromic nitrate, 3.3 g/kg; and chromic acetate, 11.3 g/kg (EPA, 1984). Intravenous LD_{50}s for various Cr(III) salts in mice are: chromium sulfate, 85 mg/kg; chromic chloride, 400-800 mg/kg and chromic acetate, 2290 mg/kg (IARC, 1980).

Cr(VI) compounds are more toxic than those of Cr(III), regardless of the route of administration. The range of oral LD_{50}s in rats has been reported to be 80 to 114 mg/kg, with death occurring within hours to about 3 days. Symptoms and pathologic findings included cyanosis, gastric ulceration, diarrhea and tail necrosis (EPA,1984). The principal potentially lethal effect of acute Cr(VI) exposure is renal toxicity, resulting in acute renal failure. Microscopic pathologic changes have been reported in the glomerulus and proximal and distal convoluted tubules in a variety of species, including rats, monkeys, and rabbits, given toxic parenteral doses of Cr(VI), usually as potassium dichromate or sodium chromate. It has been estimated that renal toxicity occurs at a dose level of 1-2 mg Cr(VI)/kg body weight (Tandon, 1982).

Other organs and systems affected by high-dose parenteral administration of both Cr(III) and Cr(VI) include the central nervous system, myocardium and liver (Tandon, 1982).

4.1.2 Human

The estimated range for a lethal dose of ingested Cr(VI), based on reported fatal cases, is between 1.5 and 16 g (IARC, 1980). Reported pathology includes gastrointestinal hemorrhage, intravascular hemolysis and acute renal failure. No such cases have been reported for Cr(III) compounds, which are considerably less toxic by ingestion (see below). As of 1973, no fatalities had been reported due to exposure to airborne Cr(VI) (NIOSH, 1973). Exposure to Cr(VI) aerosols results in mucous membrane irritation and probably bronchospasm, although the latter is not well-documented in the literature (Bidstrup, 1983). Since occupational exposure measurements were not often taken and in the past were not often reliable, no dose-response estimates have been made here, although one would not expect any such effects in the general population from current levels of ambient chromium concentrations. This observation follows a fortiori from the conclusion in Section 4.2.2, infra, that current ambient levels of chromium would not be expected to result in any chronic effects discussed in Section 4.2.

4.2 Chronic Toxicity

Chronic toxic effects (other than genotoxicity, reproductive effects and carcinogenicity) from chromium exposure have been observed in experimental animals and among individuals occupationally exposed. The occurrence of all of the effects listed below is expected to be governed by a threshold, even if the threshold exposure level has not been precisely quantified. In the case of chromium, the difference between current ambient exposure levels and the levels at which chronic toxic effects have occurred (several orders of magnitude) leaves enough of a margin of safety so that none of these effects is expected to occur in the general population.

4.2.1 Animal

Most of the literature on chronic exposure to chromium compounds consists of reports of no observed effect levels ("NOELs") (EPA, 1984). The studies reviewed by EPA are of limited value, however, since few animals were used in each study. All but one of these studies involved ingestion. The one inhalation study reviewed involved intermittent short exposures (10-60 minutes each) over a 4-month period of two cats to chromium (III) carbonate dust at an average concentration of 58.3 mg/m^3 (range 3.3 to 83 mg/m^3) (EPA, 1984). The poor statistical power of this last investigation limits its usefulness for purposes of risk assessment.

Other inhalation experiments using Cr(III) aerosols have shown that chronic effects occur at levels lower than 58.3 mg/m^3. Three studies cited by Tandon (1982) showed that: (1) inhalation by rats of chromium (III) oxide or trisubstituted chromium (III) phosphate at a concentration of 42-43 mg/m^3 for 5 hr/day for 4 months produced chronic inflammatory changes in the bronchi and lung parenchyma and dystrophic changes in liver and kidney; (2) exposure of rats to chromium ore residue dust at 19 mg/m^3 for 1, 3 or 7 days produced swelling and desquamation of alveolar cells, while exposure to lower concentrations (1 or 10 mg/m^3) for 3 weeks resulted in alveolar wall thinning and filling of alveoli with dust-laden proteinaceous materials.

There were no Cr(VI) inhalational NOEL studies found. Two rodent inhalational assays produced chronic effects (Steffee and Baetjer, 1965; Nettesheim et al., 1971). Rabbits, guinea pigs, and rats were exposed to mixed chromate (VI) dusts and mists at a mean concentration of 3-4 mg/m for 5 hr/day, 4 days/wk for the animals' lifetimes (Steffee and Baetjer, 1965). Treatment-related effects included nasal septal perforation, alveolar and interstitial inflammation, alveolar hyperplasia, and granuloma formation. No systemic pathology was found. In another experiment, mice were exposed to calcium chromate (VI) dust at a concentration of 13 mg/m^3 for 5 hr/day, 5 days/week over their lifetimes (Nettesheim et al., 1971). After six months of exposure, pulmonary effects included epithelial atrophy, necrosis, and hyperplasia, bronchiolar epithelial replacement of alveolar cells, alveolar proteinosis and other pathology. There was decreased weight gain in relation to control animals. Other effects included tracheal and submandibular lymph node hyperplasia, and atrophy of liver and spleen.

The above discussion demonstrates that there are inadequate animal data from which to calculate a chronic inhalational NOEL. DHS staff members therefore believe that, the human experience with chromium compounds should be used for purposes of risk assessment (See Section 4.2.2)

Parenteral administration of various chromium compounds at doses greater than 1 mg/kg to a variety of animal species has resulted in damage to liver, brain, myocardium, and testis, with the effects more severe for Cr(VI) than Cr(III) compounds (Tandon, 1982).

4.2.2 <u>Human</u>

In occupational settings the most commonly reported chronic effects of chromium exposure include contact dermatitis, skin ulcers, irritation and ulceration of the nasal mucosa and perforation of the nasal septum (NIOSH, 1975). Less common are reports of hepatic and renal damage and of pulmonary effects (bronchitis, occupational asthma and bronchospasm)(IARC, 1980; NIOSH, 1975; Bidstrup, 1983).

Chromium is the most common cause of occupational dermatitis and is the second most common skin sensitizer in the general population (Polak, 1983). This condition has an immunologic etiology determined by Cr(VI) penetration of skin, followed by reduction to Cr(III) by sulfur-containing proteins in the dermis. The resulting Cr(III)-protein conjugate is then thought to act as a sensitizing antigenic complex, with Cr(III) as the hapten (Polak, 1983).

Skin ulcers, ulceration of the nasal mucosa and perforation of the nasal septum are corrosive reactions due to the oxidative actions of Cr(VI) and chromic acid (Pedersen, 1982; Burrows, 1983; Bidstrup, 1983). Skin ulcers are believed to occur only where the exposed skin has been damaged (Pedersen, 1982). Similarly, a major factor in nasal ulceration and septal perforation is thought to be a lapse in personal hygiene -- i.e., nose-picking (Bidstrup, 1983). Skin ulcers and nasal perforation often occur in the same individuals (ACGIH, 1982; Burrows, 1983).

Occupational asthma due to sensitization to chromium has occurred in industry, but is uncommon (Bidstrup, 1983). Only recently was an immunologic basis for such asthma confirmed in a case report of an electroplating worker (with a positive inhalational challenge) in whose serum specific IgE antibodies were demonstrated (Novey et al., 1983). Bronchospasm in occupational settings, due to the primary irritant effects of chromium (particularly chromates and chromic acid mist), has occurred, but is not well-documented in the literature (Bidstrup, 1983). It is unknown what levels of pulmonary exposure would be required to induce chromium sensitization.

NIOSH (1975) thoroughly reviewed the health effects from exposure to Cr(VI) compounds. On the basis of this review NIOSH recommended a permissible exposure limit of 25 $\mu g/m^3$ of Cr(VI) as adequate to protect against noncarcinogenic effects for a 40 hr/wk time-weighted average exposure. Assuming such levels are protective against the above-noted effects,[*†] and adjusting for continuous exposure (168 hr/wk), there is still an approximately 3 orders of magnitude difference between this recommended level and current ambient concentrations. Thus, DHS staff members conclude that none of the chronic effects discussed in this section is likely to occur at current ambient levels of exposure[†]. From this conclusion it can be inferred that no acute toxic effects would be expected either.

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[*]EPA (1984) cited a NIOSH Health Hazard Evaluation of an electroplating plant in which typical symptoms and signs of chromium toxicity occurred at Cr(VI) exposure levels of 1 to 20 $\mu g/m^3$. DHS staff has reviewed this NIOSH report, which indicates that the chromium-associated toxicity was due to inadequate work practices rather than airborne chromium.

[†]As noted in the text, there is not enough information to determine a threshold for immunologic sensitization.

5. GENOTOXICITY

Mutagenic and clastogenic effects have been reported almost invariably for Cr(VI), but not Cr(III), compounds. The nature of chromium's genotoxic effects is complex and has been extensively investigated. Chromium's interactions with genetic materials have been reviewed by Leonard and Lawreys (1980), IARC (1980), Heck and Costa (1982), Levis and Bianchi (1982), and EPA (1984).

5.1. Mutagenicity

Cr(VI) has been indisputably demonstrated to induce genotoxic effects in all of the major assay systems, suggesting that the carcinogenicity of this substance (See Section 7) is at least partially explicable on a genotoxic basis. Principal aspects of the genotoxicity of chromium are summarized below.

(1) Bacterial assays

In the standard Ames *S. typhimurium* test, Cr(VI) compounds induced mutations in tester strains responsive to both base-pair substitution and frameshift mutagens at doses of 10-20 μg/plate, while Cr(III) compounds were observed to be nontoxic and nonmutagenic at concentrations of up 20 mg/plate. The mutagenic potency of Cr(VI) compounds could be diminished by addition of liver microsomal S-9 preparations, erythrocyte lysates, ascorbic acid, sodium sulfite, sodium nitrate, and several reducing metabolites (i.e., GSH, NADH, NADPH), presumably due to extracellular reduction of Cr(VI) to Cr(III) (IARC, 1980; Petrilli and De Flora, 1978). Addition of potassium permanganate, a strong oxidizing agent, to liver microsome and erythrocyte preparations completely blocked the ability of the latter to inhibit Cr(VI)'s mutagenicity (Petrilli and De Flora, 1978). Petrilli and De Flora (1978) observed that rat lung microsome preparations were only very weakly active in reversing Cr(VI) mutagenicity, which is interesting in view of chromium's ability to cause lung cancer in humans (See Section 7).

Similarly, mixing potassium permanganate with Cr(III) compounds resulted in a positive Ames test, which was attributed to extracellular oxidation of Cr(III) to Cr(VI). While most Cr(III) compounds are nonmutagenic in the Ames assay, some containing aromatic ligands cross bacterial cell walls and membranes and are active mutagens in the Ames test and in the E. Coli repair assay (Warren et al., 1981).

In E. Coli assays, experimental results with Cr(VI) were not as consistently positive as those in Ames tester strains. However, several Cr(VI) compounds (including salts of potassium, calcium, lead and sodium as well as stainless steel welding fumes) have been reported as positive in a variety of E. Coli mutagenesis assays. Generally Cr(III) tested negative, although chromic acetate was positive at very high concentrations (16-130 mM) in one E. Coli arg^- strain (Heck and Costa, 1982).

(2) Cultured Mammalian Cell Assays

In V79 Chinese hamster cells, soluble potassium dichromate (VI) and slightly soluble zinc chromate (VI) both induced dose-related mutagenesis, while soluble chromic (III) acetate and insoluble lead chromate (VI)(both given at substantially higher doses than $K_2Cr_2O_7$ and $ZnCrO_4$) did not. In the same cell line, potassium chromate and dichromate and welding fumes, but not chromic acetate, caused 6-thioguanine resistance (Levis and Bianchi, 1982). In C3H mouse cells, potassium dichromate and chromium (VI) trioxide induced chromosomal aberrations and 8-azaguanine resistant mutants, while potassium chromate (VI) and chromic (III) sulfate did not. In the L5178Y mouse lymphoma cell $TK^{+/-}$ assay, potassium chromate and dichromate both tested strongly positive (IARC, 1980). In the above assays, all Cr(VI) compounds, with the exception of lead chromate, tested positive. The insolubility and hence low bioavailability of lead chromate may have affected the outcome of this investigation.

5.2 Chromosomal Damage

Numerous studies have demonstrated that chromium compounds, particularly those of Cr(VI), cause clastogenic effects *in vitro* and *in vivo*. These studies have been extensively reviewed elsewhere (Leonard and Lawreys, 1980; IARC, 1980; Levis and Bianchi, 1982; EPA, 1984). Relevant conclusions from the review articles are presented in this section.

Every Cr(VI) compound tested in at least 8 different _in vitro_ cell culture systems has produced chromosomal aberrations, most commonly gaps and breaks. Cr(VI) compounds tested included chromium trioxide, potassium chromate and dichromate, sodium chromate and dichromate, lead chromate, calcium chromate, zinc chromate and welding fume particles (EPA, 1984; Levis and Bianchi, 1982). Cell culture sources included human lymphocytes, primary human embryo fibroblasts, primary hamster embryo cells, three hamster cell lines (CHO, DON and V79), primary mouse fetal cells, and a mouse mammary carcinoma line. Cr(III) compounds have also occasionally tested positive for clastogenicity _in vitro_, but only at doses substantially higher (by one to two orders of magnitude) than those for Cr(VI) compounds tested in similar systems. Such anomalous results may be partially explained by Cr(VI) contamination of Cr(III) compounds and possibly by the action of lysosomal nucleases released through destabilization of lysosomal membranes (IARC, 1980; Levis and Bianchi, 1982).

Consistent with the above observations, sister chromatid exchange (SCE) was induced by every Cr(VI) compound tested (including all of those listed in the previous paragraph) in primary human lymphocyte and fibroblast cultures, 2 hamster cell lines (CHO and DON), and a primary mouse lymphocyte culture. Except where contaminated by Cr(VI) or when mixed at dose levels 300 to 1,000 times higher than those of Cr(VI), Cr(III) compounds were invariably negative in the SCE assays (EPA, 1984).

Observations of chromium's chromosomal effects *in vivo* have generally confirmed the results of the *in vitro* experiments. Micronuclei (nuclear fragments due to chromosomal breaks or a delayed anaphase) were found in immature erythrocytes in mice administered potassium chromate (VI) intraperitoneally. However, chromic (III) nitrate and the carcinogen calcium chromate (VI) did not produce significant increases in micronuclei (Levis and Bianchi, 1982).

Chromosomal aberrations have been reported in fish and rats treated with sodium dichromate (EPA, 1984; Levis and Bianchi, 1982). Workers exposed to a variety of Cr(VI) compounds, including sodium chromate, chromium trioxide and others, have had significant increases in chromosomal aberrations in peripheral lymphocytes compared to unexposed controls (IARC, 1980). Similarly, workers exposed to chromium trioxide showed significantly increased number of SCEs and chromosomal aberrations (EPA, 1984). Interestingly, this phenomenon was observed only in the youngest workers, allegedly because these were the least experienced and would thus be more likely to incur significant exposures.

In summary, there is overwhelming evidence that Cr(VI) compounds are capable of causing chromosomal damage. Cr(III) compounds may also be clastogenic, but it is unclear whether this is a real effect or an artifact.

5.3 Transformation

Morphological transformation of mammalian cells is considered to provide a good, short-term method for assessing carcinogenic potential. All Cr(VI) compounds tested have been shown to be capable of cell transformation in several *in vitro* systems, while, with one exception, Cr(III) (as chromic chloride) has not. Levis and Bianchi (1982) reviewed these experiments and their conclusions are summarized below.

(1) Potassium chromate (VI) and dichromate (VI) and sodium chromate (VI) transformed mouse and hamster primary cell cultures. Chromic chloride also did so in fetal mouse cells, but not Syrian hamster embryo cells.

(2) Cr(VI) salts of calcium, lead, zinc, and potassium enhanced viral transformation of hamster cells.

(3) Cr(VI) (as potassium chromate) enhanced benzo(a)pyrene-induced transformation of hamster embryo cells, whereas Cr(III) (as chromic chloride) did not.

(4) Cr(VI) (as potassium dichromate or calcium chromate) induced anchorage-independent growth in hamster cells, whereas Cr(III) (as chromic chloride) did not.

(5) Sodium chromate (VI) administered intraperitoneally to pregnant mice resulted in transformation of cell cultures derived from the embryos. Cr(III) was not tested in this system.

Thus, assays for <u>in vitro</u> transformation provide additional qualitative confirmation of the carcinogenic potential of Cr(VI) compounds.

5.4. <u>Mechanisms Proposed for Genetic Toxicity</u>

Cr(VI) compounds are active in every major assay for genotoxicity, while Cr(III) compounds show activity in some systems only at high doses, which has led numerous investigators to propose that Cr(VI) is genetically active, whereas Cr(III) typically is not (Levis and Bianchi, 1982). This hypothesis is clearly correlated with the relative abilities of these oxidation states of chromium to cross biological membranes. As noted earlier, the site of reduction of Cr(VI) to Cr(III) may well be determinative of the extent of genetic toxicity. Extracellular reduction diminishes or abolishes mutagenicity of Cr(VI), while oxidation of Cr(III) has the opposite effect (Petrilli and DeFlora, 1978). Intranuclear reduction of Cr(VI) appears to be the key element in chromium's genotoxicity, resulting in direct oxidation of DNA and/or the formation of stable Cr(III) complexes with nucleophilic sites in DNA (Langard, 1982).

Since Cr(III) compounds possess clear abilities to damage DNA in cell-free systems and, when complexed to certain ligands, in bacterial assays, it is possible that Cr(III) is the ultimate carcinogen

(Fornace et al., 1981; Warren et al., 1981). Interactions of Cr(III) with nucleic acids include binding to cytosine and guanine and to phosphate groups. Unlike Mg (II), which stabilizes DNA through its interactions with phosphate groups, Cr(III)'s effects include inter- and probably intramolecular cross-linking between phosphate moieties, chelation between bases and phosphates, and cross-linking with proteins (Tamino et al., 1981; Levis and Bianchi, 1982).

Experimental evidence from several laboratories supports the notion that intracellular reduction of Cr(VI) to Cr(III) is crucial. Fornace et al. (1981) reported that in several mammalian cell cultures, including bronchial epithelial cells, Cr(VI) (as potassium chromate) produced persistent, dose-dependent protein-DNA cross-linking, measured by alkaline elution. However, in isolated nuclei and in buffered solution with [^{3}H] DNA and bovine serum albumin, Cr(III) (as chromic chloride), but not Cr(VI), induced DNA-protein cross-links. Sirover and Loeb (1976), using a cell-free system, found that Cr(III) decreased the fidelity of DNA synthesis by avian myeloblastosis virus DNA polymerase at a concentration 25 times lower than that of Cr(VI) required to achieve the same result, which may be due to DNA-protein cross-linking (Fornace et al., 1981). Similarly, Tkeshelashvili et al. (1980) reported that Cr(III) (as chromic chloride) was more effective than Cr(VI) (as chromium trioxide) in diminishing the fidelity of DNA synthesis by _E. Coli_ DNA polymerase I.

Using a rat liver microsome/NADPH system, Tsapakos and Wetterhahn (1983) showed that enzymatic reduction of Cr(VI) in the presence of NADPH was required to effect chromium binding to double-stranded DNA. Cr(III) binding was 2 - 3 times lower and was not dependent on the presence of NADPH or microsomes. Binding to single-stranded DNA was substantially higher for both Cr(VI) and Cr(III), with binding of Cr(VI) greater than that of Cr(III). The Cr(VI), microsomes and NADPH bound substantially more protein (bovine serum albumin in this system) to DNA than did Cr(III). Protein and chromium binding to DNA and RNA were linearly correlated. Incubating Cr(VI) with DNA homopolymers showed that binding to poly(G) was favored (by an order of magnitude) over the other homopolynucleotides. This last observation is consistent with the suggestion by Venitt and Levy (1974) that Cr(VI) mutagenicity is due (at least in part) to attack on GC base-pairs, causing GC-->AT transitions in subsequent DNA replication, which is typical of electrophilic mutagens.

Thus, there are at least two pathways in the uptake-reduction model of chromium's genotoxicity. Damage to DNA, with protein cross-linking, is caused most effectively when Cr(VI) is enzymatically reduced in close proximity to DNA (e.g., by the electron transport system cytochrome P-450 complex located in the nuclear membrane). (Tsapakos and Wetterhahn, 1983). This may involve reactive Cr(V) intermediates (Wetterhahn Jennette, 1982; Polnaszek, 1981). Cr(III) produced by other reducing systems may also interact with DNA and protein, but at a slower rate because of its kinetic stability. Common to both pathways, however, is reduction of Cr(VI) to Cr(III), with cross-linking of macromolecules.

6. REPRODUCTIVE EFFECTS

Potential reproductive effects of chromium have not been investigated epidemiologically. In view of Cr(VI)'s genotoxicity, however, there is reason to believe a priori that it may adversely affect reproduction, unless germ cells or the fetus were resistant to such toxicity. This is clearly not the case, since animal experiments demonstrate adverse effects on male reproductive systems and fetal development.

6.1 Male Reproductive Effects

Both Cr(III) and Cr(VI) are capable of crossing the blood-testis barrier and damaging the testis. Administered intraperitoneally to rabbits at a dose of 2 mg/kg for 3 or 6 weeks, Cr(III) (as chromium nitrate) and Cr(VI)(as potassium dichromate) caused depression of enzyme activity, degenerative histological changes and spermatotoxic effects (i.e., multinucleated germ cells and spermatocyte degeneration in the lumen of the seminiferous tubules)(EPA, 1984). Pagano et al. (1983) showed that Cr(VI)(as sodium chromate) in sea urchins depressed mitotic activity in sperm. Consistent with these observations is the report by Paschin et al. (1981) that potassium dichromate was positive in a dominant lethal mutation assay in mice given a single dose at 20 mg/kg or daily doses for 21 days at 2.0 mg/kg. Male rats treated with a daily intraperitoneal dose of 1 mg Cr(III)/kg were found to have a mean testicular Cr(III) concentration of 3.2 μg/g tissue, lower than the liver and kidney concentrations of 14.1 μg/g and 8/1 μg/g, respectively (Lee, 1983). The lower accumulation in the testis was attributable in part to the protective effect of the blood - testis barrier. Chromium has also been reported to accumulate in the testes of men exposed occupationally, which may be due to reduction of Cr(VI) by testicular microsomes (Levis and Bianchi, 1982). Both Cr(III) and Cr(VI) are thus capable of crossing the blood-testis barrier and of affecting spermatogenesis: the risk to humans cannot be assessed from these data, however.

6.2 Placental Transport

There is direct as well as indirect evidence that chromium can cross placental membranes. As an essential nutrient, chromium (III) must be transported to the developing fetus. Fetal chromium concentrations reportedly increase during gestation, peaking in the neonate, with subsequent declines in various tissues during childhood (Guthrie, 1982).

Cr(III) placental transfer has been examined in several animal studies. In a study using whole-body radioautography, Cr(as chromic (III) chloride) was detected in fetal skin and bone one hour post-injection to the mother, with increasing amounts detectable in later gestation (Langard, 1982). Similarly, Iijima et al. (1983) reported that concentrations of ^{51}Cr mouse embryos increased at 4-hour intervals after a single intraperitoneal injection of $^{51}CrCl_3$, to the point where the concentration of radioactivity in the fetus exceeded that in maternal blood. Relatively little inorganic chromium (III) (<0.5% of the administered dose) has been found to cross the placenta. In contrast, when administered in a biologically active form (brewer's yeast) by gavage, twenty to fifty percent of the initial maternal radioactivity was found in the litters (EPA, 1984). In one study comparing transplacental uptake of intravenously administered Cr(III)(as chromic chloride) and Cr(VI)(as sodium dichromate), 0.4% of the dose of Cr(III) and 12% of the dose of Cr(VI) were recovered in embryonic mice (Danielsson et al., 1982). The embryotoxicity and fetotoxicity of these chromium compounds (see below) provides additional, but indirect evidence of chromium's transplacental passage.

6.3 Effects on Fetal Development

Gale (1978) gave single intravenous injections of Cr(VI) (as chromium trioxide) to early gestational (day 8) hamsters at dose levels of 5, 7.5, 10 or 15 mg/kg. Fetuses taken from the treated dams were examined for external, internal and skeletal malformations. There was a dose-dependent increase in the frequency of resorptions and internal and external anomalies. The most common malformation was cleft palate (up to 84% of treated animals in the high-dose group compared to 2% in controls) and the most common internal anomaly was hydrocephalus (55% of the low-dose group versus 0% in controls). Other fetotoxic effects included delayed ossification and edema. There was maternal toxicity, as evidenced by decreased weight gain and renal tubular necrosis, at dose levels of 7.5 mg/kg and above. On the basis of this experiment, the author concluded that chromium trioxide is embryolethal and teratogenic.

To evaluate the possible contribution of genetic background to chromium teratogenesis, Gale (1982) treated 5 inbred hamster stains and 1 outbred strain with one, 8 mg/kg intravenous injection of chromium trioxide. Similar outcomes (high incidence of resorptions, cleft palate, hydrocephalus) were detected in 3 strains, while the others were noted to be relatively resistant to the embryotoxicity of chromium trioxide.

Cr(III) (as chromic chloride) was shown to be teratogenic in mice given a single intraperitoneal injection on the 7th, 8th or 9th day of gestation (Matsumoto et al., 1976). Doses ranged from 9.76 mg/kg to 24.4 mg/kg. The only statistically significant effect observed in the low-dose group (9.76 mg/kg) was decreased fetal weight. Possible maternal toxicity was not reported. The most common external anomalies were exencephaly, anencephaly and open eyelids. The authors suggested that the more severe cranial anomalies might be due to incomplete neural tube closure. This suggestion received support in later experiments in which pregnant mice treated with a single dose of chromic chloride on day 8 of gestation were serially sacrificed at 4-hour intervals post-injection (Iijima et al, 1983).

Embryos examined histologically had numerous pyknotic neuroepithelial cells in the neural ectoderm at 8 hours post-injection. The authors suggested that Cr(III) has a direct effect on the neural tube, which closes at about 8 1/2 days of gestation. However, an indirect effect on the placental or maternal system cannot be ruled out by this investigation.

EPA (1984) reviewed these and other studies, summarized in Table 6-1. Since the lowest administered dose of Cr(VI) (5mg/kg) noted was teratogenic without significant maternal toxicity, a risk assessment for humans using a safety factor approach cannot be used. A similar rationale applies to the study of Matsumoto et al. (1976), in which (except for fetal weight gain) a no effect level of 9.76 mg/kg for Cr(III) administered intraperitoneally was reported. However, internal malformations were not investigated and it cannot be stated definitively that, from the standpoints of embryolethality and teratogenesis, this dosage is truly a no observed effect level. Furthermore, this represents a single dose exposure while, for purposes of risk assessment, chronic exposure by a more relevant route would be more appropriate. (Single dose studies do, however, illustrate the intrinsic potential of chromium to induce reproductive failure and demonstrate that only one exposure is required to elicit the response.) Thus, the experimental data are inadequate to calculate reproductive risks to humans from ambient exposures to either Cr(VI) or Cr(III).

Table 6-1

Teratogenic and Fetotoxic Effects of Chromium

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
CrO_3	i.v.	hamster	5, 7.5, 10, or 15 mg/kg on day 8 of gestation	increased fetal death in 7.5, 10, and 15 mg/kg groups, increased incidence of cleft palate in all groups, hydrocephaly and skeletal defects	depressed weight gain and kidney tubular necrosis at all doses above 5 mg/kg	Gale, 1978
CrO_3	i.v.	hamster	8 mg/kg on day 7, 8, 9, 10, or 11 of gestation	increased fetal death following administration on day 7, increased incidence of cleft palate following administration on days 7, 8, or 9	weight loss, tubular necrosis of kidneys	Gale and Bunch, 1979
$CrCl_3$	i.p.	mouse	9.76, 14.64, 19.52, or 24.4 mg/kg on day 8 of gestation	depression of fetal weights in all Cr treated groups, increase in rate of external abnormalities for groups treated with 14.64, 19.52, or 24.4 mg/kg	not reported	Matsumoto et al., 1976
CrO_3	i.v.	hamsters (strain LVG)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	Gale, 1982
		hamsters (strain CB)	8 mg/kg on day 8 of gestation	no effect	no effect	"

Table 6-1 (Cont)

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
		hamsters (strain LHC)	8 mg/kg on day 8 of gestation	no effect	no effect	
		hamsters (strain LSH)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	
		hamsters (strain PD4)	8 mg/kg on day 8 of gestation	no effect	no effect	
		hamsters (strain MHA)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	
[illegible]	s.c.	mouse	10 or 20 mg/kg on day 7, 8, 9, 10, or 11 of gestation	increase in external malformations in 20 mg/kg group when dosed on day 8, as well as increase fetal death when dosed on day 8 or 11	lethal to 1/3 of dams	Iijima et al., 1979

Table 6-1 (Cont)

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
$CrCl_3$	i.p.	mouse	9.8 mg/kg on day 8 of gestation	Cr increased gradually and peaked at 24 hr, exceeding maternal blood Cr level.	Maximum blood Cr at 4 hr post-i.p. and gradually decreased	Iijima et al., 1983
$CrCl_3$	i.p.	mouse	19.5 mg/kg/day	Pyknotic cells in neuroepithelium of neural ectoderm in 2 of 5 embryos after 4 hr; in all 5, after 8 hr.	NR	Iijima et al., 1983
$CrCl_3$	i.v.	mouse	10 mg/kg on days 13 and 16 of gestation	Fetal Cr(III) was 0.4% of maternal serum Cr 1 hr post-i.v.; high accumulation of Cr in yolk sac placenta. In late gestation, Cr accumulated in calcified areas of fetal skeleton.	NR	Danielsson et al., 1982
		[in vitro]	0 to 15 µg/mL	No overt cytotoxicity at 15 µg/mL in embryonic cell cultures (chick cells).	NA	Danielsson et al., 1982
$Na_2Cr_2O_7$ (Cr(VI))	i.v.	mouse		Fetal Cr(VI) was 12% of maternal serum Cr 1 hr post-i.v. In late gestation, Cr accumulated in calcified areas of fetal skeleton.	NR	Danielsson et al., 1982
Cr(VI)		[in vitro]	0.1 to 0.28 µg/mL	Affected cartilage production at ≈0.1 µg/mL in embryonic cell cultures (chick cells).	NA	Danielsson et al., 1982

i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous

NR = Not reported; NA = Not applicable

Source: EPA, 1984

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7. CARCINOGENICITY

Epidemiologic studies of cohorts exposed to chromium aerosols occupationally provide clear evidence of carcinogenicity. However, because of mixed exposures and the dearth of reliable exposure data, the relative carcinogenic potencies of different compounds cannot be distinguished on the basis of epidemiologic data alone. However, animal studies involving inhalational exposure to various chromium compounds have been unsuccessful in even confirming the results of these epidemiologic studies, much less resolving issues of identities and potencies of different chromium-containing compounds as respiratory carcinogens. Several chromium compounds have been demonstrated to be carcinogenic when administered to animals by invasive methods. In this section the results of nonhuman studies will be summarized briefly, with greater attention given to the epidemiologic evidence.

7.1 Animal studies

There have been at least eighty reported attempts to induce cancer in rodents by administration of chromium compounds by various routes. These have been reviewed by IARC (1980, 1982), Hayes (1982) and EPA (1984). Appendix I consists of a summary table of studies adapted from EPA (1984). Most early studies have inadequate experimental designs by today's standards. Relevant findings from the above literature reviews are:

(1) No chromium compound has been unequivocally shown to cause a significantly increased number of neoplasms in experimental animals after

exposure by inhalation. At least 7 experiments involving dusts containing Cr(VI) and/or Cr(III) compounds have been conducted. Although Nettesheim et al. (1971), reported a significantly increased incidence of alveologenic (not bronchogenic) adenomas and adenocarcinomas in mice exposed to calcium chromate dust (13 mg/m^3) over their lifetimes for 5 hr/day, 5 days/wk, this conclusion cannot be confirmed on the basis of the data reported. The authors' statistical methodology was not reported. Fourteen treated animals (6 males and 8 females) developed tumors, whereas only 5 control animals (3 males and 2 females) did. However, the numbers of exposed and control animals were not reported, nor was the distribution of tumor types, so that the claim of a significant increase of treatment-related tumor incidence cannot be validated. IARC (1980) considers that there was no statistically significant increase in this experiment.

The failure of inhalational cancer bioassays to confirm the results of human experience is puzzling and may have no satisfactory explanation. Since respiratory neoplasms have been produced by intratracheal instillation and intrabronchial implantation of Cr(VI)-containing substances, a partial explanation for the negative results in the inhalational studies is that insufficient doses of the carcinogenic materials were deposited and retained in the lung. To some extent this may have been due to deficiencies in experimental methodology. The animal experiments almost all used whole-body inhalation chambers, in which exposures to particulates can be difficult to control. For example, there can be significant losses of particulate materials to the chamber surface due to electrostatic precipitation (Phalen, 1976).

Unlike head- or nose-only exposures, in inhalation chambers animals may be able to avoid exposure by burying their noses in their own or others' fur, which may also be capable of precipitating particulates. An additional impediment to the deposition of particulates in the lungs is the filtration efficiency of rodent nasal turbinates (although for particles < 2μm in diameter--as was the case in the studies cited here--this may not be an important consideration).

It should be noted that similar difficulties in confirming positive results in epidemiologic studies have been encountered with other metal particulates, such as arsenic and cadmium. Thus, it may be that, for metals and other particulates, bioassays involving rodents may not be a good experimental model for inhalational carcinogenesis. For example, pulmonary clearance in rats and mice appears to be more efficient than in humans, so that the latter tend to accumulate a greater burden of particulate materials , as was reported in the study of Baetjer et al. (1959). This phenomenon may be a reflection of significant interspecies anatomic differences: nonciliated respiratory bronchioles are not found in the lungs of rats and mice whereas they are in humans (Tyler, 1983; Phalen and Oldham, 1983).

Recently a cadmium bioassay produced positive results after 24 months of exposure (Takenaka et al., 1983). Tumor development in animals, as in humans, was characterized by a very long latency, so that a significant increase probably would not have been detected in a standard bioassay protocol, which involves termination at 24 months.. Such a latency period may also apply to chromium inhalational assays. It is interesting that in the only chromium inhalational study purporting to find an increase in pulmonary tumors, the mice were exposed until their demise, unlike the other experiments, which involved terminal sacrifices (See Appendix V).

Other considerations that may explain the discrepancy between the results of animal inhalation studies and occupational epidemiologic investigations include the following:

1. Humans may be more susceptible to pulmonary carcinogenesis than rodents.

2. The occupational cohorts were exposed to other carcinogens and cocarcinogens (e.g., such as those in cigarette smoke), whereas the animals were not.

(2) No chromium compound has been unequivocally shown to cause a significantly increased number of neoplasms in experimental animals (rats, mice, guinea pigs, and rabbits) after exposure by ingestion. Only three studies of orally administered chromium (III) compounds (as chromic acetate or chromic oxide) were noted by IARC (1980) and EPA (1984), and each of these involved dose levels that produced no overt signs of toxicity, indicating that higher exposure levels could have been tolerated. No ingestion studies using Cr(VI) were reported. In view of the poor gastrointestinal absorption of Cr(III), its nearly nonexistent genotoxicity in systems where cellular membranes are

intact, and the suboptimal dosing used in these bioassays, the negative results are not surprising.

(3) When administered by methods other than ingestion or inhalation, several Cr(VI) compounds have been shown to be carcinogenic. Since these all have involved injection or implantation of chromium-containing compounds, the lack of correspondence to typical routes of human exposure render these experiments of dubious utility for risk assessment. These bioassays, which are by far the most numerous, provide the basis for the conclusion by IARC (1980, 1982) that there is sufficient evidence for carcinogenicity of calcium chromate, which produces tumors in rats after administration by a variety of routes. Following subcutaneous, intrapleural and/or intramuscular administration in rats, the following substances produced application-site sarcomas: lead chromate (VI), lead chromate oxide (VI), cobalt-chromium alloy, sintered calcium chromate (VI), sintered chromium (VI) trioxide, strontium chromate (VI) and zinc chromate (VI) (IARC, 1980). Lead chromate also reportedly caused systemic (renal) carcinomas after intramuscular application. IARC (1980) concluded that there were inadequate data to evaluate the carcinogenicity of numerous Cr(III) and Cr(VI) compounds, including:

Cr(III)	Cr(VI)	Cr(0)
chromic acetate	barium chromate	chromium metal
chromic oxide	chromium trioxide	
chromite ore	mixed chromate dust	
chromium carbonyl	potassium chromate	
chromium sulfate	potassium dichromate	
roasted chromite ore	sodium chromate	
	sodium dichromate	
	zinc potassium chromate	
	zinc yellow	

It has been proposed that water solubility of chromates influences their carcinogenicity (NIOSH, 1975). Hueper and Payne (1959) had proposed that chromium carcinogenicity is a function of a compound's biological availability, which would depend on solubility, total dose, and "the proper rate of release of chromium ion from the introduced chromium compound." Compounds of greater solubility would be expected to be rapidly transported away from application or deposition sites and inactivated in erythrocytes (NIOSH, 1975). With respect to pulmonary carcinogenesis, however, solubility may be less important than other factors, such as the size distribution of chromium aerosols, total dose received, and host factors affecting deposition and clearance.

In view of the observation that both soluble and insoluble Cr(VI) compounds are genotoxic and may be implicated in carcinogenesis, it has more recently been suggested that the issue of water solubility has probably been overemphasized (Bidstrup, 1983). In any case, resolution of the solubility/carcinogenesis issue, although relevant, is not necessary for the purposes of risk assessment.

7.2 Epidemiologic Studies

7.2.1 Introduction

Several reviewers have recently summarized the epidemiologic studies pertaining to chromium (EPA, 1984; IARC, 1980; Hayes, 1982). The purpose of this section is to evaluate key studies with the goal of determining the general health effects associated with chromium exposure and, in particular, whether chromium or certain classes or compounds of chromium are carcinogenic in humans. A summary of some salient features of these studies appears in Table 7-1.

Virtually all epidemiologic studies regarding health effects of chromium were conducted in occupational settings. The studies arose following case reports of lung cancer in workers in the chromium industry dating back to the late 1800s. Based on these reports, in 1936 German authorities recognized lung cancer associated with chromate dust as a possible occupational disease.

7.2.2 Chromate Producing Industry

The most studied sector of the chromium industry has been the chromate producers. Here, chromite ore (Cr(III)) is the raw material and sodium chromate (Cr(VI)) and calcium chromate (Cr(VI)) are the principal intermediate and end products, respectively, of the chromate extraction

Table 7-1. Salient Features of Selected Epidemiologic Studies on Chromium

AUTHOR	INDUSTRY	DESIGN	NO. STUDIED	EXPOSURE	RESULTS	COMMENTS
Machle & Gregorius, 1948	chromate producing	mortality survey of U.S. plants	about 1000 from 6 plants	mixture; not quantified	all cancer RR[2] = 5.3; SS[3] resp ca, RR = 20.7, SS GI ca, RR = 1.0; SS	no cohort defined
Baetjer 1950	chromate producing	case-control in two hospitals (a,b)	290 cases	mixture; not quantified	a) lung ca, OR = 32; SS b) lung ca, OR = 23; SS	
Mancuso & Hueper 1951	chromate producing	historical prospective	not stated	mixture .05 - 1.5 mg/m^3 (total Cr)	resp ca, PMR = 18.2% vs 1.2% in control group, SS	pulmonary fibrosis seen in necropsied cases
Mancuso 1975	chromate producing	historical prospective	332	mixture .05 - 1.5 mg/m^3 (total Cr)	demonstrated a dose-response relationship	
Bidstrup & Case 1956	chromate producing	survey	723	bichromates (Cr(VI)); not quantified	lung ca, RR = 3.6, SS	no cohort defined
Taylor 1966	chromate producing	historical prospective	1212	mixture; not quantified	resp ca, RR = 8.5, SS	dose response with cumulative years of experience
Hayes et al. 1979	chromate producing	historical prospective	2101	mixture; not quantified	a) lung ca, RR = 2; SS b) lung ca, RR = 2.9; SS (mostly Cr(VI)) c) lung ca, RR = 1.3 (mostly Cr(III))	dose response with duration of exposure

(continued)

Table 7-1 - (continued)

AUTHOR[2]	INDUSTRY	DESIGN	NO. STUDIED	EXPOSURE	RESULTS	COMMENTS
Langard & Vigander 1983	chromium pigment	historical prospective	133	Lead & zinc chromates .01 - 1.35 mg/m^3	Lung ca, RR = 44, SS	exposure data from 1975-80
Davies 1978,79,84	chromium plating	historical prospective	1152 in 3 plants	Lead & zinc chromates	Plant A:Lung ca, RR = 2.2:SS Plant B:Lung ca, RR = 4.4:SS Plant C:Lung ca, RR = 3.2	plant C used lead chromate only
Royle 1975	chrome plating	survey	1238	mostly Cr(VI)	maligant neoplasms;RR=1.9,SS resp ca, RR = 1.8	no cohort defined
Franchini et al. 1983	chrome plating	historical prospective	178	mostly Cr(VI)	Lung ca, RR = 5.0;SS in thick plating department	
Pokrovaskaya & Shabynina 1973	ferro-chromium	survey	not stated	mixture; .02-.07 mg/m^3 (estimated Cr(VI))	all ca, RR = 3.3; SS lung ca, RR = 6.7; SS esophageal ca, RR = 2.0; SS	no cohort defined; few study details given
Axelsson et al. 1980	ferro-chromium	historical prospective	1876	mostly Cr(III),Cr(0) Cr(III)0-2.5mg/m^3 Cr(VI)0-.25mg/m^3	respir ca, RR = 4, SS for subcohort of maintenance workers; 2/4 cases were mesotheliomas	
Langard et al. 1980	ferro-chromium	historical prospective	976	mixture; < 1 mg/m^3 (total chromium)	Lung ca, RR = 2.3 (general population control) Lung ca, RR = 0.5, SS	exposure datafrom 1975

[1] Mixture implies that both soluble and insoluble and trivalent and hexavalent substances were present.

[2] RR Estimated relative risk.

[3] SS Statistically significant, p < 0.01.

process. Thus, chromium exposure is likely to encompass a mixture of oxidation states, solubilities and specific compounds.

Machle and Gregorius (1948) reported on the mortality of workers in 6 of 7 chromate producing plants in the U.S. Worker cohorts were not defined; instead, life insurance records were reviewed for cause of death for all previous years in which each plant had adequate employment and mortality records. This time period ranged from 4 to 17 years for the different plants. Comparing cancer mortality rates to those of oil refinery workers, statistically significant ($p < 0.05$) increases in the crude rates of cancer at all sites (4.17/1000 chromate vs 0.78/1000 refinery), cancer of the respiratory system (2.9/1000 vs 0.14/1000), and cancer of the digestive tract (0.09/1000 vs 0.05/1000) were found. Though the data were not age-adjusted, the differences persisted when the data were stratified into two groups: age 50 and under and age greater than 50. This suggests that the higher rates observed among chromate workers is not likely to stem from a disproportionate number of older workers in this group.

Limited exposure data were available in this study. The overall range of airborne "chromates" reported by 4 plants was 0.003 -21.0 mg/m^3, but there was considerable variation by plant and by location within each plant. The authors stated that the incompleteness of these data render them inadequate for further epidemiologic application.

Baetjer (1950) conducted a case-control study of 290 lung cancer patients in two Baltimore hospitals to determine if a relationship existed with employment in the local chromate plant. (The plant in question and the time period covered are part of the Machle and Gregorius study above.)

Controls were age-matched males randomly selected from each hospital's records. Statistically significant ($p < 0.05$) crude odds ratios were found for having lung cancer and exposure to chromium at each hospital. The odds ratios were 32 and 23, respectively.

Mancuso and Hueper (1951) studied the lung cancer-chromium association in employees of the Painesville, Ohio chromate plant. A cohort of workers was defined as consisting of employees who had worked for at least one year during the period 1931-1949. The male population of the county in which the plant was located served as the comparison group. Denominator data were not reported; rather, the results were presented as proportionate mortality ratios (PMR). The PMR for cancer of the respiratory system was 18.2% (6/33) among chromate workers and 1.2% among the general male population. This difference is significant at $p < 0.01$. The authors also stated that about 96% of the workers were exposed predominantly to insoluble chromium (chromite ore Cr(III)), suggesting that insoluble chromium, because of its relatively long pulmonary retention time (see Section 3.4), may have played a causal role in carcinogenesis. However, since all work environments were contaminated with both trivalent and hexavalent chromium, (i.e., both insoluble and soluble chromium) the data are too limited to ascribe the carcinogenic form.

Mancuso (1975) followed up a segment of this population (new employees for the years 1931-37). A major concern of the author was to determine whether an association existed between lung cancer deaths and exposure to chromium of different oxidation states and solubilities. Data from a 1949 industrial hygiene study of the plant were used to derive weighted average exposures to insoluble, soluble and total chromium which were then applied to the worker cohort. Water-soluble chromium was considered to be hexavalent while insoluble chromium was assumed to be trivalent. The author noted that since the plant's inception in 1931, production had dramatically increased, possibly increasing chromium dust concentrations. This was likely to have continued until 1949, when the company instituted control measures, which markedly reduced the exposure. Thus, the 1949 exposure data probably represent an average exposure for the cohort; that is, the data underestimate exposure from 1931 to 1949 and overestimate it subsequently.

Of the 332 cohort employees, 173 (52%) had died by 1974, including 41 from lung cancer. No comparison to a reference group was made. The age-adjusted data showed an increase in lung cancer rates with increasing exposure to chromium, regardless of solubility (and hence oxidation state). No statistical evaluation of those trends was reported, but the staff of DHS tested the data and found a statistically significant positive trend ($p < 0.001$). Mancuso concluded that the carcinogenic potential of chromium extends to all forms. However, given that employees were exposed to both trivalent and hexavalent compounds and that increases in one form were positively correlated with the other, this conclusion appears unwarranted.

The mortality experience of 723 workers in the bichromate-producing industry in Great Britain was studied by Bidstrup and Case (1956). Lung cancer mortality was significantly higher among workers than would be expected using national death rates: 12 lung cancers were observed versus 3.3 expected ($p = 0.005$). Mortality from other neoplasms or other causes of death was not elevated. The authors discuss, but do not adjust for, place of residence, social class and smoking habits, noting that differences between the worker cohort and the general population for the factors were minimal and therefore could not account for the 3.6 fold increase in lung cancer mortality that was observed.

Taylor (1966) identified a cohort of 1212 workers from 3 U.S. chromate plants who had worked for at least 3 months during 1937-40. The cohort was followed for 24 years using Social Security records; mortality data were obtained from death certificates. Seventy-one deaths due to cancer of the respiratory system were observed while 8.3 were expected using the U.S. male population for comparison (estimated relative risk = 8.51, $p < 0.001$). A dose-response effect was seen using specific cumulative years of chromate experience as an indicator of "dose" (no exposure data were reported). This effect was also observed for cardiovascular deaths and noncancer respiratory disease.

Hayes et al. (1979) reported on a cohort of 2101 workers who were initially employed between 1945 and 1974 and who worked at least 90 days in a Baltimore chromate plant. The plant was partially rebuilt in 1950-51 and in 1960 in an effort to reduce chromium exposures. In mid-1977 the vital status of 88% of the cohort had been ascertained. Compared to the male population of Baltimore, workers initially employed between 1945 and 1959 experienced a two-fold increase in lung cancer mortality ($p < 0.05$). Employees beginning work after 1959 were deemed to have had insufficient follow-up in view of the presumed long latency period and were not included in the analysis. Chromium concentrations were not reported, but a dose-response effect was found between duration of employment and mortality (adjusted for age). Also, a history of employment in the departments producing chromic acid and other hexavalent compounds was associated with increased lung cancer (estimated relative risk - 2.9, $p < 0.05$) in contrast to workers with a history of work in the chromite ore Cr(III) processing departments (estimated relative risk - 1.3, $p > 0.05$).

Other groups in the chromium industry have been less extensively studied than chromate producers. However, epidemiologic investigations have been reported for the chromium pigment and plating industries as well as the ferrochromium industry.

7.2.3 Chromium Pigment Industry

Exposures in the chromium pigment industry are mainly to hexavalent compounds, including sodium chromate (soluble), lead chromate (insoluble), and zinc chromate (insoluble).

Langard and Vigander (1983) reported the results of a study of a cohort of 133 employees who began work in Norwegian chromate pigment plants in 1948; the followup period extended through 1980. Workers commencing employment after 1972 were excluded. Early exposure was to both lead and zinc chromates, but production of lead chromate terminated after 1956. Historical exposure levels were not known, but routine measurements between 1975-80 showed chromium levels of 0.01 - 1.35 mg/m^3. Thirteen cancers were observed in the cohort: 7 were lung cancer. Among 24 workers who had been exposed more than 3 years, 6 lung cancers were observed versus 0.135 expected based on the Norwegian male population (estimated relative risk = 44, $p < 0.001$).

Davies (1978, 1979, 1984) reported on lung cancer mortality among workers making lead and zinc chromate pigments at 3 English factories. No specific cohorts were defined; instead all non-office male workers completing at least one year's service by June 30, 1975, from as early a date as records permitted were followed. Exposure levels were not reported. Rather, workers were classified into low, medium, and high categories depending on work activity and likely exposure to chromates. Also, the exposure in one of the plants (plant C) was exclusively to lead chromate. For workers on the job for at least one year and for whom plant records were available, no significant increases in lung cancer among the low exposure group were noted in any plant relative to the general male population of England and Wales. However, since there were less than 100 men in this exposure class in any plant, these results should be interpreted cautiously. Also, since cohorts were not defined there may well have been large numbers of recently employed workers for whom the followup period was too short (i.e. - all those starting work after 1960). Statistically elevated increases in lung cancer mortality were found for workers with high or medium exposures in only two plants (plant A estimated relative risk = 21/9.5, $p < 0.001$; plant B estimated relative risk = 11/2.5; $p < 0.001$). Davies interpreted the absence of lung cancer excesses in the 167 workers in Plant C as an indication that lead chromate is not carcinogenic in man. The qualitative nature of the exposure data and the small worker cohort in plant C militate against such a definitive conclusion.

7.2.4 Chrome Plating Industry

Exposures in the chrome plating industry are predominantly to hexavalent chromium compounds, including chromium trioxide, sodium and potassium dichromate, and chromic acid. These compounds are soluble in water.

Royle (1975) studied 1238 past and current plater workers in 54 plants in the United Kingdom. A minimum of 3 months of consecutive employment in a plant was required for entry into the cohort. A reference population consisting of manual workers from non-plating departments of the larger plants and from other industrial plants was the source of individually matched controls for the platers. Matching was based on age, sex, and when last known to be alive. The rate of death due to malignant neoplasms among platers was 3.2/100 (39/1238) versus 1.6/100 (21/1284) in the control group ($p < 0.05$). Mortality rates for cancers of the lung and pleura, gastrointestinal tract, and "other sites" were elevated among platers, but did not reach statistical significance. Increases were also reported for death due to non-neoplastic respiratory disease. No exposure concentration data were reported.

Franchini et al. (1983) reported on the mortality of a cohort of 178 chromeplating workers from 9 plants in Parma, Italy. Workers employed for at least one year between 1951 and 1981 were included. Though airborne chromium concentrations were reported, it is not clear when the measurements were made; there is, however, some indication that the measurements were taken in recent years when the hygienic conditions in the plants had substantially improved. The air levels in the plants engaged in the use of "thick" plating were 7 mg/m^3 (range 1 - 50) near the plating baths and 3 mg/m^3 (range 0 - 12) in the middle of the room. The authors refer to another industrial hygiene survey of these plants (reporting levels about ten times higher) which indicated air levels would be about one-tenth as great where thinner plating was used.

Stratifying on thick/thin plating and restricting the cohort to those who had a minimum of 10 years of follow-up, there was a significant increase in lung cancer mortality among the thick plating workers: 3 cases were observed versus 0.6 expected, based on the general Italian male population (adjusting for age), ($p < 0.05$). Since only 62 men were in the thin plating subcohort, the lack of an observed response in these workers may be related in part to the small sample size.

7.2.5 Ferrochromium Industry

A limited number of epidemiologic studies have also been published concerning the cancer mortality of workers in the ferrochromium industry. This industry uses both trivalent and hexavalent chromium in the production of steel alloys.

Pokrovskaya and Shabynina (1973, as cited in EPA, 1984) compared the cancer mortality of a group of ferroalloy workers in the Soviet Union to the local population for the time period 1955-69. No specific cohort was defined nor were the numbers of cancer cases, individuals in the comparison groups, and person-years at risk given. Workers in the plant were reported to be exposed to low-solubility chromium compounds with concentrations of hexavalent chromium exceeding the allowable level of 0.01 mg/m^3 by 2 to 7 times. In addition, some workers were exposed to smelting process fumes for the chromium ore, which included benzo(a)pyrene.

Age-specific cancer mortality ratios (MR) were reported. The ratios for cancers in males aged 50-59 were significantly increased ($p < 0.001$) for all sites (MR - 3.3), lung (MR - 6.67), and esophagus (MR - 2.0). Esophageal cancer mortality was also elevated among 60-69 year old males (MR - 11.3, $p < 0.001$). However, the lack of methodological detail reported as well as the absence of a defined worker cohort leave the results of this study open to question.

Axelsson et al. (1980) investigated the mortality and incidence of tumors among 1932 ferrochromium workers in a Swedish plant. A cohort of 1836 men was defined as all male workers who had worked at the plant for at least one year during 1930-75 and who were alive on January 1, 1951. Expected rates were based on the county in which the plant was located. Exposures in their plant were predominantly to trivalent and metallic chromium, although hexavalent chromium was present in some stages of production. According to the authors, "recent" measurements and discussions with various plant personnel allowed estimation of exposure levels; the range for Cr(0) and Cr(III) was 0 - 2.5 mg/m^3 while that for Cr(VI) was 0 - 0.25 mg/m^3. Of specific work categories, arc-furnace and maintenance employees were most heavily exposed.

The total number of deaths from tumors was less than expected (69 versus 76.7) for the entire cohort but a non-significantly elevated number was found among maintenance workers (18 vs 13.6). The elevation in maintenance workers was due in part to an increase in mortality from respiratory cancers (3 vs 1.3, $p > 0.05$). This latter finding was paralleled in the incidence data, where 4 respiratory cancers among maintenance workers were observed against one expected ($p = 0.038$). Two of these cases were pleural mesotheliomas and could be related to exposure to abestos, which was used in the plant. Exposure data for asbestos was not presented.

Langard et al. (1980) studied the incidence of cancer in male workers at a Norwegian ferroalloy plant (chromium and silicon alloys were produced). The cohort studied included all men who had worked at least one year in the period 1928-77, but the analysis focused on 976 workers who started before January 1, 1960. Both overall cancer mortality and incidence were lower than would have been expected based on national data. Lung cancer incidence was elevated; however, 7 cases were found among ferrochromium workers while 3.1 were expected ($p > 0.05$). The authors note that the expected rate may be inflated because the age-corrected lung cancer rate in the population of the county in which the plant is located is only 58% of the incidence in the whole country. Applying 58% to the expected rate results in a significant increase in the incidence ratio ($p < 0.01$). Furthermore, using non-ferrochromium workers as an internal referent population resulted in an 8.5-fold increase in lung cancer incidence ($p = 0.026$).

Exposure data were based on a 1975 industrial hygiene survey of the plant. The total chromium content of dust was "with few exceptions" below 1 mg/m^3. This level probably underestimates past exposures. Water-soluble chromium (assumed to be hexavalent) ranged from 11-33% of the total. The presence of high levels of Cr(VI) in previous years was also confirmed by the finding of 2 workers with nasal septum perforations. Exposure to asbestos and low levels of polycyclic aromatic hydrocarbons also occurred, but concentrations were not reported. However, since the 243 ferrosilicon workers studied were similarly exposed yet experienced no lung cancers, the effect of these exposures may be minimal.

7.2.6 Other Epidemiologic Studies

Epidemiologic studies have also been conducted in users of chromium products, particularly welders. Certain welding fumes contain chromium, manganese, nickel, and trace amounts of arsenic and lead. Stern (1983) reviewed the literature and found 22 studies of cancer incidence and welding. Five studies showed statistically significant ($p < 0.05$) increases in the relative risk (range of relative risks: 1.3 - 5). The results in all 22 studies were consistent with a relative risk of 1.3, based on a 95% confidence interval. Because of the mixed exposure to several metals, each of which has demonstrated mutagenicity or is suspected of being a human carcinogen, these studies are not as useful for identifying chromium as a carcinogen and will not be further discussed.

Only one study was found that looked at the carcinogenic potential of chromium in a nonoccupational setting. Axelsson and Rylander (1980) studied lung cancer mortality in communities exposed to chromium emissions from the ferroalloy industry. No statistically significant difference was found for lung cancer mortality rates between communities affected by the emissions and rural communities having no industrial emissions. Though chromium exposure levels were measured, they were not speciated in terms of chromium oxidation state or specific compounds. Since the ferrochromium industry predominantly uses trivalent chromium, the absence of an effect in this study may be due to exposure to the form of chromium that is not established as a carcinogen. Moreover, any Cr(VI) formed during the processing of Cr(III) could have been subsequently reduced to the trivalent form in the atmosphere (NAS, 1974), which could also account for the lack of increase in lung cancer mortality in the communities. Another possibility to account for the lack of increased lung cancer could be that the chromium was on particles whose size would preclude them from being respired or deposited in the lung.

7.2.7 Summary of Epidemiologic Studies

The health outcomes studied in the published chromium epidemiologic studies are narrow in scope. Based on case reports from the chromium industry, investigators quickly focused on testing the lung cancer hypothesis. Total mortality and mortality from all cancers were also routinely reported and, occasionally, data on cancer for non-respiratory sites were presented. Few authors mentioned any acute effects or other chronic conditions, although nasal perforations were reported as an indication of high hexavalent exposure in several studies. Therefore, the epidemiologic studies are not adequate to evaluate non-carcinogenic effects.

Several different study designs and worker groups were used to study the chromium-lung cancer relationships. The finding of statistically significant associations between worker exposure to chromium and lung cancer on an international basis and from a variety of study designs provides strong evidence to identify chromium as a human carcinogen. However, the studies have not been able to answer all the questions concerning chromium's carcinogenicity for two reasons: control of potential confounding variables and quality of the exposure data.

The major potential confounders are cigarette smoking and exposure to other respiratory carcinogens, such as asbestos and benzo(a)pyrene. Because personal histories typically were not obtained, most authors made the assumption that workers' smoking habits were identical to those of the general population (i.e. the usual comparison group). To the extent this is not true, the observed number of lung cancer cases can be over- or under-estimated. For example, if workers smoked more than their comparison group counterparts, it would not be clear how much of the excess lung cancer observed was due to cigarettes and how much to chromium. Some authors did qualitatively consider the smoking issue and concluded that it did not exert a confounding effect or that smoking could not by itself have accounted for the excesses of the magnitude seen. Staff members of DHS agree with this conclusion: it is not likely that the estimated relative risks, which exceeded 20 in many cases, could be explained solely on the basis of smoking.

Similarly, there cannot be a definitive resolution to the problem of exposure to multiple carcinogens. Since exposure data were generally lacking, quantification of exposure to other carcinogens is tenuous, at best. The impact of these exposures could reduce or invalidate the chromium-lung cancer relationship. Invalidation does not seem likely, however. For example, asbestos exposure is likely to occur in smelter operations among selected workers (furnace operators and perhaps maintenance workers). The finding of a positive association between chromium exposure and lung cancer in other workers within the same plant and in other chromium industries suggests that chromium has at least an independent role in carcinogenesis.

The second major problem with the epidemiologic studies -- the poor chromium exposure data -- limits the specificity of the cancer-chromium relationship vis-a-vis oxidation state, solubility, and individual compounds. As was indicated earlier, levels of exposure were rarely known. Where exposure levels were given, they were incomplete relative to the period of worker exposure. Further, since employees were exposed to mixtures of chromium-containing materials, the available data are insuffient to differentiate effects based on oxidation state, solubility or specific compounds. The observation by Baetjer (1950) that respiratory cancer was not associated with the mining of chromite ore (trivalent, insoluble) and the findings of lower cancer risks in those industries mainly using trivalent chromium (e.g. ferrochromium) and those with exposure to trivalent and <u>insoluble</u> hexavalent chromium (e.g. Davies, 1984 chrome pigments) suggest that trivalent chromium may not be as carcinogenic as the soluble hexavalent form.

In summary, the epidemiologic data identify chromium as a respiratory system carcinogen, but are insufficient to refine the carcinogenic potential in terms of individual compounds, the trivalent or hexavalent oxidation state, or differing solubilities. Furthermore, while the findings of some studies suggest chromium is associated with nonrespiratory cancers, the evidence is insufficient to consider this to be of a causal nature.

8 QUANTITATIVE RISK ASSESSMENT

8.1 Introduction

EPA has recently published a health assessment for chromium (EPA, 1984). The report was independently peer-reviewed in public sessions of the Environmental Health Committee of EPA's Science Advisory Board. The quantitative risk assessment of this document has been adopted for this report based on the rationale given below. The assessment focuses on hexavalent chromium, since Cr(VI) compounds have demonstrated both mutagenic and carcinogenic effects while evidence implicating Cr(III) as either a mutagen or carcinogen is weak. The staff of DHS believes this is a reasonable and appropriate interpretation of the health effects data on chromium.

To be protective of public health, a risk assessment should be based on the adverse health effect which arises from the lowest exposure to a substance. Both carcinogenic and non-carcinogenic effects must be considered.

8.2 Nonc ~cinogenic Risks

Noncarcinogenic ~fects of hexavalent chromium include skin ulceration and dermatitis, nasal ~sa irritation and septum perforation, and kidney and liver damage, while r(III) has been implicated in causing pulmonary fibrosis (see Section 4.~.2; ACGIH, 1984). These effects have been reported from exposures in occupational settings. As a result, occupational standards have been set at levels presumed not to cause these effects given repeated exposures. The American Conference of Governmental and Industrial Hygienists (ACGIH) has established the occupational threshold limit value (TLV) for Cr(VI) at 0.05 mg/m^3 while the permissible exposure level (PEL) recommended by NIOSH is 0.025 mg/m^3 (water-soluble, noncarcinogenic Cr(VI)) and 0.001 mg/m^3 (water-insoluble, carcinogenic Cr(VI)). The TLV for Cr(III) is 0.5 mg/m^3. These occupational standards are not necessarily directly applicable to the general population because of the potential greater susceptibility to disease among the general population. In fact, the ACGIH has cautioned against the general application of TLVs stating that:

> These limits are intended for use in the practice of industrial hygiene and should be interpreted and applied only by a person trained in this discipline. They are not intended for use, or for modification for use, (1) as a relative index of hazard or toxicity, (2) in the evaluation or control of community air pollution nuisances, (3) in estimating the toxic potential of continuous, uninterrupted exposures or other extended work periods, (4) as proof or disproof of an existing disease or physical condition...(ACGIH, 1984).

However, temporarily holding these caveats in abeyance, the lowest PEL of 0.025 mg/m^3 can be modified to account for a 24 hour per day and 365 day per year exposure yielding a concentration of about 0.01 mg/m^3 which is "theoretically" protective against nasal irritation, septal perforation, dermatitis, and liver and kidney dysfunction. Further, to be more cautious, an additional conservative safety factor can be applied, e.g., 100, yielding a "population threshold" of 100 ng/m^3. This level is 5 to 6 times greater than ambient levels. Thus, using this crude and extremely conservative approach, noncarcinogenic respiratory, renal, hepatic or cutaneous effects would not be expected to appear at ambient levels.

8.3 Carcinogenic Risks

8.3.1 Sources of Data

Typically, bioassays and/or epidemiologic studies are used for quantitative risk assessment of carcinogens. Both sources of data are available for chromium. In general, however, the use of epidemiologic data is preferable since effects in humans are being evaluated, obviating the need for inter-species extrapolation. Moreover, in the case of chromium, the route of exposure in the epidemiologic studies, inhalation, is the route of primary concern to the ARB.

Animal carcinogenicity studies have not been successful in demonstrating a significant increase in tumor incidence following inhalation or ingestion (see Appendix I). This finding holds for both trivalent and hexavalent compounds. However, some studies have shown significant tumor increases at site of contact, particularly for some hexavalent compounds, following sub-cutaneous injection, intratracheal instillation, or intrabronchial, intrapleural, intramuscular or intratracheal implantation. While support-ing the identification of chromium as a potential carcinogen, these latter studies are not used for quantitative risk assessment for reasons described below.

Determination of comparable inhalational dose levels from the above-noted, atypical routes of exposure, that yielded carcinogenic excesses is problematic. In the case of implantation studies, since tumors appear to develop only at the site of contact, the dosage producing the effect (as opposed to the amount of material implanted) is not readily discernible: high local concentrations are likely to appear at the site of exposure and without good absorption data, it is difficult to quantify dosage. For the instillation studies, difficulty arises with respect to relating the delivered dose, to the ambient levels that would have to exist to produce this dose through inhalation, given the anatomy and physiology of the animals' upper respiratory tract. The differential cancer response by route of administration indicates that the dose distribution is affected by the route of exposure. It also points to the need for physiochemical and pharmacokinetic information relating the distribution of chromium in lung tissues after inhalation or intratracheal administration. Such information is not available. Furthermore, the physiologic mechanism of dose distribution by intratracheal administration may depend in a non-linear fashion on the dose levels used in the experiment (EPA, 1984). The study by Steinhoff et al. (1983), in which a weekly dose of sodium dichromate induced a carcinogenic response in rats but failed to do so when one-fifth this dose was given five times per week, supports this contention. Thus, the staff of DHS believes that it is not appropriate to attempt to derive the dose-response curve for an inhalation exposure where the dose parameter is as poorly defined as in the case of the chromium animal studies, particularly when adequate epidemiologic data are available for quantifying the excess risk.

8.3.2 Selection of Chromium Compound(s) For Risk Assessment

As the toxicological data suggest, chromium's health effects are related to the oxidation state, solubility, and the metal elements in the test compounds (e.g. lead, zinc, calcium). In general, trivalent chromium compounds do not show evidence of mutagenicity in short-term genotoxicity tests. Experiments in several animal species further suggest that Cr(III) compounds (e.g. chromic acetate, chromic oxide, chromite ore) are not likely to be carcinogenic. IARC (1980) concluded, however, that these data were inadequate to either confirm or refute the carcinogenicity of trivalent chromium. The staff of DHS agrees with this conclusion.

In contrast, several hexavalent chromium compounds have been shown to cause genotoxic effects in prokaryotic and eukaryotic systems, both in vitro and in vivo. Moreover, studies in rats have demonstrated the carcinogenicity of several Cr(VI) compounds: lead chromate (insoluble), zinc chromate (insoluble), strontium chromate (insoluble), and sintered chromium trioxide (insoluble).

Since these data are not in conflict with the epidemiologic findings, the staff of DHS believes the risk assessment should be based on hexavalent chromium compounds. However, because the DHS assessment will use epidemiologic data to estimate risk, and because these data do not permit differentiation of risk with respect to solubility or compound specificity, the assessment will pertain to the general class of Cr(VI) compounds. The staff of DHS recognizes that, in assuming all hexavalent chromium compounds are equally carcinogenic, the estimated risk per unit dose (potency) may be underestimated due to the inclusion of potential noncarcinogenic compounds in the cancer potency calculation. The staff also recognizes that the application of this potency factor to a mixed Cr(VI) exposure may overestimate the predicted cancer risk (by assuming exposure to a higher dose of carcinogen than is actually present).

8.3.3 Threshold

A threshold in classical toxicology is a level at or below which a toxic response does not occur. The concept of a threshold is accepted for health effects which are not self-propagating. In theory the threshold represents an absolute level; however, in practice the threshold level is defined where no effect can be detected. The practical threshold is thus a function of technology, i.e., the ability to measure small effects, and of sample size, i.e., the ability to observe a rare event in a given exposed population. Practical thresholds are typically determined by applying a safety factor to the lowest no observed effect level (NOEL) or no observed adverse effect level (NOAEL) among all health effects of concern, as determined from experimental data or observational reports. The safety factor provides an additional degree of protection to account for more susceptible individuals in the genetically heterogenous general population.

Whether carcinogenesis (a self-replicating process that may continue after the exposure has ended) is characterized by a threshold is controversial. Empirically, a threshold level cannot be proven using either animal or human studies (e.g. if there were no effect observed in 25,000 animals, one could not be absolutely assured of a similar outcome in 100,000 animals or

1 million animals). Therefore, the issue of a carcinogenic threshold can only be resolved based on knowledge of the mechanism by which a substance causes cancer. Science has yet to validate proposed mechanisms. It is believed, however, that cancer is a multistage process that can be initiated with an attack by a carcinogen on DNA. The result can ultimately be expressed as a tumor. Theoretically, despite the body's defense mechanisms, the initiating event can be caused by a single molecule of the carcinogen, making the threshold dose indistinguishable, for practical purposes, from zero. This is in contrast to other toxic effects that are believed to occur only after the reserve capacity of the biologic target to withstand and rapidly repair damage has been exceeded.

Some compounds associated with carcinogenic responses do not appear to interact directly with DNA. Although it is possible that these compounds may have thresholds, their mechanisms of action are not well-understood. These compounds are currently treated for purposes of risk assessment as non-threshold substances.

The mechanism by which chromium induces cancer is not known. Levis and Bianchi (1982) have described a possible mechanism which requires exposure to hexavalent chromium because, in contrast to trivalent chromium, Cr(VI) can readily penetrate the cell membrane. However, as noted in Section 5.4, trivalent chromium, formed from either intracellular enzyme-mediated reduction or by reaction with reducing agents, may be the ultimate carcinogen. Thus, it is not known if the "initiating" event is the binding of Cr(III) to DNA, the reduction of Cr(VI) to Cr(III), or some other process. In any case, the proposed mechanism predicated on the occurrence of a genotoxic event is consistent with the assumption of a nonthreshold process.

One critic of the EPA chromium health assessment document (Hathaway, 1985) interpreted the findings from some short-term genotoxicity studies, metabolic studies, and an animal study as demonstrating the existence of a threshold. The points cited to support this were: 1) Cr(III) appears to be neither mutagenic nor carcinogenic, 2) treatment of Cr(VI) with chemical or biological reducing agents renders Cr(VI) nonmutagenic, 3) treatment of Cr(III) with strong oxidizing agents results in a positive mutagenic response, 4) Cr(VI) is reduced to Cr(III) both extra- and intracellularly, and 5) an unpublished animal study in which a weekly dose of sodium chromate (Cr(VI)) for life yielded a carcinogenic response while one-fifth this dose administered five times per week resulted in no tumors (Steinhoff et al., 1983). In other words, the genotoxicity tests suggest that exogenous Cr(VI) is a carcinogen whereas Cr(III) is not, even if Cr(III) is the valence state with which DNA is ultimately complexed. The implication is that, to the extent that Cr(VI) is reduced extracellularly or even intracellularly prior to reaching the nucleus, the likelihood of a significant genotoxic effect is correspondingly diminished. If the reduction process occurs in a non-linear fashion, a practical threshold may exist. The differential carcinogenic response observed in the animal study also supports the concept of a practical threshold.

The staff of DHS agrees that some of these findings may be consistent with the existence of a metabolic threshold, but do not believe that they constitute compelling proof of a threshold or, in particular, of a threshold that could be numerically applicable to humans. Other factors need to be considered. For example, possible pharmacokinetic differences between the aforementioned test systems and man limit the direct generalization of these findings to man. Also, even if the reduction of hexavalent chromium were a non-linear process, these metabolic defenses have not convincingly been demonstrated to be completely effective. Furthermore, the demonstration of a dose-rate response (Steinhoff et al., 1983) does not exclude the possibility that a carcinogenic response could have been seen in the low-dose group had a larger population been studied. Alternatively, the dose-rate response observed by Steinhoff could be interpreted as showing that the lifetime-averaged daily dose may not be appropriate for modelling the risk of chromium.

The evidence presented in support of a threshold is inconclusive and perhaps is more suggestive of a nonlinear low-dose response than an absolute threshold. Hathaway (1985) acknowledged these difficulties: "... this evidence does not permit quantification of the threshold or a description of the dose-response at low doses." The staff of DHS concurs with Hathaway on these latter points. Therefore, in accordance in Section 39650 of the Health and Safety Code which stipulates that DHS should be protective of public health, and given that the assumption of low-dose linearity is conservative (i.e., public health protective) the hexavalent chromium risk assessment should be based on a linear non-threshold model.

8.3.4 Extrapolation Models

Chromium exposures in the occupational epidemiologic studies tended to be in the milligram/m^3 range. Ambient exposures to atmospheric chromium are in the nanogram/m^3 range, or about one million times lower. Therefore, a model and a procedure are required to estimate effects resulting from exposure to ambient levels, when the only demonstrated response occurred at much higher occupational levels.

Empirically, most extrapolation models fit the observable dose-response data equally well, but can give vastly disparate results in the low-dose, nonverifiable range of concern. However, mutagenic studies with both ionizing radiation and a wide variety of chemicals support a linear, non-threshold, dose-response relationship, particularly for low-dose exposures (EPA, 1984). Epidemiologic studies of radiation-induced leukemia, breast and thyroid cancer, and liver cancer induced by aflatoxins in the diet also support this type of relationship (EPA, 1984). Therefore, the DHS risk assessment will adopt the EPA linear nonthreshold model to estimate low-dose chromium exposure carcinogenic risks, recognizing that such a model, although biologically plausible, has scientific limitations. A linear nonthreshold model is also likely to be health-protective because, for example, the linearity assumption may provide an upper limit to the dose-response.

Two procedures were used by EPA to calculate the potency. The first requires age-specific mortality data and calculates the carcinogenic potency taking competing risks of death into account. (A more detailed description of this procedure is given in Appendix II.) The lifetime probability of lung cancer given continuous lifetime exposure to dose d is given by:

$$P(L,d) = \int_0^L h(s,d)\exp\{-[\int_o^s h(y,d)dy + A(s)]\}ds,$$

where L is the maximum human lifetime, exp [-A(s)] is the probability of surviving to age (s) without acquiring lung cancer, and h(t,d) is the age-cause-specific mortality after adjusting for the background rate. Once the function h (t,d) is specified, its parameters can be estimated from the epidemiologic data; A(s) is estimated from vital statistics.

The second procedure is less complex and is applicable where age-specific information is not given. The method assumes that the risk among exposed individuals (R_e) is a function of the exposure dose (d) and background cancer rate (R_b):

$$R_e = R_b + Bd,$$

where B is the potency factor. The relative risk (i.e., the ratio of risk between exposed and non-exposed individuals) is therefore:

$$\frac{R_e}{R_b} = \frac{R_b + Bd}{R_b} = RR.$$

Solving for B yields:

$$B = [(RR - 1) \times P_0]/d.$$

Data from epidemiologic studies are used to estimate the relative risk while information concerning dose levels, if available, is typically presented in either an epidemiologic study or in an associated industrial hygiene survey. The background rate of cancer is typically obtained from vital statistics data.

The excess lifetime probability of lung cancer, given a continuous lifetime dose of hexavalent chromium, P(L,d), is then given by:

$$P(L,d) = 1 - \exp(-Bd).$$

8.3.5 Selection of Studies for Quantitative Risk Assessment

Many epidemiologic studies have demonstrated the carcinogenicity of chromium, but few have been able to quantify the exposure, particularly in a manner representative of the experience of exposed individuals. Indeed, only one study (Bourne and Yee, 1950 with reference to Mancuso & Hueper, 1951) addressed the issue of particle size which could be a critical factor in establishing dosage. Since the inhalation exposure was most likely due to chromium dust or aerosol (chromic acid mist), actual worker exposures would probably be restricted to respirable particles that would be retained in the lungs (i.e., less than 5 μm (Task Group on Lung Dynamics, 1966)). Thus, it is possible that the exposure data available to calculate the potency are inflated which has the practical effect of underestimating the potency factor. Similarly, the use of respirators would decrease actual exposures relative to ambient measurements, resulting in an underestimated potency factor. The extent of respirator usage was not, however, discussed in the epidemiologic studies used for the risk assessment.

Exposure data were reported for the Mancuso (1977), Langard et al.(1980), Axelsson et al. (1980), and Pokrovskaya et al. (1973) studies. The analytic group in the Langard study consisted of a cohort of men who began work some time between 1928 and 1960 but the exposure data were based on an industrial hygiene study conducted in 1975. The authors noted that several changes in production routines occurred during the plant's 50 years of operation and that no data were available on chromium exposure levels for previous years. Since the industrial hygiene of the plant undoubtedly improved during the period the cohort was exposed, the 1975 exposure data are likely to significantly underestimate the cohort's average exposure. These data will then yield a spuriously high potency factor. For this reason the staff of DHS do not believe the Langard et al. study should be used for the hexavalent chromium risk assessment.

The Axelsson et al. study also provides exposure data, but the ill-defined sources for these data and the ambiguity of the health findings in this study render it inappropriate for a quantitative risk assessment. The exposure data are based on "recent measurements and discussions with retired workers and foremen employed in the 1930s" (Axelsson et al., 1980). As such, the accuracy of these exposure data is questionable. More importantly, however, was the finding that the subcohort of maintenance workers, which was the only group found to have a statistically significant elevated respiratory cancer risk, was also exposed to asbestos. Two of the four respiratory cancers observed were mesotheliomas, a neoplasm generally considered to be almost exclusively associated with prior exposure to asbestiform fibers. With one cancer expected and excluding the mesotheliomas, the observed relative risk (2/1) was not statistically significant. Given the synergistic relationship between cigarette smoking and asbestos exposure (i.e., a 50-fold increase in lung cancer risk among smokers who are also exposed to asbestos) and the absence of smoking data for cohort members, the staff of DHS does not believe that the one extra case of lung cancer observed in the Axelsson study can be reliably attributed to chromium. Therefore, this study will not be included in the DHS cancer risk assessment.

Of the remaining studies, the investigation by Mancuso is most appropriate for use in a quantitative risk assessment. The inadequate reporting of the Pokrovskaya et al. study in terms of cohort definition and details concerning the results renders the validity of study's findings somewhat questionable. Therefore, this risk assessment will focus on the Mancuso study. An estimate of chromium's potency based on the Pokrovskaya et al. study is also presented for comparative purposes only with the understanding that it may be less valid.

8.3.6 Risk Assessment Based on the Mancuso Study

Mancuso (1977, see Appendix III) reported on the cancer mortality of 332 men who began work in the chromate (Cr(VI)) producing industry between 1931 and 1937. Forty-one lung cancer deaths had occurred by 1974. Since age-specific deaths were reported, both the competing risk and crude extrapolation models are used to estimate potency.

The risk assessments are based on data in the table below, (Table 8-1) which includes the exposure, lung cancer mortality given this exposure, and expected lung cancer mortality without chromium exposure for the study cohort. The reported weighted average worker exposures were assumed to be equivalent to the continuous exposure d (in ug/m^3) calculated by:

$$d = \frac{D}{f\,L_e} \times \frac{8}{24} \times \frac{240}{365} \times 10^3 \ \mu g/mg$$

where D is the reported exposure (in mg/m^3-years), L_e is the midrange of the age category, f is the fraction of time exposed to chromium, and 8/24 and 240/365 are the fractions of a day and year, respectively, that a worker spent at the plant. It was assumed that f = .65 which implies that the cohort exposure to chromium began approximately at age 20.

Exposure data are in units of total chromium and are based on a 1949 industrial hygiene study of the plant (Bourne and Yee, 1950; see Appendix IV). Since exposures occurred between 1931 and 1972 (the life of the

Table 8-1. Combined Age Specific Lung Cancer Death Rates and <u>Total</u> Chromium Exposure (in $\mu g/m^3$) for the Mancuso Study (Mancuso, 1975).

Age at Death [a]	Average Lifetime Exposure ($\mu g/m^3$) [b]	Deaths [c]	Person years At Risk	Background Rate [d]	Estimated Relative Risk	Exposure Range (mg/m^3 - yr)
50	5.66	3	1345	6.05×10^{-4}	3.7	≤ 1.99
50	25.27	6	931	6.05×10^{-4}	10.7	2.0 - 5.99
50	46.83	6	299	6.05×10^{-4}	33.2	6.0 - 7.99
60	4.68	4	1063	1.44×10^{-3}	2.6	≤ 1.99
60	20.79	5	712	1.44×10^{-3}	4.9	2.0 - 5.99
60	39.08	5	211	1.44×10^{-3}	16.5	6.0 - 7.99
70	4.41	2	401	1.57×10^{-3}	3.2	≤ 1.99
70	21.29	4	345	1.57×10^{-3}	7.4	2.0 - 7.99

[a] Midpoint of 10-year interval.

[b] These values are calculated by first using the formula given in the text (pg 86) and then taking the person year weighted average for the Mancuso-reported exposure subcategories (which have been combined in this table because of small numbers).

[c] Only 35 deaths are included in the risk assessment. The remaining six were among workers with exposures greater than 8 mg/m^3-year but the exact level is unknown and is unlikely to be identical across all age groups.

[d] Background rate is estimated from 1964 U.S. Vital Statistics. The year 1964 is selected because it was estimated by EPA that a large proportion of lung cancer deaths occurred during that year.

plant), exposures based on 1949 data represent an average exposure. Bourne and Yee indicate that, in view of the improvements in equipment and processes after 1946, it is extremely likely that chromium levels pre-1949 were greater than post-1949 levels, which supports the notion that the 1949 data represent average levels.

A review of the EPA risk assessment (Hathaway, 1985) raised the point that the use of the 1949 exposure data would underestimate the true exposure by 20- to 40-fold. This is based on the cumulative effects of three factors. First, the exposure data represent normal plant operating conditions and not plant upset conditions. Using maintenance workers' exposures, which were five to ten times greater than production worker exposures, as a basis of upset exposure levels, Hathaway indicated that a 2- to 4-fold underestimate had been used by EPA. Since it is not known what percentage of the general workforce was exposed to upset conditions or for how long, Hathaway's estimate cannot be verified. However, other estimates for this effect are consistent with the data. For example, if non-maintenance workers were exposed to five times (based on DHS' calculated average of maximum maintenance worker exposures) their usual exposure for three hours per week (based on Bourne and Yee), their increase in exposure is only 30%: $[37(x) + 3(5x)]/40 = 1.3x$, where x is the exposure estimate based on normal operating conditions.

Second, Hathaway stated that Mancuso had assumed that worker exposure post-1949 was zero. This assumption was based on their finding that Mancuso had not obtained worker job assignments after 1949. Hathaway presumed that the failure to account for post-1949 exposures might result in a two-fold underestimation of exposure. Third, Hathaway alleged that exposures prior to 1949 could have been five times greater than those measured in the 1949 industrial hygiene survey. Thus, these latter two points account for a ten-fold underestimation of exposure levels. Clearly, exact exposure levels cannot be calculated because the requisite data have not been collected. However, by invoking some crude assumptions, alternatives to Hathaway's estimate of exposure underestimation can be formulated. For example, Mancuso has indicated that although post-1949 work histories were not obtained, only about 25% of the worker cohort could have been exposed beyond 1949 (Mancuso, 1985 personal communication).

Therefore, assuming all cohort members were exposed to 5 times the 1949 levels for an average of 15 years (i.e., the median time between cohort formation and 1949) and additionally, 25% of the cohort was exposed to one-half the 1949 levels (estimated from Bourne et al., 1951) for the remaining 23 years that the plant was in operation, the overall weighted average exposure can be estimated as:

$$.75[\{(15yrs)(5x) + (0yrs)(.5x)\}/(15yrs)] + .25[\{(15yrs)(5x)+(23yrs)(.5x)\}/(15+23yrs)\} = 4.3x$$

where x is the 1949 exposure level.

The total underestimation of exposure may be only 5.6-fold (1.3 x 4.3) and not 20 to 40 fold, i.e., if indeed it has been underestimated at all. With knowledge of Hathaway's comments, EPA still felt that the exposure data might be underestimated by a factor of two.

Estimation of the hexavalent fraction of the total chromium levels reported by Mancuso can also be calculated from the industrial hygiene survey data. Bourne and Yee reported that the ratios of trivalent chromium to hexavalent chromium concentrations in the airborne dust in nine major departments ranged from 1 to 3, except for two departments where chromite ore (Cr(III)) was extensively used; the Cr(III) to Cr(VI) ratios here were 6 for the lime and ash operation and 52 for the ore preparation. Excluding the ore preparation department, exposure data yield an estimate for hexavalent chromium levels no less than one-seventh the amount reported for total chromium.

8.3.6.1 Potency Based on Competing Risks Model

Applying the competing risks model to the exposure and mortality data from Table 1 and estimating the probability of survival to age t (exp[-A(t)]) from U.S. Vital Statistics yield an estimate for the excess lifetime probability of cancer from exposure to chromium of 1.16×10^{-5} per ng/m^3. Assuming that the hexavalent chromium fraction alone is carcinogenic yields an excess lifetime risk of 8.12×10^{-5} per ng/m^3. Alternately, assuming the chromium levels have been underestimated by a factor of 5.6, the excess risk per ng $chromium/m^3$ would be 2.07×10^{-6}.

8.3.6.2 Potency Based on "Crude" Model

Estimation of the potency factor, B, using the "crude" model is also based on the data in Table 8-1. The estimated relative risk is calculated by taking the weighted average of the age-exposure-specific relative risks where the number of person-years is the weighting factor. Thus, the cohort average RR equals 7.2. The dose, d, is estimated as the weighted average of the age-exposure specific concentrations also weighting by person-years. The dose estimate is 15.5×10^3 ng/m^3. The background rate of lung cancer (R_b) is based on the lung cancer mortality rate for the 1964 U.S. population and is equal to 0.036. Therefore, the potency is calculated as follows:

$$B = [(7.2 - 1) \times 0.036]/(15.5 \times 10^3) = 1.44 \times 10^{-5}/ng/m^3.$$

Accounting for the estimated hexavalent fraction of the exposure or the possible underestimation of the total exposure yields potency estimation of 10.1×10^{-5}/ng/m^3 and 2.57×10^{-6}/ng/m^3, respectively.

These risk estimates may be too high if the workers smoked more than the general white male population, which the background rates are based upon. Mancuso provided no data on smoking habits, but it is generally accepted that the proportion of smokers is higher among industrial workers than the general population. EPA explored the impact of differential smoking habits on the risk assessment (EPA, 1984). As an example, if the background rate of lung cancer mortality for the Mancuso cohort is increased by 40% the corresponding potency would be reduced by 25%, or from 1.16×10^{-5} to 8.70×10^{-6}/ng/m^3. A 40% increase in background lung cancer mortality could arise assuming that 80% of the chromate workers are ever-smokers while only 50% of the general white male population are ever-smokers.

EPA concluded that the application of other reasonable assumptions about smoking habits of the cohort compared to the general white male population would not reduce the potency estimate by more than 50%. Therefore, the lowest estimates of potency "adjusting" for smoking and the possible under-estimation of dose (e.g. a factor of 5.6 from the sample DHS calculation) would be 11.2 times lower than those previously given or 1.04×10^{-6} /mg/m^3 for the competing risks model and 1.29×10^{-6} /ng/m^3 for the crude model.

A summary of potency estimates under different scenarios is presented in Table 8-2.

Table 8-2. Excess Cancer Risks from Continuous Lifetime Exposure to Hexavalent Chromium

	Estimated Excess Lifetime Risk per ng/m³ per Million Population: Competing Risks Model	Estimated Excess Lifetime Risk per ng/m³ per Million Population: Crude Model
Mancuso Data		
Exposure = Total Chromium[1] (best estimate)	11.6	14.4
a) underestimated exposure by 5.6	2.1	2.6
b) smoking rate higher among workers	5.8	7.2
c) a + b	1.0	1.3
d) 95% UCL[2] for best estimate	--	20.9
Exposure = Hexavalent Chromium[3] (best estimate)	81.2	100.8
a) underestimated exposure by 5.6	14.5	18.0
b) smoking rate higher among workers	40.6	50.4
c) a + b	7.3	9.0
d) 95% UCL[2] for best estimate	--	146.0
Pokrovskava et al. Data[4]		
a) high dose estimate	--	52.0
b) low dose estimate	--	180.0
c) geometric mean of a + b	--	97.0

[1]Potency calculated based on total chromium levels.

[2]Upper limit of the 95% confidence interval for estimated relative risk. Estimates [illegible] available for parameters in competing risks model.

[3]Concentration of hexavalent chromium assumed to be 1/7 the level of total chromium. See text for further explanation.

[4]Insufficient data provided to calculate confidence limits.

8.3.7 Risk Assessment Based on the Pokrovskaya et al. Study

This is a Russian study that was not published in English and hence, was not directly reviewed by the staff of DHS. The potency estimation below is excerpted from the EPA chromium health evaluation (EPA, 1984). The data reported by the authors are only appropriate for use in the crude model.

POTENCY ESTIMATION BASED ON POKROVSKAYA ET AL. (1973)

Although this study showed a significant increase of lung cancer mortality over the control group, the validity of the data is questionable because the study cohort is not clearly defined. The report indicates that the cancer mortalities over the period 1955-1969 in workers from a ferroalloy plant in the Soviet Union were compared with the population of similar ages in the city where the plant was located, but it fails to indicate the criteria by which workers were included in the cohort. The lung cancer mortality ratios were reported to be 4.4 (not statistically significant) for the age group 30-39 and 6.6 ($p = 0.001$) for the age group 50-59 among male workers. Concentrations of hexavalent chromium were reported to exceed the marginally allowable value (0.01 mg/m^3) by 2 to 7 times on the average. The length of employment was from 7 to 20 year, with an average of 15 years.

Based on the information that the average ambient concentrations of hexavalent chromium exceeded the marginally allowable value 0.01 mg/m^3 by 2 to 7 times, workers' exposure to hexavalent chromium ranged from 0.02 mg/m^3 to 0.07 mg/m^3. The lifetime doses corresponding to 0.02 mg/m^3 and 0.07 mg/m^3 are, respectively, as follows:

$$d_1 = 0.02 \times 10^3 \times (8/24) \times (240/365) \times (1/4) = 1.1 \text{ ug/m}^3$$

and

$$d_2 = 0.07 \times 10^3 \times (8/24) \times (240/365) \times (1/4) = 3.8 \text{ ug/m}^3$$

(where the factor of 1/4 represents the 15-year average exposure among the 60-year-old cohort members). If 6.6 is taken to be an estimate of the average relative risk for the cohort, then the carcinogenic potency for hexavalent chromium (Cr(VI)) is calculated to range from:

$$B = (6.6-1) \times 0.036/3.8 = 5.2 \times 10^{-2}/\text{ug/m}^3$$

to

$$B = (6.6-1) \times 0.036/1.1 = 0.18/\text{ug/m}^3.$$

The geometric mean of the two limits is 9.7×10^{-2}/ug/m^3. It is about 8 times larger than 1.2×10^{-2}/ug/m^3, the potency calculated on the basis of the Mancuso (1977) data.

Converting to ambient levels (i.e. nanograms/m^3) yields an estimate of 9.7 x 10^{-5}/ng/m^3. This potency estimate is about 8 times greater than the best estimate derived from the Mancuso data using the competing risks model.

8.3.8 Summary of the Risk Assessment

Both animal and epidemiologic studies have demonstrated that chromium causes cancer. However, for the purpose of quantifying the carcinogenic potential of chromium, no animal study and only one epidemiologic study was found to be appropriate. This conclusion was also reached by the Carcinogen Assessment Group (CAG) of EPA (EPA, 1984).

The cohort of chromate workers studied by Mancuso is the basis of the DHS risk assessment. While providing the best data for a risk assessment, four important issues could not be completely resolved. Thus, the carcinogenic potency contains some degree of uncertainty. The four issues are: (1) speciation of exposure with respect to trivalent and hexavalent chromium, (2) possible underestimation of worker exposures, (3) separation of the effect of chromium from that of cigarette smoking, and (4) potency of specific chromium compounds.

Speciation of chromium was based on the assumption that the trivalent form was insoluble in water whereas the hexavalent form was water soluble. This is not completely accurate since some Cr(VI) compounds are insoluble (e.g. lead chromate) and some Cr(III) compounds are soluble (e.g. chromium potassium sulfate). Therefore, the assumption that hexavalent chromium is one-seventh the amount of total chromium in the plant Mancuso studied, and hence the carcinogenic potency of hexavalent chromium is seven times greater than that based on the total chromium concentration, should be recognized as as source of uncertainty in the risk assessment.

The assertion that chromium levels have been underestimated must also be viewed cautiously, because it is not based on documented evidence from the plant in question. Thus, while the staff of DHS has provided potency estimates assuming a 5.6-fold underestimation in the exposure levels, the staff does not recommend that such an assumption or any assumption with regard to a possible exposure underestimation be used as the basis for a recommended potency level.

With respect to cigarette smoking, Mancuso did not address the potential confounding effect this may have had on the chromium-lung cancer relationship. Rather, the risk assessment assumes that the chromate workers had the same smoking habits as their general population counterparts. EPA, assuming no synergistic effect between chromium and smoking, estimated that even if the Mancuso cohort smoked more than their comparison group it would be unlikely that the potency factor could have been overestimated by more than a factor of 2. (If there is a synergistic effect, the independent role of chromium would be much less than indicated in this risk assessment. Available data are insufficient to verify or refute the existence of a synergistic relationship.) Again, while the DHS risk assessment has shown the estimated impact of smoking, staff members do not believe that the recommended range of potency levels should be based on possible differential smoking patterns.

The matter of potency for specific chromium compounds cannot be resolved with current epidemiologic data. Exposures tended to be mixed or, where only a single compound was present, exposure levels were not quantified. Thus, the staff of DHS recommends that the carcinogenic potency of different hexavalent chromium substances be considered equivalent.

The above issues notwithstanding, the conclusion of the staff of DHS is that hexavalent chromium is a human carcinogen without a threshold. The estimated excess cancer risk incurred from continuous lifetime exposure to hexavalent chromium is given by the range: $1.16 \times 10^{-5}/ng/m^3$ to $14.6 \times 10^{-5}/ng/m^3$. The lower limit represents the estimate based on using the average total chromium exposure data in the Mancuso study and the upper bound is based on the upper limit of the 95% confidence interval for the estimate of the relative risk in that epidemiologic study and assuming the concentration of hexavalent chromium was one-seventh that of the total. The staff of DHS does not present a lower confidence limit for potency estimates because the true risk may be considerably below even the lower boundary of the 95% confidence interval limit, yet there is no scientific basis for locating this risk. The upper boundary for the confidence interval is given since it represents a conservative estimate that is unlikely to be exceeded by the actual risk and is thus in accordance with Section 39650 of the Health and Safety Code which stipulates that DHS "shall utilize scientific criteria which are protective of public health consistent with current scientific data."

The risk estimates can also be applied to smaller geographic areas, such as those around point source emitters of chromium. In Part A (section III.C) data from two point sources located in populated areas were given (this is reprinted below). One area was comprised of a 20 x 20 kilometer area centered on a chromium plating facility. The other area was a 40 x 40 kilometer area centered on a bank of cooling towers.

Plating Facility

Annual Average Chromium Concentration, ng/m^3	Population Exposed	Cumulative Population
550	1,960	1,960
450	-0-	1,960
350	-0-	1,960
250	1,925	3,885
150	5,825	9,737
100	-0-	9,737
90	-0-	9,737
80	-0-	9,737
70	8,803	18,540
60	1,945	20,485
50	7,742	28,227
40	14,870	43,097
30	22,982	66,079
20	61,829	127,908
10	452,709	508,617
.05 to 5.0	2,400,000	2,993,262

Cooling Towers

Annual Average Chromium Concentration, ng/m^3	Population Exposed	Cumulative Population
5.0	8,886	8,886
4.0	2,993	11,879
3.0	23,942	35,821
2.0	96,565	132,386
1.0	730,336	862,722

Table 8-3 shows the theoretical cancer impact each of these point sources would have on the surrounding population using potency estimates of 1.16×10^{-5} /ng/m^3 and 14.6×10^{-5} /ng/m^3. For each source these are small subgroups within the population that are exposed to (relatively) high chromium levels and they would be subject to a correspondingly high estimated excess lifetime cancer risk. However, because so few people are exposed, the expected excess number of cancer cases would be small. Conversely, more cases would be predicted among population groups with low exposure because of the large number of people so exposed. It should be noted that the average lifetime risk of lung cancer in the U.S. population is about 8,700 per 100,000 in white males and 4,200 per 100,000 for white females (Seidman et al., 1985). Some of the incremental risks in table 8-3 would be large enough to be detected epidemiologically.

Table 8-3. Theoretical cancer impacts of lifetime exposure to Cr(VI) in populations near high point source emission locations.*

	Plating Facility	Cooling Tower
Range of Exposure**	0.05 - 550 ng/m^3	1 - 5 ng/m^3
Population Exposed	2,993,262	862,722
Population-weighted average exposure	7.55 ng/m^3	1.22 ng/m^3
EXCESS LIFETIME CANCER RISK AND NUMBER OF CASES		
A. Potency = $1.16 \times 10^{-5}/ng/m^3$		
Overall Population Risk	8.8×10^{-5}	1.4×10^{-5}
a) No. of cases	262	12
Risk at Highest Exposure	6.4×10^{-3}	5.8×10^{-5}
a) No. of cases	13 (pop. 1,960)	< 1 (pop. 8,886)
Risk at Lowest Exposure***	5.8×10^{-5}	1.2×10^{-5}
a) No. of cases	139 (pop. 2,400,000)	9 (pop. 730,336)
B. Potency = $14.6 \times 10^{-5}/ng/m^3$		
Overall Population Risk	1.1×10^{-3}	1.8×10^{-4}
a) No. of cases	3,299	153
Risk at Highest Exposure	7.7×10^{-2}	7.3×10^{-4}
a) No. of cases	151	7
Risk at Lowest Exposure***	7.3×10^{-4}	14.6×10^{-5}
a) No. of cases	1,752	107

* Based on data provided in Part A, Section III.C "Concentrations Close to Sources.

** For this table, it is assumed all chromium is hexavalent although the reported levels are for total chromium.

***For Plating Facility, the lowest exposure was taken as the upper bound of the range i.e., 5 ng/m^3.

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APPENDIX I

Summary of Bioassays
(Source: IARC, 1980)

Table 8 Summary of carcinogenicity studies of chromium and chromium compounds in animals

Compound	Species	Route and dosage	Findings	Reference
Chromium powder	Mouse	4 i.p. injections of 0.2 ml of a 0.005% solution	1 myeloid leukaemia in 50 treated animals	Hueper, 1955
	Mouse	6 i.v. injections of 0.05 ml of a 0.005% solution	No tumours	Hueper, 1955
	Mouse	6 intrapleural injections of 0.2 ml of a 0.005% suspension	No tumours in 50 treated mice	Hueper, 1955
	Rat	1 intratracheal injection of 10 mg	No squamous-cell carcinomas of the lung in 12 treated rats	Mukubo, 1978
	Rat	1 i.m. injection of 2 mg	No local tumours in 22 surviving treated animals	Sunderman et al., 1974
	Rat	6 i.p. injections of 0.1 ml of a 0.05% suspension	No increase in round-cell sarcoma incidence compared with controls. 2 insulinomas in treated animals, none in controls	Hueper, 1955
	Rat	6 i.v. injections of 0.15 ml of a 0.05% suspension	2 rats with pulmonary adenomas; no increase in sarcomas compared with controls	Hueper, 1955
	Rat	6 intrapleural injections of 0.05 ml of a 33.6% (by weight) suspension or 6 intrapleural injections of 0.1 ml of a 0.5% suspension	2 haemangiomas and 1 angiosarcoma in 50 treated animals and 0/25 controls	Hueper, 1955
	Rat	Intramedullary injection into the femur of 46 mg	No injection-site tumours in 25 treated animals	Hueper, 1955

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Chromium powder (contd)	Rabbit	18 i.v. injections of 0.5 ml/kg bw of a 5% suspension	1 carcinoma of lymph node in 3 treated survivors and 0/4 controls	Hueper, 1955
Unroasted chromite (III) ore	Mouse	Intrapleural injection of 10 mg in 0.5 ml distilled water	Granulomas	Davis, 1972
	Rat	6 intrapleural injections of 0.05 ml of a 73.4% (by weight) suspension	Injection site sarcoma in 1/25 treated animals	Hueper, 1955
	Rat	Intramedullary injection into the femur of 58 mg	No injection site tumours in 25 treated rats	Hueper, 1955
	Rabbit	12 i.v. injections of 5 ml of a 5% suspension	No tumours	Hueper, 1955
Roasted chromite (III) ore	Mouse	i.m. implantation of 10 mg (equivalent to 0.79 mg chromium)	No implantation site tumours	Payne, 1960b
	Rat	i.m. implantation of 25 mg	Sarcomas at implantation site in 3/31 treated animals and 0 vehicle controls	Hueper, 1958
	Rat	i.m. implantation	Tumours (type unspecified) at implantation site in 1/34 treated animals and 0/32 vehicle controls	Hueper, 1961
	Rat	Intrapleural implantation	Tumours (type unspecified) at implantation site in 5/32 treated animals and 0/34 controls	Hueper, 1961

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Roasted chromite [III] ore [illegible]	Rat	[illegible] of 25 mg	[illegible]	[illegible]
	Rat	Intrapleural [illegible] of 25 mg [illegible] to 2 mg [illegible]	Implantation site tumours [illegible] in 3/25 treated rats and [illegible] controls	Payne [illegible]
Mixed chromate (VI) dust[a]	Mouse	Inhalation, 4 hrs/day, 5 days/wk for 16 [illegible] wks (total dose chromium [illegible] 400 1200 mg [illegible])	[illegible] adenomas in 500 treated animals compared with controls	[illegible]
	Mouse	5 6 intratracheal instillations of dust (equivalent to 0 24 mg chromium trioxide)	No more lung tumours in 500 treated mice than in controls	[illegible]
	Mouse	4 intrapleural injections of 0 05 ml of a 2 or 4 [illegible] suspension	No increase in lung tumour incidence [illegible] 55 treated animals compared with 41 controls	[illegible]
	Rat	Inhalation, 4 5 hrs/day, 4 days/wk for lifespan (chromic oxide concentration of 3 4 mg/m³)	No significant increase in tumour [illegible] in 78 treated rats compared with controls	[illegible]

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Mixed chromate dust + potassium dichromate (VI)	Rat	16 intratracheal injections of 0 1 ml of suspension of 0 5% roasted chromate + 0 6% potassium dichromate (equivalent to 0 07 mg chromium/dose)	No significant increase in tumour incidence compared with controls	Steffee & [illegible]
Mixed chromate (VI) dust + potassium dichromate (VI) + sodium chromate (VI) + pulverized residue dust	Rabbit	Inhalation, 4 days/wk for 50 months	No increase in tumour incidence compared with controls	Steffee & Baetjer 1965
	Guinea-pig	Inhalation, 4 days/wk for lifespan	Pulmonary carcinomas in 3/50 treated animals	Steffee & Baetjer [illegible]
Barium chromate (VI)	Rat	i.m. implantation of 25 mg	No implantation site tumours in 35 rats	Hueper & Payne [illegible]
	Rat	i.m. implantation	No implantation site tumours in 34 rats	Hueper 1961
	Rat	Intrapleural implantation	Implantation site tumours in 1/31 treated rats and 0/34 controls	Hueper 1961
Calcium chromate (VI)	Mouse	Inhalation, 13 mg/m³ 5 hrs/day, 5 days/wk for lifespan	Lung adenomas in 14/136 treated animals and 5/136 controls	Nettesheim [illegible]
	Mouse	i.m. implantation of 10 mg	Implantation site sarcomas in 2/50 and in 0/50 controls	Payne [illegible]
	Mouse	i.s.c. injection of 10 mg	[illegible] site sarcomas in [illegible] and in 0/[illegible] controls	Payne [illegible]

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Calcium chromate (VI) (contd)	Rat	Bronchial implantation	6 squamous cell carcinomas and 2 adeno-carcinomas of the lung in 100 treated rats; 0/24 controls	Laskin et al., [illegible]
	Rat	Bronchial implantation	Increased incidence of bronchial squamous cell carcinomas	Levy & Venitt, [illegible]
	Rat	Inhalation, 2 mg/m³, 583 exposures of 5 hrs over 811 days	1 squamous cell carcinoma of lung, 1 of larynx, 1 peritruncal tumour (no. of treated animals unspecified)	Laskin, 1972
	Rat	I.m. implantation of 12.5 mg	Malignant tumours at implantation site in 4/3 treated animals	Hueper & Payne, [illegible]
	Rat	20 injections, total dose 10 mg	Injection site sarcomas in 19/24 and 0 in vehicle controls	Roe & Carter, [illegible]
	Rat	12 injections of 4 mg	Injection site sarcomas in 5/45 and 0/22 in vehicle controls	Furst et al., 1976
	Rat	I.m. implantation of 25 mg	Injection site sarcomas in 5/35 treated animals and 0/32 controls	Hueper & Payne, [illegible]
	Rat	I.m. implantation	Tumours (type unspecified) at implantation site in 9/32 treated animals and 0/22 controls	Hueper, 1961
	Rat	Intrapleural implantation of 12.5 mg	Malignant tumours (unspecified) at implantation site in 8/14 treated animals	Hueper & Payne, [illegible]
	Rat	Intrapleural implantation	Tumours (type unspecified) at implantation site in 20/32 treated animals and 0/34 controls	Hueper, 1961
	Hamster	Inhalation, 2 mg/m³, 589 exposures	1 squamous cell carcinoma and 1 papilloma of larynx (no. of treated animals unspecified)	Laskin et al., [illegible]

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Sintered calcium chromate (VI)	Mouse	I.m. implantation of 10 mg	Implantation site sarcomas in 9/46 treated animals and 0/50 controls	Payne, [illegible]
	Mouse	S.c. injection of 10 mg	No injection site sarcomas	Payne, [illegible]
	Rat	I.m. implantation of 25 mg	Implantation site sarcomas in 5/35 treated animals and 0 controls	Hueper & Payne, [illegible]
	Rat	I.m. implantation	Tumours (type unspecified) at implantation site in 12/34 treated animals and 0/32 controls	Hueper, [illegible]
	Rat	Intrapleural implantation	Tumours (type unspecified) at implantation site in 17/33 treated rats and 0/34 controls	Hueper, [illegible]
Chromic (III) acetate	Mouse	P.o., 5 mg/l drinking water for life	No increase in tumour incidence	Schroeder et al., [illegible]
	Rat	P.o., 5 mg/l drinking water for life	No increase in tumour incidence	[illegible]
	Rat	8 i.m. implantations of 25 mg each, over 24 months	Implantation site sarcoma in [illegible] treated animals	Hueper & [illegible]
	Rat	I.m. implantation	Implantation site tumours (type unspecified) in 1/34 and in 0/32 controls	Hueper, [illegible]
	Rat	9 intrapleural implantations of 25 mg each over 13 months	No implantation site tumours after [illegible] years in 42 treated animals	Hueper & Payne, [illegible]

Table II (contd)

Compound	Species	Route and dosage	Findings	Reference
Chromic (III) acetate (contd)	Rat	Intrapleural implantation	Implantation site tumour (type unspecified) in 1/34 and in 0/34 controls	Hueper, 1961
Chromic (III) oxide	Rat	P.o. 1, 2 and 5% in bread on 5 days/wk for 2 years	1% dose: 3/60 mammary fibroadenomas 2% dose: 1/60 5% dose: 3/60 controls: 1/60 mammary carcinoma; 2/60 fibroadenomas	[illegible]
	Rat	Single intratracheal application of 50 or 20 mg	50 mg dose: 7/34 with tumours (4 with lung sarcomas) 25 mg dose: 6/18 with tumours (5 with lung sarcomas) no controls	[illegible] & [illegible], 1967
	Rat	Bronchial implantation	No lung tumours in 98 animals	Laskin et al., 1970
	Rat	1 i.p. injection of 20 mg	Lung sarcomas in 4/20; no controls	[illegible] & Fedorova, [illegible]
	Rat	2 intrapleural injections of 5 mg	[illegible] cell sarcomas of lung in [illegible] treated animals; no controls	[illegible] & Fedorova, [illegible]
Chromium carbonyl	Rat	Injection of 2.5 mg into subcutaneously implanted tracheal rings	Squamous-cell carcinomas in 2/22 animals; none in 4 vehicle controls	Lane & Mass, 1977
Chromium (III) sulphate	Mouse	24 i.p. injections (total doses: 480, 1200 and 2400 mg/kg bw)	No significant increase of pulmonary adenoma incidence in 60 treated rats compared with 40 vehicle and untreated controls	Stoner et al., 1976
Chromium (VI) trioxide	Rat	Bronchial implantation	[illegible] increase in lung tumour incidence in 100 treated rats compared with 24 [illegible]	Laskin et al., 1970

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Sintered chromium (VI) trioxide	Mouse	1 s.c. injection of 10 mg	[illegible] injection site tumours in 32 treated animals	Payne, 19[illegible]
	Rat	i.m. implantation of 25 mg	Implantation site sarcomas in 15/35 treated animals and 0/35 controls	Hueper & Payne, 1962
Cobalt-chromium alloy	Rat	i.m. injection of 28 mg	Injection site sarcomas in 7/74 treated rats; other tumours in 7/74	Heath et al., 1971
Lead chromate (VI)	Mouse	4 i.m. injections of 3 mg	2 lymphomas and 3 lung adenocarcinomas in 17 mice necropsied; similar incidence in controls	Furst et al., 1976
	Rat	1 s.c. injection of 30 mg	Injection site sarcomas in 26/42 treated animals and 0/60 vehicle controls	Maltoni, [illegible]
	Rat	9 i.m. injections of 8 mg	Injection site sarcomas in 31/47 treated rats; 3 renal carcinomas; 0/22 in vehicle controls	Furst et al., 1976
	Rat	i.m. implantation	Tumour (type unspecified) at implantation site in 1/33 treated rats and 0/32 controls	Hueper, 1961
	Rat	Intrapleural implantation	Tumours (type unspecified) at injection site in 3/34 treated rats and 0/34 controls	Hueper, 1961
Lead chromate (VI) oxide	Rat	1 s.c. injection of 30 mg	Injection site sarcomas in 27/40 treated rats and 0/60 vehicle controls	Maltoni, [illegible]

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Potassium chromate (VI)	Rat	Bronchial implantation	No increased incidence of lung tumours	Levy & Venitt, 1975
Potassium dichromate (VI)	Rat	Bronchial implantation	No increased incidence of lung tumours	Levy & Venitt, 1975
Sodium chromate (VI)	Rat	Bronchial implantation	No increased incidence of lung tumours	Levy & Venitt, 1975
Sodium dichromate (VI)	Rat	16 i.m. injections of 2 mg	No injection site tumours	Hueper & Payne, 1962
	Rat	i.m. implantation	No implantation site tumours	Hueper, 1961
	Rat	16 intrapleural injections of 2 mg	1 lung adenocarcinoma in 39 treated animals; no injection site tumours in 60 vehicle controls	Hueper & Payne, 1962
	Rat	Intrapleural implantation	No injection-site tumours in 26 treated animals	Hueper, 1961
	Rat	Bronchial implantation	No increase in lung tumours	Levy & Venitt, 1975
Strontium chromate (VI)	Rat	i.m. implantation	Implantation-site tumours in 15/33 treated animals and 0/32 controls	Hueper, 1961
Zinc potassium chromate (VI)	Rat	Bronchial implantation	Increased incidence of bronchial squamous cell carcinomas	Levy & Venitt, 1975
Zinc yellow	Mouse	6 intratracheal injections of 0.03 ml of a 0.2% suspension	No pulmonary carcinomas; pulmonary adenomas in 31/62 treated animals and 7/18 untreated controls	Steffee & Baetjer, 1965

Table 8 (contd)

Compound	Species	Route and dosage	Findings	Reference
Zinc yellow (contd)	Rat	i.m. implantation	Tumours (type unspecified) at implantation site in 16/34 treated animals and 0/32 controls	Hueper, 1961[a]
	Rat	Intrapleural implantation	Tumours (type unspecified) at implantation site in 22/33 treated animals and 0/34 controls	Hueper, 1961[b]

[a] See footnote on p. 254.

[b] It was not specified whether this compound was zinc chromate, zinc potassium chromate or zinc yellow

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APPENDIX II

Estimation of Parameters for the Competing Risks Model
(Source: EPA, 1984)

7.2.3.1.2. Choice of Dose-Response Model -- It has been widely recognized (e.g., Doll 1971) that the age-specific incidence curve tends to be linear on doubly logarithmic graphs, or equivalently, the age-specific incidence follows the mathematical form

$$I(T) = bT^{k-1}$$

where b and k are parameters that may be related to other factors such as dose, and T may be one of the following three cases:

1. T is age when cancer is observed,
2. T is the time from the first exposure to observed cancer, or
3. T is the time from exposure to cancer minus the minimum time for a cancer to be clinically recognized.

This model has been shown to arise from the somatic mutation hypothesis of carcinogenesis (Armitage and Doll 1954, Whittemore 1978, Whittemore and Keller 1978). It has also been shown to arise from the epigenetic hypothesis when the reversible cellular change is programmed to occur randomly (Watson 1977). These authors and many others have used this model to interpret and/or estimate potency from human data.

Since the data that could be used for risk estimation are limited, a simple model that fits the data should be used. Therefore, the observed age-specific incidence is assumed to follow the model

$$I(t,d) = B(t) + h(t,d)$$

where B(t) is the background rate at age t and $h(t,d) = Q(d)\, t^{k-1}$ with $Q(d) = q_1 d + q_2 d^2$, a function of dose d.

Once the parameters q_1, q_2, and k are estimated, the lifetime cancer risk associated with an exposure d by age t, taking into account the competing risk, can be calculated by

$$P(t,d) = \int_0^t h(s,d)\exp\left\{-\left[\int_0^s h(y,d)dy + A(s)\right]\right\}ds$$

where exp[-A(s)] is the probability of surviving to age s and h(t,d) = I(t,d) - B(t), the age-specific incidence after adjusting the background rate.

7.2.3.1.3. Estimation of the Risk Model -- To estimate the parameters in h(t,d) we assume, as is usually done, that the number of lung cancer deaths, X, at age t, follows the Poisson distribution with the expected value

$$E(X) = N \times (B + Q(d)\ t^{k-1})$$

where N is the person-year associated with X, B is the background rate at age t, and $Q(d) = q_1 d + q_2 d^2$.

Using the BMDP computer program P3R and the theory relating the maximum likelihood and non-linear least square estimation by Jennrich and Moore (1975), the parameters q_1, q_2, and k are estimated by the method of maximum likelihood as $q_1 = 1.11 \times 10^{-7}$, $q_2 = 1.84 \times 10^{-9}$, and k = 2.915; the corresponding standard deviations are respectively 7.8×10^{-7}, 1.2×10^{-8}, and 1.7.

Thus, the age-specific cancer death incidence at age t due to chromium exposure d ug/m^3 is given by

$$h(t,d) = Q(d)\ t^{1.915}$$

where

$$Q(d) = 1.11 \times 10^{-7}d + 1.84 \times 10^{-9}d^2$$

The model fits the data well, as can be seen from the goodness of fit statistic

$$X^2 = \Sigma\ (O-E)^2/E = 1.60$$

which has, asymptotically, a chi-square distribution with 5 degrees of freedom under the model specified. The observed and predicted values used in calculating X^2 are (3, 2.5), (6, 7.2), (6, 5.1), (4, 3.1), (5, 6.7), (5, 4.1), (2, 1.4) and (4, 4.3).

Taking into account the competing risk, the lifetime probability of lung cancer death due to exposure to chromium d ug/m^3 is given by

$$P(L,d) = \int_0^L h(t,d)\exp\left\{-[(Q(d)/2.915)\ t^{2.915} + A(t)]\right\}dt$$

where L is the maximum human lifetime and is mathematically equivalent to infinity, since the probability of surviving beyond L is 0.

At low doses, approximately,

$$P(L,d) = d \times P(L,1)$$

where P(L,1) is the lifetime cancer risk due to exposure to 1 ug/m^3 of chromium. The unit risk, P(L,1), has been adopted by the CAG as an indicator of the carcinogenic potency of a chemical compound.

7.2.3.1.4. Calculation of the Risk at 1 ug/m^3 -- To calculate the unit risk, P(L,1), it is necessary to know exp[-A(t)], the probability of surviving to age t. Since this probability can only be estimated, it is assumed that the survival probability is constant over a 5-year interval, as provided in the U.S. Vital Statistics.

Using this approximation and by integrating the formula P(L,1), we have

$$P(L,1) = \Sigma[\exp(-3.87 \times 10^{-8}\ t_{i-1}^{2.915}) - \exp(-3.87 \times 10^{-8} t_i^{2.915})] \times P_i$$
$$= 1.16 \times 10^{-2}$$

where (t_{i-1}, t_i) is a 5-year interval and P_i is the probability of survival up to the age t_{i-1}. P_i is assumed to be a constant over the interval and is estimated from the 1975 U.S. Vital Statistics.

APPENDIX III

Mancuso Study of Workers Exposed to Chromium

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CONSIDERATION OF CHROMIUM AS AN INDUSTRIAL CARCINOGEN

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ABSTRACT

Cohorts of employees (1931-1937) of a chromate plant were followed to 1974. Lung cancer deaths accounted for 62% of the total cancers observed. The clustering of lung cancer deaths occurred after 27-36 years of observation. The lung cancer death rates increased by gradient level of exposure to insoluble (trivalent) chromium, soluble (hexavalent) chromium and to total chromium. The lung cancer risk is primarily re[illegible] to the total chromium exposure regardless of the form of chromium. Extensive depositions of chromium were found in the lungs many years after exposure to chromium ceased. The identification of the lung cancer risk for insoluble (trivalent) form of chromium among workers broadens extensively the potential risk to other populations exposed to chromium in other industries. It is concluded that all forms of chromium are carcinogenic.

RÉSUMÉ

On a examiné en 1974 des cohortes d'employés d'une usine de chromate nés entre 1931 et 1937. Au total, 62% de la mortalité due au cancer provenait d'un cancer du poumon. La mortalité due à ce cancer se produisait après 27 à 36 ans d'observation. Le taux de mortalité par cancer du poumon variait avec l'exposition au chrome insoluble (trivalent), au chrome soluble (hexavalent) et au chrome total. Le risque de cancer dépend avant tout de l'exposition nette au chrome, quelle que soit sa forme. D'importants dépôts de chrome ont été observés dans les poumons plusieurs années après que l'exposition eut cessé. Le fait que la forme soluble du chrome puisse provoquer un cancer du poumon chez les ouvriers en élargit considérablement le danger aux ouvriers exposés au produit dans d'autres secteurs. Nous concluons que toutes les formes de chrome sont carcinogènes.

INTRODUCTION

The excessive lung cancer death rate identified with workers engaged in the manufacture of chromates has been previously established (Machle 1948;

Mancuso 1949; Baetjer 1950; Public Health Service 1953; Taylor 1966).There has been much speculation, during the past 27 years since the original epidemiological observation, concerning the chemical form of the chromium which may be responsible for the development of the high death rate for cancer of the lung among chromate workers.

In brief, virtually all of the postulations concerning the etiology of lung cancer during the span of years, has centered on the hexavalent form of chromium. The principal exception has been the report by Mancuso and Hueper (1951), who emphasized the importance of the insoluble form of chromium (trivalent) in the development of lung cancer and further concluded that exposure to other not readily soluble chromium compounds (chromium pigments, chromium alloys) also be considered.

The present study is a continuation of the first study initiated in 1948-1949, in which epidemiological, medical, engineering and chemical investigations were carried out (Bourne and Fosdick 1950; Bourne and Yee 1950; Urone *et al.* 1950; Urone and Anders 1950; Mancuso 1951; Mancuso and Hueper 1951; Bourne and Rushin 1951). A sufficient number of years has now elapsed, with a corresponding increase in lung cancer deaths, to provide the basis for further evaluation of the carcinogenic potential of chromium in various forms.

Our present study is concerned with the following major questions:

1 What is the span of the latent period and how does this affect observations of lung cancer at different points in time?

2 Do successive groups of employees new to a chromium exposure sustain similar high rates for lung cancer?

3 Is there any association between lung cancer death rates and exposure to a particular form of chromium, insoluble, soluble or to total chromium?

METHODS

In the early part of 1949 the industrial hygiene engineering study of this chromate plant was conducted. Careful time studies, for the full 8 hours and 40 hour week, were made for each of the occupations of the production workers and together with air sampling, the true exposure in terms of the weighted average of exposure to insoluble, soluble and total chromium (per cubic meter) was calculated for each occupation and for each worker for every department.

All personnel records of the chromate plant since its inception, 1931, were microfilmed. A complete work history was prepared on each worker.

Each job held in each department was identified and the duration of employment in the respective occupations and changes in occupations and departments were recorded. In essence then, for every worker in the plant, we had established the weighted average exposure to the type of chromium and the duration of exposure in each respective job the man had. The duration in time (years and months) for each job held was multiplied with its corresponding weighted average exposure for calculation of the exposure years.

The atmospheric concentrations of chromium in our industrial hygiene study of this plant were expressed in terms of elemental chromium, a departure from the customary industrial hygiene procedure in which concentrations are expressed in terms of chromic acid (Cr_2O_3). This method was adopted at the inception of the study in 1949 to avoid the inference of implicating any specific compounds in subsequent cancer effects.

This means that the concentrations calculated per elemental chromium would be lower, by about one half of the level for that calculated as chromic acid (Cr_2O_3). Therefore, whatever associations are presented in the findings with levels of concentration of chromium, it is in terms of the elemental chromium. In the reports of the chemical analyses, the soluble chromium is essentially hexavalent and the insoluble (in water) is chiefly trivalent.

There is another more apparent point, and that is the comparability of the concentrations of chromium found (insoluble, soluble and total chromium) in the environmental appraisal of the plant in the early part of 1949, with the concentrations in the early years of operation, 1931-1937.

The tremendous progressive increase in production in the succeeding years from zero could have brought about a concomitant increase in the dust concentrations to 1949 that could have exceeded the level of the first years of operation. The company instituted control measures after the 1949 study which markedly reduced the exposure.

Since no precise environmental study had ever been conducted in the early years of operation for this plant and none therefore was available, the 1949 weighted average exposures (insoluble, soluble and total chromium) were applied to all workers employed 1 year or more in the 1931-1937 cohort and the 1938-1948 cohort. (The initial exploration of the 1938-1948 cohort has been started and 9 deaths due to lung cancer and 2 cases of cancer of the sinuses have already been identified.)

The data to be presented are confined to the 1931-1937 cohort with 41 lung cancer deaths. All deaths were uniformly coded by an experienced nosologist according to the 7th Revision of the International Classification of Causes of Death.

The age adjusted mortality rate for the cohorts was calculated by the direct method using as the standard the distribution of person years by age group for the total chromate population.

RESULTS

The chromate plant under study began operations in the 1931-1932 period and we have established a cohort of all employees for the period 1931-1937, which has been followed through 1974.

Table 1 shows the number and distribution of chromate workers by the years of first employment in the chromate plant, arranged into successive cohorts, representing new employees who entered employment in the years designated, according to age at the time of first employment.

There were 332 employees in the combined cohort (1931-1937) in which 173 (over 50%) died by 1974. A higher percentage of deceased occurred in the 1931-1932 cohort, which had the longest period of observation and conversely the lower percentage of deaths occurred in the 1935-1937 cohort with the shortest period of observation.

The number of employees, as cohorts, is indeed exceptionally small (78, 154 and 100) for an epidemiological study. Nevertheless, this approach was

TABLE 1

Number of White Male Employees* in a Chromate Plant According to Age at First Employment. Successive Cohorts and Those Living and Deceased.

Age at First Employment	1931-32 Cohort L	1931-32 Cohort D	1933-34 Cohort L	1933-34 Cohort D	1935-37 Cohort L	1935-37 Cohort D	1931-37 Cohort L	1931-37 Cohort D
< 25	12	2	31	19	44	19	87	40
25-34	12	20	26	26	15	11	53	57
35-44	3	17	13	22	2	5	18	44
45-54	0	10	0	14	1	2	1	26
55-64	0	2	0	3	0	1	0	6
65+	0	0	0	0	0	0	0	0
Total	27	51	70	84	62	38	159	173

*Includes 3 deaths due to war casualty and 1 death without death certificate.

utilized to reflect and detect whether similar observations of a high lung cancer rate would occur among the successive new employees, who entered the same work place and were similarly exposed to the same work processes and air concentrations of chromium. Further, the observation on successive cohorts would reflect and provide some indication whether there had been any change in the nature, extent, or degree of exposure in the work place in the succeeding years, as measured in terms of similar or lesser mortality due to lung cancer. Because of the small numbers of employees in the early cohorts, a few deaths not found have more importance than usual. In this respect, the interpretation which can be made of the 1935-1937 cohort with only 7 lung cancer deaths is markedly limited.

Table 2 shows, for the successive cohorts of new employees arranged according to years of first employment, and the combined cohort (1931-1937), the ratios in percent of cancer of the lung to all deaths and to all cancers.

For the first two cohorts (1931-1932 and 1933-1934) with the longest interval of observation, the percentage of lung cancer among all cancers was 63.6 and 62.5. The 1935-1937 cohort had 58.3% and the combined cohort (1931-1937) had 62.1% lung cancer. It is evident that the lung cancer risk was higher in each of the cohorts of new employees in succeeding time periods. Not shown in the table is one case of lung cancer of a worker employed in 1934, who had a pneumonectomy (1956) and is still living.

Figure 1 shows the latent period for the 1931-1937 cohort and demonstrates the clustering of lung cancer cases at the 27-36 year latent period. This is one illustration of the importance of the long-term follow-up in industrial epidemiological studies.

TABLE 2

Ratios (in percent) of Deaths from Cancer to Total Deaths in a Chromate Producing Plant

	All Causes No.	All Causes Percentage	All Cancers No.	All Cancers Percentage	Cancer of Lung No.	Cancer of Lung Percentage of All Deaths	Cancer of Lung Percentage of All Cancers
1931-1932 Cohort	51	100.0	22	43.1	14	27.5	63.6
1933-1934 Cohort	84	100.0	32	38.1	20	23.8	62.5
1935-1937 Cohort	38	100.0	12	31.6	7	18.4	58.3
1931-1937 Cohort	173	100.0	66	38.2	41	23.7	62.1

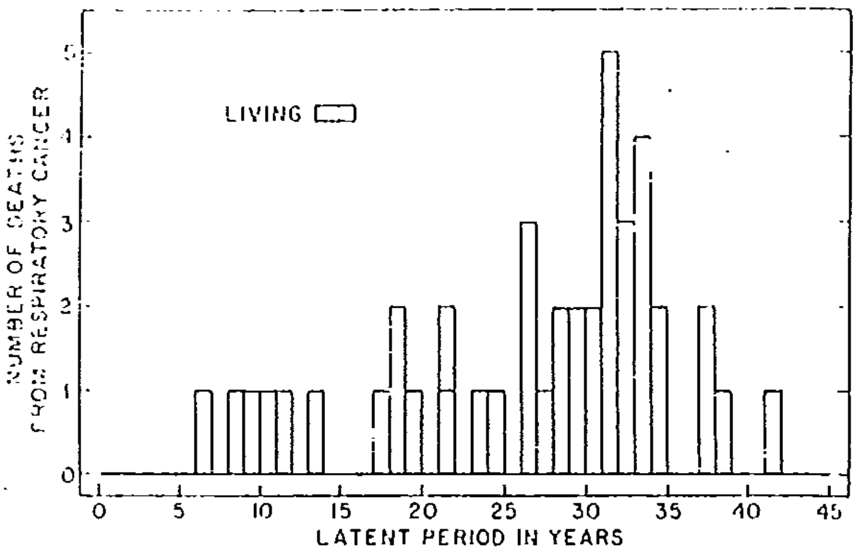

Fig. 1. Latent period for 1931-1937 cohort of new employees in plant manufacturing chromates.

Table 3 demonstrates the influence of the length in years of the period of observation of the successive cohorts, over designated periods of time, on mortality rates due to lung cancer for workers employed five years or more.

For the combined cohort (1931-1937) at less than 15 years period of observation, with a rate of 97.2 there is no reflection of the true magnitude of the excess of lung cancer risk. Yet this period, precisely 14.5 years, was the limited period of observation in the Public Health Service study of a chromite brick plant, (1953). The observation by the PHS of only one lung cancer within that period of 14.5 years has been repeatedly cited in the literature as conclusive evidence that the trivalent form of chromium was not carcinogenic (National Academy Science Review 1974).

We know, of course, that for any industrial carcinogen the magnitude of the risk is reflected over a much greater number of years of observation, because of the latent period required for the development of cancer. Although the occupational cancers may occur early, nevertheless, the largest number of cases appear after a long latent period of many years, as has been observed in asbestos workers and now is shown for chromate plant workers.

TABLE 3

Age Adjusted Mortality Rates* for Cancer of the Lung for Employees in a Chromate Plant Followed According to Designated Years of Observation for Workers Employed 5 years or more.

Years of Observation	Cohort 1931-1932		Cohort 1933-1934		Cohort 1935-1937		Cohort 1931-1937	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
< 15	3	162.8	2	65.7	1	77.5	6	97.2
< 21	5	271.3	4	131.5	1	77.5	10	161.9
< 27	5	271.3	7	230.1	1	77.5	13	210.5
< 29	6	325.6	9	295.9	1	77.5	16	259.1
< 31	8	434.1	10	328.7	2	154.9	20	323.8
< 33	12	651.1	12	394.5	3	232.4	27	437.2
< 36	12	651.1	16	526.0	6	464.8	34	[illegible]
< 39	12	651.1	17	558.8				
< 43	13	705.4						

*Per 100,000.

The rates for the combined 1931-1937 cohort show, very clearly, the increasing mortality rate for lung cancer with increasing years of observation. The mortality rate observed for the period of 15 years or less was 97.2 and when the cohort was followed for 39 years, the rate (604.1) was six times greater.

When the years of observation are held constant at 36, the age adjusted mortality rates are: 651.1 for 1931-1932, 526.0 for 1933-1934 and 464.8 for 1935-1937.

Table 4 shows the mortality rate for lung cancer by age at first employment for the successive cohorts. Because the total number of lung cancer deaths was only 7 in the 1935-1937 cohort, comments are confined to the first two cohorts. (We believe our follow-up of the 1935-1937 cohort is incomplete.)

The table demonstrates that for those employed at age 25 or less at the chromate plant for the 1931-1932 and 1933-1934 cohorts, the mortality rate was high, 340.1 and 370.4 respectively. This plant began operations in the 1931-1932 period, so these workers at this young age would represent those without any prior industrial employment, who were exposed for the first time

TABLE 4

Age Adjusted Mortality Rates* for Cancer of the Lung for Employees in a Chromate Plant by Age at First Employment for Successive Cohorts Followed to 1974.

Age at First Employment	Cohort 1931-1932		Cohort 1933-1934		Cohort 1935-1937		Cohort 1931-1937	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
< 25	2	340.1	7	370.4	3	134.3	12	254.7
25-34	8	721.4	8	438.1	3	336.7	19	496.6
35-44	2	343.6	5	485.0	0	0.0	7	382.7
45-54	2	803.2	0	0.0	0	0.0	2	314.0
55-64	0	0.0	0	0.0	1	10,000.0	1	1,136.4
65 +	0	0.0	0	0.0	0	0.0	0	0.0
All	14	544.5	20	393.8	7	203.4	41	369.7

*Per 100,000.

to the dust of chromium compounds in a plant just starting operations in a rural community. This age group provides a good index of the lung cancer risk due to exposure to chromium compounds.

For those employed at ages 25-34, the rate rose to 721.4 and 438.1 for the first two cohorts. Any further consideration must be deferred until the number of deaths in these respective age groups is enlarged by additional follow-up.

Table 5 shows the age adjusted lung cancer death rates per 100,000 by gradient of insoluble chromium exposures, from less than 0.25 milligrams per cubic meter to over four milligrams. The mortality rate has a "zero" death rate at exposure less than 0.25 milligrams and rises consistently with the increase in levels of exposure, 144.6, 174.6, 327.9, 630.7 and 649.6.

Table 6 shows the age adjusted lung cancer death rate by gradient of soluble chromium exposures. There is a corresponding rise in death rate with the rise in level of exposure. The rates were 80.2, 306.0, 441.5, 462.2 and 998.7.

Table 7 shows the age adjusted lung cancer death rate by total chromium exposure. The mortality rate has "zero" death rate at less than 0.50 milligrams of chromium per cubic meter, with an increase in rate by rise of level of exposure. There was a slight dip at the 2.00-3.99 milligrams per

TABLE 5

Age Adjusted Lung Cancer Death Rates/100,000 by Insoluble Chromium Exposures mg/m³ – Years.

Insoluble mg/m³ – Yrs.	Person Years at Risk	Number of Deaths	Age Adjusted Death Rate
< 0.25	1,399	0	0.0
0.25-0.49	1,499	2	144.6
0.50-0.99	1,708	3	174.6
1.00-1.99	2,039	7	327.9
2.00-3.99	2,409	15	630.7
≥ 4.00	2,037	14	649.6
Total Chromium	11,091	41	369.7

TABLE 6

Age Adjusted Lung Cancer Death Rates/100,000 by Soluble Chromium Exposure mg/m³ – Years.

Soluble mg/m³ – Yrs.	Person Years at Risk	Number of Deaths	Age Adjusted Death Rate
< 0.25	3,612	3	80.2
0.25-0.49	1,690	5	306.0
0.50-0.99	2,206	10	441.5
1.00-1.99	2,358	11	462.2
≥ 2.00	1,225	12	998.7
Total Chromium	11,091	41	369.7

cubic meter exposure range. The rates were 0.0, 225.7, 322.7, 255.6, 770.7 and 741.5.

Since the lung cancer death rates are related to the gradient of both the insoluble and soluble chromium, the question was posed whether the relationship was due, principally, to one form of chromium compound, either insoluble (primarily trivalent) or soluble (chiefly hexavalent).

To investigate this, the age adjusted mortality rates were calculated by classifying the workers by the levels of insoluble and by the levels of total chromium exposure. This is shown in Table 8. Within the table, it is seen that

TABLE 7

Age Adjusted Lung Cancer Death Rates/100,000 by Total Chromium Levels.

Total Chromium mg/m³ – Yr.	Person Years at Risk	Number of Deaths	Age Adjusted Death Rates
< 0.50	2,051	0	0.0
0.50-0.99	1,558	3	225.7
1.00-1.99	1,758	6	322.7
2.00-3.99	2,336	6	255.6
4.00-5.99	1,397	10	770.7
≥ 6.00	1,991	16	741.5
Total Chromium	11,091	41	369.7

TABLE 8

Age Adjusted Lung Cancer Death Rates/100,000 by Insoluble Chromium and Total Chromium Exposures in mg/m³ – Years.

Mg/m³ - Yrs. Total Insoluble	Total Chromium < 0.50	0.50-0.99	1.00-1.99	2.00-3.99	4.00-5.99	≥ 6.00	All Levels Total Insoluble
< 0.25	0.0						0.0
0.25-0.49	0.0	309.1					144.6
0.50-0.99		135.2	198.1				174.6
1.00-1.99			451.4	260.4			327.9
2.00-3.99				260.5	904.7	1,732.5	630.7
≥ 4.00					284.7	683.7	649.6
All Levels Total Chromium	0.0	225.7	322.7	255.6	770.7	741.5	369.7

Blank cells indicate no person years at risk.

for a fixed level of insoluble chromium – example: 0.50-0.99 - the lung cancer risk appears to increase as the total chromium increased. In spite of the relatively small numbers of person years at risk and the number of lung cancer deaths in individual cells in the table, this result is consistent for all insoluble levels, except one (1.00-1.99 mg/m³ yr.).

In essence, the data in Tables 5 to 8 are consistent with the lung cancer risk being a function of both the soluble and insoluble chromium; i.e., to total chromium rather than to one class of chromium compound.

In Table 9, which shows the age specific death rates by gradient of exposure to chromium, there is an increase by age group: 528.7 for age 45-54, 685.2 for age 55-64, and 1,088.3 for age 65-74.

Further, although the numbers are small in each cell, there is a pattern of increasing death rates by increasing level of total chromium for each of the age groups.

Comprehensive data on the deposition of chromium in every type of tissue from former chromate workers have been developed and will be presented as a separate report.

Table 10 is confined to the chemical analyses of the lungs and shows, for six deaths due to lung cancer, the level of chromium remaining in the lungs according to the time interval since last exposure to chromium, ranging from 15 months to 16 years and 3 months. It is readily apparent that there is an extensive deposition of chromium in the lungs retained over long periods

TABLE 9

Age Specific Rates Per 100,000 for Cancer of the Lung for Age Groups 45-54, 55-64 and 65-74 by Gradient Exposure to Total Chromium.

[illegible]	< 1.00	1.0-1.99	2.0-3.99	4.0-5.99	6.0-6.99	7.0-7.99	8 +	Totals
Age Group 45-54								
Deaths	1	2	2	4	3	3	0	15
Person Years	886	459	583	348	159	140	262	2,837
Rate	112.9	435.7	343.1	1,149.4	1,886.8	2,142.9	0.0	528.7
Age Group 55-64								
Deaths	1	3	1	4	2	3	1	15
Person Years	707	356	462	250	113	98	203	2,189
Rate	141.4	842.7	216.5	1,600.0	1,769.9	3,061.2	492.6	685.2
Age Group 65-74								
Deaths	1	1	2	1	1	0	3	9
Person Years	235	166	182	80	42	41	81	827
Rate	425.5	602.4	1,098.9	1,250.0	2,381.0	0.0	3,703.7	1,088.3

TABLE 10

Chemical Analysis by Interval Since Last Exposure to Chromium.

	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5		Case No. 6
Interval Since Last Exposure	15 Mos.	3 Yrs. 5 Mos.	8 Yrs. 9 Mos.	10 Yrs.	14 Yrs.		16 Yrs. 3 Mos.
					Lung	W/Tumor	
Lung (Pneumonectomy And Biopsy)					429.0	337.0	
					514.0	227.0	
						117.0	
Right Lung	156.0		1575.0	78.7			11.7
	155.0		975.0				46.9
							68.5
							~114.0
With Tumor			0.94				21.4
Left Lung	312.0	330.0	450.0			63.2	39.1
	330.0	380.0	250.0			4.1	57.2
		456.0	625.0				141.0
With Tumor		26.0					
Bronchus			1450.0				

of time. In control analyses, the lung showed 3.0 micrograms of chromium per 10 grams of tissue.

The table provides adequate confirmation of the hypothesis expressed by Mancuso and Hueper, relative to the retention of chromium, its slow release and the development of lung cancer.

We did find high levels of chromium in the testicle among chromate plant workers, which confirms the animal experimental observation of Hopkins (1965), who found a dramatic uptake of trivalent chromium in the testes. We have also noted a high level of chromium in the adrenal and this may be important in the consideration of the cancer mechanism.

We also have analyzed the chromium content of the lung of a chrome plater at the time of biopsy and found 58 micrograms per 10 grams of tissue. Subsequently, he died of lung cancer.

CONCLUSION

The study demonstrated a high lung cancer risk among new employees entering the same chromate plant and work exposure in successive time periods (1931-1932, 1933-1934, 1935-1937).

Epidemiological evidence is provided that the carcinogenicity of chromium includes the insoluble form of chromium.

The data indicate that the carcinogenic potential extends to all forms of chromium and is directly related to the total amount of chromium taken into the respiratory system.

The national cancer impact of exposure to chromium should be reassessed.

ACKNOWLEDGEMENT

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THE LONG-TERM HEALTH OF TETRAETHYL LEAD WORKERS

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ABSTRACT

A mortality study with a 100% 20-year follow-up showed a death rate 26% lower for tetraethyl lead (TEL, an antiknock additive for gasoline) workers than for the general population, with no unusual causes of death. A study of absences from work due to illness among TEL workers with 20 or more years of service showed no statistically significant differences from a matched control group of non-TEL workers, either overall or in disease categories. Other medical data (primarily from periodic medical examinations) on these same workers showed no appreciable differences. The conclusion is drawn that the TEL workers at the facility studied have not suffered detectable impairment of their health as a result of their occupation.

RÉSUMÉ

Une étude de la mortalité due au plomb-tétraéthyle, utilisé comme [illegible] dans l'essence, a permis de suivre pendant 20 ans 100% d'un échantillon. Nous [illegible] trouvé que le taux de mortalité chez les ouvriers en contact avec ce produit était [illegible] de 26% à celui de la population générale si l'on exclut les causes [illegible] de [illegible] l'étude de l'absentéisme pour raisons de maladies chez les ouvriers en contact avec [illegible] produit et ayant au moins 20 ans de service n'a pas dégagé de différence significative par rapport à un groupe témoin d'ouvriers d'un autre secteur, que ce soit au niveau de toutes les absences ou de celles dues à une maladie au sens strict. Des données médicales portant sur les mêmes ouvriers et provenant essentiellement d'examens périodiques n'ont pas montré de différences appréciables. Nous concluons donc que les ouvriers en contact avec le plomb tétraéthyle, à l'usine étudiée, n'ont pas souffert de problèmes décelables qu'aurait causé ce produit.

Tetraethyl lead (TEL) has been produced as an antiknock additive for gasoline for about 50 years. The marked potential of the TEL and the

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APPENDIX IV

Industrial Hygiene Study of Plant in Mancuso Study

Occupational Cancer in a Chromate Plant
—An Environmental Appraisal—

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In 1948, Machle and Gregorius reported[1] the crude death rate for cancer of the lung among workers in seven United States plants engaged in the extraction of chromates from ore as 25 times the normal. They suggest that monochromates may be the compounds responsible.

With the object of adding to the knowledge of the role of chromium compounds in the incidence of respiratory cancer, epidemiological and environmental studies were conducted by the Ohio Department of Health in a single plant manufacturing sodium bichromate from chromite ore. A mortality study by Mancuso[2] revealed that the proportion of deaths from cancer of the respiratory system to that of all employee deaths in this plant was 14.7 times that in a non-exposed control group. The environmental phase presented here was undertaken to ascertain as far as possible the specific chromium compounds and magnitude of exposure experienced by workers according to their occupation and location.

Although a maximum allowable concentration of chromic acid and chromates was approved[3] in 1943, the role of chromium compounds as carcinogenic agents was not suggested in this country until 1948. There is no useful guide at present by which one may compare the carcinogenic hazards associated with exposure to specific concentrations of chromium compounds. Monochromates, as has been suggested, may be the causative agents, yet the evidence is fragmentary and one cannot exclude at the present time elemental chromium (Cr^{0}), trivalent (Cr^{+3}), or bichromate which also has a valence of +6. Therefore, the atmospheric chromium concentrations reported are expressed in terms of chromium ion, a departure from the customary industrial hygiene procedure in which concentrations are expressed in terms of chromic acid (CrO_3). Adopting this method of expression avoids the inference of implicating any specific chromium compounds for cancerous reactions.

The plant in which this study was undertaken has been in operation since 1932. In order to meet price and quality competition, improvements in equipment and processes have been made periodically during the past 18 years, and it is the universal experience of industrial hygiene personnel that greater process efficiency is almost invariably associated with a more healthful working environment. Therefore, there seems little doubt that atmospheric contamination in the past was greater than in early 1949 when the present work was commenced. Later in the same year the company initiated a comprehensive program designed further to improve the manufacturing efficiency and to reduce the exposure of the employees. Thus it is evident that the concentrations which have been recorded do not represent a static condition but only the situation prevailing during the first half of 1949.

The mean latent period for respiratory cancer in the chromate producing industry, according to Machle and the German literature, is approximately 15 years. Thus any present relationship between environmental exposure and incidence of cancer in the plant under study must be predicated on the assumption that the concentrations which are reported are probably the minimum values attained in the past 15 years.

Raw Material

Chromite ($FeO.Cr_2O_3$), lime, soda ash and sulfuric acid are the raw materials commonly used for the manufacture of sodium bichromate.[4] Typical proximate analyses of two South African ores,[5] the country of origin of the ore used by the plant under study, are shown in Table 1.

Table 2 gives a spectrographic analysis of a sample of ore dust obtained from the ore preparation department.

Table 1.
Proximate Analysis Typical South African Chromite Ore

	Percentage					
Country	Cr_2O_3	FeO	Al_2O_3	SiO_2	MgO	CaO
Rhodesia	51.1	11.4	15.2	4.8	12.7	0.9
Transvaal	43.6	25.8	14.2	1.1	11.9	trace

Table 2.
Spectrographic Analysis of a Chromite Ore

Element	Percentage	Element	Percentage
Aluminum	0.1 — 0.01	Magnesium	> 2.0
Calcium	0.1 — 2.0	Manganese	0.01 — 0.001
Cadmium	?	Sodium	< 0.001
Cobalt	0.01 — 0.001	Nickel	0.01 — 0.001
Chromium	> 2	Phosphorus	0
Copper	< 0.001	Lead	0
Iron	0.1 — 2.0	Silicon	0.1 — 2.0
Potassium	0	Titanium	< 0.001
		Vanadium	0.01 — 0.001

[Editor's Note: This engineering material, dealing with the environmental background leading to chromium exposures, is to be followed by a report of clinical investigation. This report is not immediately available for examination and publication. While these present engineering data embrace several chromium compounds, it will not necessarily follow that all may act or act equally as cancerigens.]

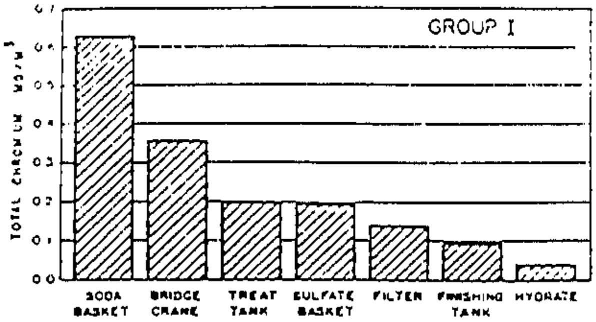

Fig. 2.

Weighted exposure according to occupations having Cr^{+3}: Cr^{+6} ratio of 1 or less. Sodium bichromate and sulfate centrifuges are known in company nomenclature as soda and sulfate baskets respectively

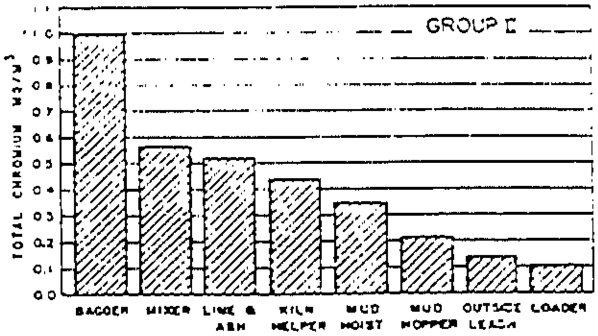

Fig. 3.

Weighted exposure according to occupations having Cr^{+3}: Cr^{+6} ratio of 1.1 to 4.9

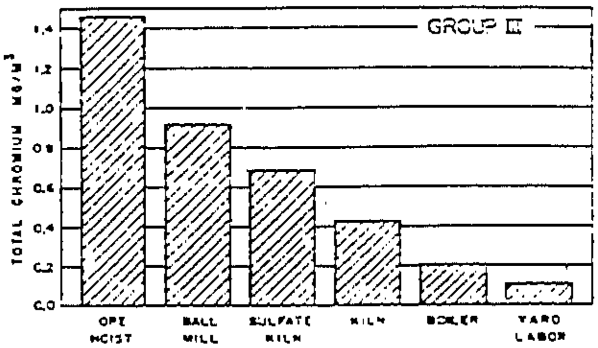

Fig. 4.

Weighted exposure according to occupations having Cr^{+3}: Cr^{+6} ratio of 5 or more

in Fig. 1. The values are based on 121 samples collected by the filter paper technique and analyzed using the polarographic method. The rate of air flow was measured with an orifice-variable area meter.[10]

Exposure of Production Workers by Occupations

ON THE basis of company employment classifications, observation of work performed and degree of exposure as estimated by visual observation, the 128 production workers were grouped into 21 occupational classifications. One or more representative individuals of each occupation were then time-studied for eight-hour periods, and the data so obtained were applied by a method described in the literature[11] to arrive at a weighted average eight-hour daily exposure. From the weighted exposures the ratio of Cr^{+3}:Cr^{+6} was also computed for each occupational classification.

On the basis of Cr^{+3}:Cr^{+6} ratio, the 21 work classifications were sorted into three groups. Group I has a ratio 1.0 or less. It contains the individuals processing sodium monochromate and bichromate liquor and those required to work in close physical proximity to such operations. Their exposure in total chromium is shown in Fig. 2. Group II with a ratio greater than 1 and less than 4.9 (Fig. 3) appears to have a distinctly dual exposure, i.e., sodium monochromate and ore dust; shippers (bagging, loading) are exposed to bichromate and ore. Group III, whose ratio is 4.9 or greater (Fig. 4), comprises occupations primarily exposed to trivalent chromium. It should be pointed out that while the average Cr^{+3}:Cr^{+6} ratio for all kiln operators is 7, for those whose work location adjoins the filtering department it is 1.4. Therefore, these particular operators might be included in Group II.

Distribution of Maintenance Workers' Time

THE 76 maintenance workers comprised approximately 30% of the total plant personnel, and observation of the conditions under which much of their work was performed indicated a potentially high degree of exposure. It was deemed necessary, therefore, to time study this group as thoroughly as the production workers.

Obviously, the nature and location of repair work is non-repetitious and must be performed as the occasion demands. A time study similar to that used for production workers could not be properly applied to maintenance personnel; hence a different approach became necessary.

Using the cost of maintenance labor over a year's time as charged to each department by the company accounting office the average man-hours of maintenance expended in each department per day were calculated. Based on the records of the maintenance superintendent and types of process equipment repaired and installed, man-hours maintenance according to crafts were then ascertained for each department. Since time charged to a specific work order might involve work in both the plant and the maintenance

TABLE 4.

DISTRIBUTION OF MAINTENANCE TIME BY CRAFTS

Craft	Ore Preparation	Leach	[illegible]	[illegible]	[illegible]
Welders	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Electricians	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Millwrights	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pipefitters	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Boilermakers	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

building, further adjustments were necessary.

In Table 4 the time distribution of five crafts according to selected departments is shown as an example.

Exposure of Maintenance Workers

UNLIKE production employees, maintenance workers seldom work under normal conditions in a plant. The work necessary to complete their assignments almost invariably results in abnormally high local exposures. The plant under study is no exception since it was observed huge volumes of dust were generated during the repair and cleaning of dust collectors, process equipment or building structure overlaid with an accumulation of dust. It is thus logical to assume the maintenance group receives, in most instances, a greater exposure than production workers.

In Table 5 a minimum and maximum weighted average exposure derived from time study and concentrations, as well as $Cr^{+3}:Cr^{+6}$ ratio, of maintenance employees by crafts are shown. The minimum levels are based on average departmental concentrations measured under normal operating conditions, and the maximum levels are reported on the basis of the highest concentration recorded in each department.

? % of time were these upset conditions

TABLE 5.
EXPOSURE OF MAINTENANCE EMPLOYEES BY CRAFTS

Craft	Weighted Average 8 Hour Exposure, mg/m³ Total Cr Minimum	Maximum	$Cr^{+3}:Cr^{+6}$ ratio
Handy Men	1.15	1.62	27.8
Millwrights	0.66	3.34	7.3
Maintenance Superintendent	0.55	2.13	4.5
Electricians	0.48	5.67	3.0
Boilermakers	0.44	4.43	2.4
Painters and Riggers	0.42	1.32	4.3
Oilers	0.41	1.94	2.2
Pipefitters	0.28	2.31	2.1
Carpenters	0.27	0.43	3.5
Welders	0.23	2.20	4.8
Machinists	0.07	0.13	6.0

Exposure of Administrative and Technical Personnel

THE administrative and technical staffs together constituted only a small minority of the plant's personnel, accounting for the remaining 21 of the 226 plant employees. With the exception of the plant superintendents and supervisors, this group's work was largely carried out in an office building situated nearby the production buildings, and it is believed their exposure is the result of infiltrated air and contaminated apparel. Grinding and handling samples in the course of making control analyses undoubtedly account for the higher exposure of laboratory personnel (Table 6).

TABLE 6.
EXPOSURE OF ADMINISTRATIVE AND TECHNICAL PERSONNEL

Occupation	Weighted Average 8 Hour Exposure, mg/m³ Total Cr	$Cr^{+3}:Cr^{+6}$ ratio
Superintendents	0.18	3.5
Plant Supervisors	0.6[illegible]	3.2
Office Workers	0.06	5.0
Laboratory Personnel	0.27	17.0

Conclusions

ALTHOUGH the environmental investigation presented here pertains to a single plant, it is believed that the conclusions that follow may be applied to other plants manufacturing sodium bichromate from chromite ore.

1. Where unit operations are not isolated or adequate dust and mist control established employees may be subjected to a dual exposure, i.e., trivalent chromium (chromite) and hexavalent chromium (chromates). In the plant studied the predominant exposure, based on both magnitude of chromium concentration and number of employees, was to the trivalent compound.

2. In the plant studied, all employees were exposed to measurable amounts of chromium. The lowest concentration which is carcinogenically significant is yet to be determined.

3. Observations during the course of this study convince the authors that the carcinogenic hazard in the chromate producing industry can be controlled successfully by utilizing industrial hygiene engineering methods employed in the safe handling of other toxic chemicals, i.e.:

(a) Undertake through adequate ventilation the control of dust and mist with the ultimate goal of securing the minimum concentration consistent with good engineering practice. Removal of toxic matter from air exhausted to the out-of-doors is essential to prevent a neighborhood public health hazard.

(b) Isolate dust and mist contributory operations, and mechanize where practicable to reduce the number of employees exposed.

(c) Provide under positive pressure uncontaminated air to personal services and process observation rooms or locate such rooms in uncontaminated areas.

(d) Insure good housekeeping by proper building design and adequate janitor services.

(e) Educate employees in personal hygiene and acquaint them with provisions made for their safety.

(f) Supply personal respiratory protective devices approved by the U. S. Bureau of Mines.

4. Establish laboratory facilities and provide technical personnel to measure the concentration of air-borne chromium compounds. Current knowledge of the degree of atmospheric contamination will provide an index of the effectiveness of the control measures as well as directing attention to sources of pollution that have been overlooked.

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That Tired Feeling

THE STATE of being tired is experienced by almost everyone at some time or other. It is a natural feeling at the end of a hard working day, but one that is supplanted with new energy after a refreshing sleep. The fatigue that is always present is the fatigue brought about by a long period of overwork, or late hours with little rest, or meals that do not provide the fuel necessary to maintain the machinery of the body. The maximum of production cannot be obtained from long hours of overwork. Efficiency is lessened to the degree that a worker comes to his job as tired as he left it the night before. The physical fatigue resulting from overwork, either mental or physical, is responsible for the saying "too tired to eat." The body needs fuel, it needs to replenish its stock of energy with energy-producing foods, and this can be done by means of a well-balanced diet. Sugar is needed to combat fatigue. When the blood sugar is depleted, many cases of fatigue and tiredness occur, even to the point of collapse. Numerous conditions stem from fatigue. Again fatigue may stem from various diseases, infection, improper hygiene, too much mental effort, inadequate nutrition. Many accidents can be charged to fatigue. For that tired feeling in the overworked person, a change of hours is recommended. There should be a shorter working day and a brief spell of relaxation, as recreation is important. For exhaustion in a nervous person, it has been found that complete rest in bed aggravates rather than relieves the condition, particularly for chronic nervous exhaustion. Such a person should be encouraged to carry on consistently from day to day, if only in a limited way. In general, however, rest is the best treatment for all types of fatigue. Physical activity should be decreased as much as possible, and such stimulants as coffee, tea and "cokes" should be abandoned or, at least the use of them curtailed. Consult your doctor. He is the person to investigate the reasons for your fatigue. If a glandular disturbance is responsible, he will detect it. Self-medication won't help. Let your doctor lead you into a balanced social and business way of living. The fatigued person is one who, in his tired state, contributes little to his own enjoyment and nothing to that of any one else. Time passes too quickly to be too tired to enjoy its interest.

—Educational Committee, Illinois State Medical Society, *Health Talk*, November [illegible]

APPENDIX V

Comparison of Risk Estimates from Mancuso Study and Inhalational Bioassays

In earlier documents DHS has attempted to estimate whether cancer risk estimates based on animal bioassays were compatible with those based on the results of epidemiologic investigations. In this instance the animal bioassays from which estimates of dose would be derived - i.e, the inhalation studies, showed no significant response among exposed animals (with the possible exception of the study by Nettesheim et al., 1971. See below.) Thus, in order to compare the results of risk estimates between species, one would have to calculate the lower confidence interval of the slope predicted by the epidemiologic model and compare it with statistical upper confidence limit on one or more of the animal studies. Unfortunately, none of the animal studies was conducted in anticipation of a risk assessment and the data are not reported in a format readily usable toward that end. The inhalational studies are summarized in Table A-V-1.

TABLE A-V-1: CANCER BIOASSAYS FOR
CHROMIUM COMPOUNDS ADMINISTERED BY INHALATION

Study	Compound	MMAD[1] (µm)	Concentration[2] (mg/m^3)	Duration of Exposure	Animals	Number Exposed	Results
Baetjer al., 1959	Mixed chromate dust	0.8	a 0.6-1.2	4 hr/day, 5 days/wk for 16-46 wks	Strain A Mice	241	N.S.[3], although et pulmonary adenomas appeared at younger ages.
Baetjer et al., 1959	Mixed chromate dust	0.8	a 0.6-1.2	4 hr/day, 5 days/wk for 39-58 wks	Swiss Mice	148	N.S.[3], although pulmonary adenomas appeared at younger ages.
Baetjer et al., 1959	Mixed chromate dust	0.8	a 0.6-1.2	4 hr/day, 5 days/wk for 41-42 wks	C57BL Mice	111	N.S.[3], although pulmonary adenomas appeared at younger ages.
Baetjer et al., 1959	Mixed chromate dust	0.8	a 8-13	1/2 hr/day for 20 wks	Strain A Mice	36	N.S.[3]
Baetjer et al., 1959	Mixed chromate dust	0.8	a 8-13	1/2 hr/day for 43-52 wks	Swiss Mice	25	N.S.[3]
Baetjer et al., 1959	Mixed chromate dust	0.8	a 1.2-1.7	4 hr/day, 5 days/wk for up to 151 weeks	Mixed strain rats (Wistar/ McCollum)	100	4 exposed rats developed lymphosarcomas versus one of of 85 control rats (but see below) below)
Steffee and Baetjer, 1965	Mixed chromate dust	0.8	a 1.6-2.1	4-5 hr/day, 4 days/wk for	Wistar rats	78	N.S.[3]

TABLE A-V-1 (cont'd)

Study	Compound	MMAD[1] (µm)	Concentration[2] (mg/m^3)	Duration of Exposure	Animals	Number Exposed	Results
Steffee and Baetjer, 1965	Mixed chromate dust plus chromate mist	0.8	≅ 1.6-2.1	4-5 hr/day, 4 days/wk for 40-50 months	Rabbits	8	N.S.[3]
Steffee and Baetjer, 1965	Mixed chromate dust plus chromate mist	0.8	≅ 1.6-2.1	4-5 hr/day, 4 days/wk for 40-50 months	Guinea Pigs	50	N.S.[3]
Nettesheim et al., 1971	Calcium chromate dust	< 1	≅ 4.33	5 hr/day, 5 days/wk for life	C57BL/6 Mice	≅272	Authors reported 14 adenomas in exposed versus 5 in control animals. Statistical significance is indeterminate (See text).

1. Mean mass aerodynamic diameter

2. Concentration as chromium

3. No significant increase in tumor incidence in exposed versus control animals.

The results of the bioassays conducted by Baetjer et al. (1959) are presented in a variety of ways (including percentage of mice surviving to the end of the experiment with lung tumors, average number of lung tumors in tumor-bearing and all surviving mice, and percentage of tumor-bearing mice with multiple lung tumors), none of which would allow a calculation of the number or percentage of experimental mice at risk that developed lung tumors at a given dose level. For the rats in this experiment, 4 of 100 exposed animals developed lymphosarcomas at various sites, while 1 of 85 control rats did, a difference which is not statistically significant. However, the authors noted that "experiments were not designed to study pathological changes in the tissues other than the lungs." Thus, limiting the findings to pathologic changes in the lungs, there was one lymphosarcoma originating in the lungs of an exposed rat and none in the control animals. Since spontaneously occurring lymphosarcomas are not uncommon in rats, Baetjer et al. (1959) repeated the experiment (reported by Steffee and Baetjer, 1965).

In the second study, Steffee and Baetjer (1965) were unable to replicate their earlier results. Under similar experimental conditions 4 of 78 exposed Wistar rats compared with 4 of 75 controls developed lymphosarcomas involving the lungs. It was not stated whether these were primary tumors or pulmonary metastastes. Three exposed rats developed alveologenic adenomas, while two controls did. Steffee and Baetjer (1965) also exposed eight rabbits to chromate dust, none of which developed any pulmonary tumors. Of fifty exposed guinea pigs, three developed alveologenic adenomas, compared with none in control animals, while one of each group had a lymphosarcoma involving the lungs.

Finally, Nettesheim et al. (1971) reported that C57BL/6 mice exposed to calcium chromate for 5 hours/day, 5 days/week for life showed an increased incidence of pulmonary adenomas and adenocarcinomas. This conclusion was based on the authors' observation that fourteen animals exposed to calcium chromate (eight females and six males) developed adenomas, whereas only five control animals did (two females and three males). As noted on page 48 of the main text of this document, the conclusions of Nettesheim et al. cannot be confirmed from the reported data. The authors' statistical methodology was not reported. The denominator--numbers of controls and exposed animals at risk--cannot be precisely ascertained from the published report. The experimental design involved exposure of 1,090 C57BL/6 mice in 2 inhalation chambers (545 mice, 272 males and 273 females/chamber). All the mice in one chamber were infected with influenza virus two weeks prior to the initiation of calcium chromate exposure. Half the mice in each chamber were subjected to 100 R whole-body X radiation four weeks prior to exposure. The gender distribution of the irradiation pretreatment was not specified: One might guess that roughly equal numbers of males and females were irradiated, but the exact numbers of chromium - exposed animals not subjected to either of these pre-treatments were not reported. Furthermore, at 6, 12, and 18 months into the experiment, 15 mice (pretreatment status and sex not reported) were removed from each chamber for microbiological testing and histopathological investigation. Three to four percent of the animals that died during the experiment were cannibalized and were thus unavailable for necropsy (distribution between control versus exposed animals and pretreatment status were not given). Thus the numbers of animals exposed only to calcium chromate dust and the periods of exposure can be conjectured but not identified with certainty.

Other difficulties with this bioassay include the following:

1. During the first half of the experiment the mortality rate of the control mice was substantially higher than that of the chromium - exposed mice, attributed by Nettesheim et al. to an epidemic of "urogenital disease" in the former. Until about 70 weeks into the experiment the cumulative mortality of the control mice was about twice that of the treated group, and the cumulative mortality curves (the data were only reported graphically) crossed only after more than 100 weeks of exposure. No data on the cumulative mortality by gender were presented. Although Nettesheim et al. were aware of the non-tumor-related early mortality in the controls, they did not correct for it in the statistical analysis.

2. Both alveologenic adenomas and adenocarcinomas were reported to have occurred. However, the distribution of these tumor types by gender and by exposure status was not reported.

Thus, for purposes of cancer risk assessment, the study of Nettesheim et al. is clearly inadequate. However, to respond to the request of SRP member Dr. Joyce McCann to evaluate the compatibility of risk estimates based on animal inhalation versus human studies, DHS staff members have selected to use this study because (1) the number of exposed animals was larger than in any of the others; (2) there may be an exposure-related increase in tumors; and (3) the animals' exposure lasted until they died, whereas the other above-noted experiments were terminated prior to the demise of all the animals.

To calculate upper confidence intervals for risks from this study, DHS staff members did the following:

(1) Assumed that the number of animals initially at risk in the experimental and the control groups was 250. (1,090 total mice minus 545 infected with influenza, minus 545/2 ≈ 273 subjected to X radiation, minus 45/2 ≈ 23 serially sacrificed during the course of the experiment. Most of the latter were removed prior to the appearance of the first tumor in either group.)

(2) Corrected for early mortality by subtracting from the numbers of animals at risk those that had died prior to the appearance of the first adenoma. (Since the cumulative mortality and the time to first tumor were presented in graphical form only, this correction was of necessity somewhat crude.) Corrected numbers were 164 controls and 222 exposed mice.

(3) Combined tumor incidence for both sexes in each group, since the cumulative mortality data were not displayed by gender. Total numbers of animals with tumors were five controls and fourteen exposed mice.

(4) Calculated average daily dose to be compatible with the human dose units used in the risk assessment as follows: $4.33\ mg/m^3 \times 5/24 \times 5/7 = .66\ mg/m^3$, where the latter two numbers correct for the fractional daily and weekly exposures of the animals. Since there are only two dose groups (control = 0 and exposed = $.66\ mg/m^3$), the dose-response curve is linear and the slope of the curve equals the carcinogenic potency.

(5) Used these values in the linearized multistage model of Crump and Howe, GLOBAL 82, which calculated maximum likelihood estimates and 95% upper confidence intervals on the slope of the dose-response curve.

The maximum likelihood estimate of the slope (q_1) is 0.052 and the upper 95% confidence limit (UCL) on the slope (q_1^*) is 0.11 $(mg/m^3)^{-1}$. Converting to nanograms gives a 95% UCL of 1.1×10^{-7} $(ng/m^3)^{-1}$. To compare this with the dose-response curve derived from the Mancuso study, the lower confidence limit on the SMR was calculated using method of Liddell (1984).* This yielded a slope of 9.3×10^{-6} $(ng/m^3)^{-1}$. Thus, there is a difference of almost two orders of magnitude between the lower confidence limit on the slope of the risk estimate derived from the Mancuso study and the upper confidence limit on that derived from the largest animal study by Nettesheim et al. As noted in the text of part B, this discrepancy may be due to a variety of factors, including differential species sensitivity to carcinogenesis, differences in delivered dose to susceptible tissues, and so forth. It is not possible to provide a compelling explanation for this discrepancy.

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* The SMR for lung cancer in the Mancuso study was 7.2, based on 35 observed cases where 4.86 were expected. The potency or slope is 1.44×10^{-5} $(ng/m^3)^{-1}$. (See section 8.3.6.2 for calculation.) The lower limit on the SMR obtained by the method of Liddell (1984) was 5.0 and the corresponding potency on slope was 9.3×10^{-6} $(ng/m^3)^{-1}$.