FIFRA Scientific Advisory Panel Background Document

Hazard Identification and Toxicology Endpoint Selection for Inorganic Arsenic and Inorganic Chromium

September 25, 2001

Timothy F. McMahon, Ph.D. and Jonathan Chen, Ph.D.
U.S. Environmental Protection Agency
Office of Pesticide Programs
Antimicrobials Division

This document provides background information on hazard and toxicity endpoint selection for inorganic arsenic and inorganic chromium, both chemical components of wood treated with Chromated Copper Arsenate (CCA). This document is being submitted to the FIFRA Scientific Advisory Panel for review prior to the October 23-25, 2001 meeting of the Panel. The Agency is seeking comment and discussion from the Panel on a number of issues related to hazard identification and toxicity endpoint selection for both inorganic arsenic and inorganic chromium as chemical components of CCA-treated wood. Input from the Panel will enable the Agency to proceed with its reassessment of the hazards and risks associated with exposure to inorganic arsenic and inorganic chromium using the best available information as part of the reregistration process for these chemicals.

In relation to hazard and toxicity endpoint selection for inorganic arsenic and inorganic chromium, the Agency is seeking comment and discussion from the Panel on the following specific issues: (1) selection of toxicity endpoints and uncertainty factors for inorganic arsenic and inorganic chromium; (2) the dataset and value chosen for dermal absorption of inorganic arsenic; (3) the dataset and value chosen for relative bioavailability of inorganic arsenic when ingested in soil; (4) use of hazard data for chromium (VI) to represent hazards associated with exposure to chromium from CCA-treated wood; (5) selection of endpoints to quantitate systemic effects from dermal exposure to inorganic chromium, and (6) whether an inhalation endpoint is needed for assessment of potential nasal effects from inhalation of chromium-contaminated soil dust.

Introduction

The Agency has become aware in recent years of concerns raised by the public regarding the potential hazards associated with the continued use of CCA-treated lumber, especially the use of this material in playground equipment to which infants and children may be exposed through direct dermal contact with the treated wood and/or soil around the treated wood structure, or through oral ingestion of chemical residue from touching of wood and/or soil and subsequent hand-to-mouth behaviors. As a result of these concerns, the Agency has embarked upon a process to assess the exposures and risks associated with the current uses of CCA-treated lumber, including exposures and risks associated with use of this wood in playground structures. In any such assessment, the toxicity of the pesticide chemical must first be adequately described, either through submission of guideline toxicology studies that are reviewed by the Agency, or through citation of scientific studies in the peer-reviewed literature. For the present assessment, the Agency recognizes that inorganic arsenic and inorganic chromium are the compounds of toxicological concern with respect to exposure to CCA-treated wood. The following sections characterize the hazards of inorganic arsenic and inorganic chromium. Information was summarized from submitted toxicology studies, the open scientific literature, and from published documents by the USEPA and the Agency for Toxic Substances and Disease Registry. It is noted for inorganic arsenic that in most cases, human data (in the form of epidemiology studies and case reports) provide the basis for the hazard identification, as most laboratory animal models appear to be substantially less susceptible to arsenic toxicity than humans.

For chromium, hazard data show clearly that Cr (VI) demonstrates more significant toxicity than Cr (III). However, there is little data delineating the valence state of chromium in compounds that leach from in-service treated wood (Lebow, 1996), but interconversion of Cr (VI) and Cr (III) in the environment is observed (Cohen et al., 1999), and at least one study has reported measurable levels of hexavalent chromium in soils (Lebow, 1996). In the absence of clear evidence, the Office of Pesticide Programs has chosen to utilize the toxicity database for the more toxic Cr (VI) in its hazard assessment and endpoint selection process for chromium.

Copper as a component of CCA-treated wood is not considered in this document. Copper is an essential nutrient which functions as a component of several enzymes in humans, and toxicity of copper in humans involves consumption of water contaminated with high levels of copper, suicide attempts using copper sulfate, or genetic disorders such as Wilson’s disease.

Hazard Characterization - Arsenic

Arsenic is a naturally occurring element present in soil, water, and food. In the environment, arsenic exists in many different forms. In water, for example, arsenic exists primarily as the inorganic forms As +3 (arsenite) and As +5 (arsenate), while in food, arsenic exists primarily in organic forms (seafood, for example, contains arsenic as arsenobetaine, a form which is absorbed but rapidly excreted unchanged). Human activities also result in the release of arsenic into the environment, such as residual arsenic from former pesticidal use, smelter emissions, and the use of chromated copper arsenicals (CCA) in the pressure-treament of wood for construction of decks, fences, playgrounds, and other structural uses.

Inorganic arsenic, prior to 1991, was used as an agricultural pesticide. In 1991, the Agency proposed cancellation of the sole remaining agricultural use of arsenic acid (As+5) on cotton. Subsequently, this registration was voluntarily canceled by the sponsor and made immediately effective by the Agency (Federal Register, 1993). However, inorganic arsenic contained within CCA-treated wood continues to be widely used for decking and fencing lumber as well as playground equipment.

Acute Toxicity

The acute oral toxicity of inorganic arsenic in humans shows lethal effects in the range of 22-121 mg/kg, which is consistent with results of animal studies showing lethality in the range of 15-175 mg/kg. There are no studies reporting death in humans after dermal exposure to inorganic arsenic, which is consistent with results of animals studies showing no mortality at dermal doses up to 1000 mg/kg. Mortality in humans from short-term inhalation exposure to inorganic arsenic has not been observed in occupational settings at air levels up to 100 mg/m^3. One study in pregnant rats reported lethality of inorganic arsenic at a concentration of 20 mg/m^3. Arsenic has been shown to result in contact dermatitis in humans exposed occupationally, and animal studies are also suggestive of mild to severe dermal irritation after application of arsenic to skin. Severe ocular irritation was observed in an acute eye irritation study (MRID # 00026356). Arsenic does not produce skin sensitization in a guinea pig model (MRID # 40646201).

Non-Acute Toxicity

Subchronic studies with arsenic in experimental animal models have produced only generalized toxicity, i.e., weight loss, and decreased survival, while data from human exposures have shown more specific toxic effects, such as neurotoxicity and hyperkeratosis of the skin of the hands and feet (ATSDR, 2000a).

Chronic toxicity studies with inorganic arsenic in experimental animals also show a lack of specific toxic effects, whereas the scientific literature that describes chronic human exposure shows a clear

relationship between chronic exposure to inorganic arsenic and the development of skin cancer as well as cancers of the lung, liver, and bladder (ATSDR, 2000; NRC, 1999).
The most notable example of this is the data of Tseng, (1968, 1977) who conducted epidemiological studies of chronic oral exposure of humans to arsenic contained in food and water. From these studies it was noted that hyperpigmentation, keratosis and possible vascular complications [Blackfoot disease] occurred at a dose of 0.17 mg arsenic per liter of water, equivalent of 0.014 mg/kg/ day. Several follow-up studies of the Taiwanese population exposed to inorganic arsenic in drinking water showed an increase in fatal internal organ cancers as well as an increase in skin cancer. Other investigators found that the standard mortality ratios (SMR) and cumulative mortality rates for cancers of the bladder, kidney, skin, lung, and liver were significantly greater in the Blackfoot disease endemic area of Taiwan when compared with the age adjusted rates for the general population of Taiwan.

Data on the developmental and reproductive toxicity of inorganic arsenic in humans is not extensive. One study conducted in Sweden among copper smelter workers showed significantly reduced live birth weights in offspring of women employed at the copper smelter and increased incidence of spontaneous abortion among those who worked at the smelter or lived in proximity to it. However, effects from exposure to lead or copper in this study could not be ruled out. Hopenhayn-Rich (2000) conducted a retrospective study of late fetal, neonatal and postnatal mortality in Antofagasta, Chile for the years 1950 to 1996. The data from this study indicated an elevation in late fetal, neonatal and postnatal mortality compared to a comparison group in Valparaiso, Chile during the period when drinking water in Antofagasta was contaminated [860 ug/L] with arsenic (1958 to 1970). There was a decline in late fetal, neonatal and postnatal mortality when the concentration of arsenic in the drinking water declined due to installation of a water treatment plant. After installation of the plant, the mortality rates in Antofagasta were indistinguishable from those in Valparaiso. It was noted that the mothers involved in this incident had characteristic arsenic-induced skin lesions.

In laboratory animals, the major teratogenic effect induced by inorganic arsenic is neural tube defect, characterized by exencephaly and encephalocele. However, this effect has not been observed in humans (IPCS, 2001). In addition, data on the developmental and reproductive toxicity of inorganic arsenic submitted to the Agency show effects on offspring only at doses that are maternally toxic.

In a developmental toxicity study (Nemac, 1968b), pregnant Crl:CD-1(ICR)BR mice (25 per dose group) received a single daily gavage of aqueous Arsenic Acid (75%) from day 6 through 15 of gestation. Doses were 0, 10, 32 and 64 mg/kg/day. Controls received deionized water. Body weights were recorded at six hour periods. Cesarean section was on day 18. Fetuses were weighed, sexed and examined for external skeletal and soft tissue malformations and variations. At the high dose, two dams died. Signs included lethargy, decreased urination and defecation, soft stool or mucoid feces. Brown urogenital matting, and red material around the eyes. Necropsy showed bilateral reddening of cortico-medullary junction (kidneys) and a red areas in the stomach. At mid and (especially) top dose, the dams showed weight loss and an elevated

incidence of total litter resorption. An increase in exencephaly occurred in the both the low (1/231 fetuses per 1 litter) and the high (2/146 fetuses per 1 litter) doses, but statistical significance was not seen. The Maternal Toxicity NOAEL was determined to be 32 mg/kg/day, and the Maternal toxicity LOAEL was determined to be 64 mg/kg/day, based on increased total litter resorption, reduced body weight, and increased maternal mortality. The Developmental Toxicity NOAEL was determined to be 32 mg/kg/day and the Developmental Toxicity LOAEL was determined to be 64 mg/kg/day, based on reduced mean viable fetuses, reduced fetal weights, increased post implantation loss and increased incidence of exencephaly (not statistically significant).

In a prenatal developmental toxicity study (Nemec, 1988a), artificially inseminated New Zealand White rabbits (20/dose) received aqueous arsenic acid (75%) by gavage from days 6 through 18 of gestation inclusive at doses of 0, 0.25, 1, and 4 mg/kg/ day. At the 4 mg/kg/day dose level, seven dams died or were sacrificed in extremis. Reduced body weight gain, clinical signs of toxicity (prostration, ataxia, decreased defacation and urination, mucoid feces), and histo-logical alterations in dams sacrificed or dead at the high dose (pale, soft, or mottled kidneys; pale and soft liver; dark red areas of the stomach; dark red lungs) were observed. Fetal data showed increased post-implantation loss at the 4 mg/kg/day dose (1.8 vs. 0.5 in control) and reduced mean viable fetuses (4.9 vs. 6.7 in control). There was no evidence from the data of increased incidence of fetal alterations (variations, malformations) related to treatment with test article. The Maternal NOAEL was determined to be 1 mg/kg/day, and the Maternal LOAEL was determined to be 4 mg/kg/day, based on increased mortality, decreased body weight gain, clinical signs, and histological alterations of the kidney and liver. The Developmental NOAEL was determined to be 1 mg/kg/day, and the Developmental LOAEL was determined to be 4 mg/kg/day, based on increased post-implantation loss and decreased viable fetuses.

With regard to the susceptibility of offspring to the toxicity of inorganic arsenic, DeSesso, (1998) in a review paper exploring the reproductive and developmental toxicity of arsenic acid (As+5) noted that in three repeated oral dose studies carried out under EPA guidelines for assaying developmental toxicity, arsenic acid was not teratogenic in: mice by oral gavage (10 to 64 mg/kg/day), rabbits by oral gavage (1 to 4 mg/kg/day) and in a mouse two-generation feeding study (20 to 500 ppm). Other animal developmental and reproductive toxicity data based on the published literature also showed no increased sensitivity to arsenic (+5) when given orally by repeated doses.

The same authors note that “there is a paucity of human data regarding inorganic arsenic exposure during pregnancy and potential adverse effects on progeny. The available epidemiological studies were neither rigorously designed nor well controlled. These studies failed to find a definitive or consistent association between arsenic exposure and adverse pregnancy outcome. Consequently, claims of potential adverse effects of inorganic arsenic on human development remain unsubstantiated.” This conclusion is consistent with ATSDR (2000a), which noted that “Although several studies have reported marginal associations between prolonged low-dose human arsenic exposure and adverse reproductive outcomes, including

spontaneous abortion, stillbirth, developmental impairment, and congenital malformation, none of these studies have provided convincing evidence for such effects. "

The January 22, 2001 Federal Register Notice (Vol. 66, No. 14, pages 7027-7028), in which the arsenic drinking water standard was discussed in relation to susceptibility of certain human subpopulations including infants and children also supports the view that inorganic arsenic does not pose a special sensitivity to children. In that notice, the Agency agreed with a report by the National Research Council noting "that there is a marked variation in susceptibility to arsenic-induced toxic effects which may be influenced by factors such as genetic polymorphisms, life stage at which exposures occur, sex, nutritional status, and concurrent exposures to other agents or environmental factors." However, the view was also shared between the EPA and NRC that "there is insufficient scientific information to permit separate cancer risk estimates for potential subpopulations...and that factors that influence sensitivity to or expression of arsenic-associated cancer and non-cancer effects need to be better characterized. The EPA agrees with the NRC that there is not enough information to make risk conclusions regarding any specific subpopulations." In the latest update to this issue (NRC, 2001), it is noted that while "evidence from human studies suggests the potential for adverse effects on several reproductive endpoints... "there are no reliable data that indicate heightened susceptibility of children to arsenic."

Neurotoxicity of inorganic arsenic is not evident in studies with experimental animals. However, there is a large body of epidemiology studies and case reports which describe neurotoxicity in humans after both acute and chronic exposures, characterized by headache, lethargy, seizures, coma, encephalopathy (after acute exposures of 2 mg/kg/day and above), and peripheral neuropathy (after repeated exposures to 0.03-0.1 mg/kg/day) (ATSDR, 2000a).

Mutagenicity studies using inorganic arsenic have shown mixed results. Sodium arsenite is not genotoxic to Chinese hamster ovary (CHO) cells (Rossman et al., 1980) or Syrian hamster embryo cells (Lee et al., 1985b) when selecting for ouabain- (ATPase) or thioguanine-resistant (hypoxanthine phosphoribosyl transferase, HPRT) mutants. In the L5178Y mouse lymphoma assay, sodium arsenite is weakly genotoxic at the thymidine kinase locus without metabolic activation (Oberly et al., 1982; Moore et al., 1997a). Sodium arsenate is even a weaker mutagen with (Oberly et al., 1982) and without metabolic activation (Moore et al., 1997a). The type of effects reported by Moore et al. (1997a) were chromosomal aberrations, micronuclei (arsenite only) polyploidy and endoreduplication.

Sodium arsenate and sodium arsenite induce sister chromatid exchanges and chromosomal aberrations in hamster embryo cells (10^{-7}mol/litre-10^{-4}mol/litre) (Larramendy et al., 1981; Lee et al., 1985b; Kochhar et al., 1996). The aberrations are characterized by chromatid gaps, breaks, and fragmentation, endoreduplication and chromosomal breaks. These clastogenic effects are observed at lower doses of arsenite than arsenate. The difference may be due to greater *in vitro* cellular uptake of arsenite than arsenate (Lerman et al., 1983; Bertolero et al., 1987). GaAs (2.5-10 μg/ml) did not induce micronuclei in Syrian hamster embryo cells (Gibson et al., 1997).

Recently, methylated trivalent forms of arsenic have been shown to nick and/or completely degrade ϕX174 DNA in vitro (Mass et al., 2001), while sodium arsenite, arsenate, and the pentavalent methylated forms of arsenic were without effect. In the single-cell gel assay (COMET assay)using human lymphocytes, inorganic arsenite and arsenate produced concentration-dependent linear increases in DNA damage, but the methylated trivalent forms of arsenic were observed to be 54-77 times more potent in this assay than the non-methylated forms. DNA damage occurred in the absence of metabolic activation in both assays.

Metabolism and Bioavailability

Metabolism of inorganic arsenic first proceeds through non-enzymatic reduction of arsenate to arsenite, which can then undergo enzymatic methylation to the products monomethylarsinic acid and dimethylarsinic acid. These products are then reduced to the monomethylarsinous acid and dimethylarsinous acid produts. The major site of methylation appears to be liver, where the methylation reaction is mediated by methyltransferase enzymes using S-adenylmethionine as a cosubstrate. The products of inorganic arsenic metabolism in urine have been identified as As(+3), As(+5), monomethylarsinous acid, and dimethylarsinous acid. Urinary products appear similar among species studied (ATSDR, 2000a), but the relative proportions of these products vary greatly.

The bioavailability of absorbed inorganic arsenic is dependent on the matrix in which it is exposed to. Arsenic in drinking water is in a water-soluble form, and it is generally assumed that its absorption from the gastrointestinal tract is nearly complete. Arsenic in soils, however, may be incompletely absorbed because they may be present in water-insoluble forms or interact with other constituents in the soil. The relative bioavailability of arsenic after it is been exposed (water versus soil) was defined as the percentage of arsenic absorbed into the body of a soil-dosed animal compared to that of animal receiving an single dose of arsenic in aqueous solution. This is a route specific issue. The Agency has considered several data sets in determination of the relative bioavailability of inorganic arsenic (soil vs. water), which are summarized below.
N

Relative Bioavailability-Oral Route

Roberts et al. 2001

The relative bioavailability of arsenic from selected soil samples was measured in a primate model. Sodium arsenate was administered to five male *Cebus apella* monkeys by the intravenous and oral routes, and urine and feces were collected over a four-day period. Pharmacokinetic behavior of arsenic and the fractions of dose excreted in urine and feces were consistent with previous observations in humans. Soil samples from four waste sites in Florida (one from an electrical substation, one from a wood preservative treatment (CCA) site, one from a pesticide application site, and one from a cattle dip vat site) were dried and sieved. Soil doses were prepared from these samples and administered orally to the monkeys. Relative bioavailability was assessed based on urinary excretion of arsenic following the soil dose compared with excretion following an oral dose of arsenic in

solution. Relatively consistent bioavailability measurements were obtained among monkeys given the same soil sample. Differences in bioavailability were observed for different sites, with relative bioavailability ranging from 10.7±14.9% (mean±SD) to 24.7±3.2% for the four soil samples.

Freeman et al. 1993

The relative bioavailability of arsenic from soil samples from Anaconda, Montana was measured. After a fasting period of approximately 16 hours, prepubescent male and female SPF New Zealand White rabbits (5/sex/group) were given a single oral (capsule) administration of soil (3900ppm As) at three dose levels (0.2, 0.5, and 1.0 g of soil/kg, corresponding to 0.78, 1.95 and 3.9 mg As/kg, respectively). Control groups included untreated controls, and an intravenous sodium arsenate group (1.95 mg As/kg). The relative bioavailability of arsenic in the soil was approximately 37 - 56 % (based on the As concentration in the excreted urine).

Freeman et al. 1995

Oral absorption of arsenic in a group of three female Cynomolgus monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at 67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The relative bioavailabilities of arsenic in the dust and soil were approximately 28.4% and 20.4% respectively (based on urine).

Groen et al. 1993

Arsenic was administered as an intravenous solution (As_2O_5) or orally as As in soil to groups of six beagle dogs, and urine was collected in 24-hour fractions for 120 hours. After 120 hours, 88% ± 16% of the dose administered intravenously was excreted in the urine, compared to only 7.0 ± 1.5% excreted in the urine after oral soil administration. The calculated bioavailability of inorganic As from urininary excretion was 8.3 ± 2.0%.

USEPA Region 10, 1996

The relative bioavailability of arsenic and lead in soil or slag from the Ruston/North Tacoma Superfund Site has been studied in immature swine that received one single oral dose of soil or sodium arsenate (EPA, 1996). Following a 12 hour overnight fast, each animal was given a single administration of the appropriate test material. Solutions of sodium arsenate and lead acetate were administered separately and not mixed together prior to administration. The group receiving environmental media received a single oral administration od one of four quantities of soils at 25, 60, 100 or 150 mg soil/kg of body weight (BW) (0.04, 0.10, 0.16, or 0.24 mg As/kg BW and 0.03, 0.08, 0.14, or 0.20 mg pb / kg BW). Control groups include intravenous or gavage doses of solution arsenic, untreated controls (received aqueous vehicle only), and an intravenous sodium arsenate

group (1.95 mg As/kg). Because several urine samples were lost during sampling procedure, urinary arsenic excretion was not used as an biomarker in estimating bioavailability. Based on the blood level of arsenic, the relative bioavailability of arsenic (soil versus water) in the soil was 78% (56 - 111%).

USEPA Region 8, 1997

The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100-300 μg/g, lead at concentrations of 3,000-14,000 μg/g. The arsenic doses ranged from 1 to 65.4 μg/kg/day. The fraction of the arsenic dose excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mea±SD, 45% ±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from7 to 5l% (mean±SD, 35%±27).

By carefully comparing data on the urinary and fecal recovery of arsenic in both experimental animals after an oral intravenous dose of sodium arsenate and in humans, the data of Robrts et al. (2001) using the monkey was considered an appropriate study model in evaluating the relative bioavailability of arsenic due to the similarity of monkeys to humans and the similarity in g.i. absorption characteristics. The Roberts et al. study also employed a variety of soil types including soil from a CCA-contaminated site. Therefore, based on the study results of Roberts et al. (2001) a relative bioavailability of 25% was chosen to represent oral bioavailability.

Relative Bioavailability - Dermal Route

Wester et al. (1993) studied the dermal absorption of arsenic from both water and soil with Rhesus monkeys. The results of this study showed that in vivo percutaneous absorption of the low dose of arsenic in water was 6.4 ± 3.9% (n=3); while 2.0 ± 1.2 % (n=4) was absorbed from the high dose. Percutaneous absorption of arsenic from soil was 4.5 ± 3.2% (n=4) from the low dose and 3.2 ± 1.9 % (n=4) from the high dose. The dermal absorption of arsenic from water was not statistically different from the absorption from soil. Therefore, the relative bioavailability of arsenic by the dermal route (water versus soil) is 100%.

For inorganic arsenic, studies by the oral route in commonly used experimental animal species have not revealed a carcinogenic response. However, human data reveal a clear carcinogenic response. In epidemiological studies by Tseng, 1968, and Tseng, 1977, where chronic oral exposure to arsenic contained in food and water occurred, symptomatology consisted of hyperpigmentation, keratosis and possible vascular complications [Blackfoot disease] at the LOAEL of 0.17 mg/L of water, equivalent of 0.014 mg/kg/ day. The NOAEL was calculated to be 0.009 mg/L of water equivalent to 0.0008 mg/kg/day. Several follow-up studies of the

Taiwanese population exposed to inorganic arsenic in drinking water showed an increase in fatal internal organ cancers as well as an increase in skin cancer. Other investigators found that the standard mortality ratios (SMR) and cumulative mortality rates for cancers of the bladder, kidney, skin, lung, and liver were significantly greater in the Blackfoot disease endemic area of Taiwan when compared with the age adjusted rates for the general population of Taiwan.

Hazard Characterization - Chromium

Chromium is a naturally occurring element found in animals, plants, rocks, in soil, and in volcanic dust and gases. In the trivalent (+3) state, chromium compounds are stable and occur in nature in this state in ores such as ferrochromite. Chromium (VI) is second-most stable relative to the (+3) form, but rarely occurs naturally and is usually produced from anthropogenic sources (ATSDR, 2000b). The general population is exposed to chromium by inhalation of ambient air, ingestion of food, and drinking of water. Dermal contact with chromium can also occur from skin contact with products containing chromium or from soils containing chromium.

In humans and animals, chromium (III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism. The biologically active form of chromium exists as a complex of chromium (III), nicotninc acid, and possibly the amino acids glycine, cysteine, and glutamic acid to form glucose tolerance factor. GTF is believed to function by facilitating the interaction of insulin with its cellular receptor sites although the exact mechanism is not known. The National Research Council recommends a dietary intake of 50-200 micrograms per day for chromium III.

Chromium in the ambient air occurs from natural sources, industrial and product uses, and burning of fossil fuels and wood. The most important industrial sources of chromium in the atmosphere originate from ferrochrome production. Ore refining, chemical and refractory processing, cement-producing plants, automobile brake lining and catalytic converters for automobiles, leather tanneries, and chrome pigments also contribute to the atmospheric burden of chromium (Fishbein, 1981). Chromate chemicals used as mist inhibitors in cooling towers and the mist formed during chrome plating are probably the primary sources of Cr(VI) emitted as mists in the atmosphere (Towill et al., 1978).

Surface runoff, deposition from air, and release of municipal and industrial waste waters are the sources of chromium in surface waters.

Ingested hexavalent chromium is efficiently reduced to the trivalent form in the gastrointestinal tract (DeFlora et al., 1987). In the lungs, hexavalent chromium can be reduced to the trivalent form by ascorbate and glutathione. Given the rapid reduction of Cr(VI) to Cr(III) in vivo, it is relevant to consider whether environmental exposures to Cr(VI) or administration of Cr(VI) in controlled animal experiments is essentially identical to environmental exposures to Cr(III) or administration of Cr(III) in controlled experiments. For chromium, hazard data show clearly that

Cr (VI) demonstrates more significant toxicity than Cr (III). However, there is little data delineating the valence state of chromium in compounds that leach from in-service treated wood (Lebow, 1996), but interconversion of Cr (VI) and Cr (III) in the environment is observed (Cohen et al., 1999), and at least one study has reported measurable levels of hexavalent chromium in soils (Lebow, 1996). In the absence of clear evidence, the Office of Pesticide Programs has chosen to utilize the toxicity database for the more toxic Cr (VI) in its hazard assessment and endpoint selection process for chromium.

In acute toxicity animal studies, administration of chromium (VI) (as chromic acid) by the oral, dermal, and inhalation routes resulted in significant acute toxicity as measured by lethality. The measured oral LD50 in rats was reported as 52 mg/kg, the dermal LD50 as 57 mg/kg, and the inhalation LC50 as 0.217 mg/L, placing chromium (VI) in Toxicity Category I for acute lethality. Human reports of death after ingestion of chromium show lethality at similar dose levels (ATSDR, 1998). Chromium (VI) is a significant eye and skin irritant, and severe allergic reactions consisting of redness and swelling of the skin have also been noted in exposed animals and humans. Case reports of humans who have intentionally or accidentally ingested chromium have also shown severe respiratory effects (pulmonary edema, bronchitis, bronchopneumonia), cardiovascular effects (cardiac arrest), and gastrointestinal effects (hemorrhage, ulceration).

In contrast to the acute toxicity of chromium (VI), acute toxicity data for chromium (III) show less severe acute toxicity, with oral LD50 values in rats reported as 183-200 mg/kg or 2365 mg/kg. There are no reports of lethality in experimental animals after acute inhalation or acute dermal exposure to chromium (III). However, skin irritation and sensitization have also been observed from exposure to chromium (III).

The dermal irritancy and sensitization potential of chromium compounds are worthy of note. The potent skin allergenicity of chromium has been well documented in the literature, and chromium compounds have been reported to be the most frequent sensitizing agents in man (IRIS, 2000). The prevalence of Cr(VI) sensitivity among the general U.S. population is estimated to be 0.08%, based on studies conducted by Proctor et al (1998). Most of the occurrences of contact dermatitis and sensitization cited are from the result of occupational exposures, but include the wood preserving industry (Burrows, 1983). For previously sensitized individuals, very low dosage of Cr(VI) can elicit allergic contact dermatitis. Several studies document the sensitization reactions observed in humans previously exposed dermally to chromium (VI) compounds. Sensitization can also be observed in humans with chromium (III) if exposure concentration is high enough (ATSDR, 2000b). Bagdon (1991) collected skin hypersensitivity data for trivalent chromium compounds in human subjects and concluded that the threshold level for evoking hypersensitivity reactions from trivalent chromium compounds is approximately 50-fold higher than for hexavalent chromium compounds.

Experimental animal models also show that sensitization to chromium compounds can occur, and in some cases, the sensitization response observed is similar using an equivalent dose of either chromium (VI) or chromium (III) (ATSDR, 2000b).

Data have been submitted to the Office of Pesticide Programs under the OPP Incident Data System showing significant dermal reactions from exposure to CCA-treated wood. These data are summarized below.

OPP Incident Data System (IDS)

Incident # I002606-001
In an incident report received 9/10/95, a woman and her child were exposed to treated wood in their condominium stairs. The child developed a film on her teeth and the woman developed dermatitis. Reported as a potential source of inhalation and dermal exposure was sap draining from the wood.

Incident # I001618-001
In an incident report received 8/1/91, a Florida man handling arsenic treated lumber, which was not properly marked with warnings, reported severe injury. He experienced itching, burning rashes, neurological symptoms, and breathing problems.

California Data - 1982 through 1996

Incident # I007824-001
In an incident report dated 01/01/95, pressure treated wood caused a chronic rash that persisted for three years. The rash was subsiding when, in 9/98, the person cut some pieces of CCA-treated wood and the rash returned.

Incident# 1992-1484
A lumber yard worker developed contact dermatitis on both palms and fingers after handling CCA-treated wood.

Non-Acute Toxicity

Subchronic toxicity studies in experimental animals have demonstrated hematologic and hepatic effects from repeated oral exposure to chromium (VI). In a 9 week study in which male and female Sprague-Dawley rats were fed diets containing potassium dichromate at dose levels of 0, 15, 50, 100, or 400 ppm potassium dichromate [NTP, 1996], there were no treatment related findings noted in mean body weights, water and feed consumption, organ weights or microscopic pathology of the liver, kidneys and ovaries. Hematology findings effects consisted of decreases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) at the high dose (8.4 and 9.8 mg/kg/day in male and female rats respectively). There were no reported hepatic effects in this study. However, Kumar and Rana (1992) reported increased accumulation of hepatic lipids after gavage treatment of rats with 13.5 mg/kg chromium (VI) (as potassium

chromate) after 20 days of treatment.

In a 9-week feeding study in mice conducted by the National Toxicology Program (1996) in which mice were fed diets containing 1.1, 3.5, 7.4, and 32 mg/kg/day chromium (males) or 1.8, 5.6, 12, and 48 mg/kg/day chromium (females), hepatic cytoplasmic vacuolization was observed to be slightly increased at the high dose in males and females, and the appearance of the vacuoles was suggestive of lipid accumulation. Additional endpoints examined in this study included body weights, feed and water consumption, organ weights, microscopic evaluation of the liver, kidney and ovaries, hematology, histology of the testis and epididymis for Sertoli nuclei, and preleptotene spermatocyte counts in Stage X or XI tubules and chromatin analysis. Slight decreases in body weight were observed during this study, but there was no significant effect of treatment on clinical signs, necropsy findings, or microscopic histology. Hematologic effects were observed and consisted of a 2-4% decrease in MCV at weeks 3, 6, and 9 in high dose males and females and at week 6 in the 100 ppm females. The MCV returned to normal in the female mice after the recovery period (week 17); however the MCV increased 2.8% in the 400 ppm males.

The MCV changes at weeks 3, 6 and 9 were, in general associated with small decreases in the RBC, and small decreases in the MCH, although only the MCH values from the 400 ppm males (week 9), the 400 ppm females (Weeks 3 and 6), the 15 and 100 ppm females (week 3) were decreased.

Occupational exposure to chromium by inhalation has been studied in the chromate manufacturing and ferrochromium industries; however, exposures all include mixed exposures to both Cr(III) and Cr(VI). The Cr(VI) species is widely considered to be the causative agent in reports of excess cancer risk in chromium workers. However, studies are inadequate to rule out a contribution by Cr(III), and Cr(VI) cannot be unequivocally demonstrated to be the causative agent for noncarcinogenic effects following inhalation.

A number of epidemiologic studies have considered the association between inhalation of chromium and noncarcinogenic endpoints, including upper respiratory irritation and atrophy, lower respiratory effects, and systemic effects. Symptoms reported from inhalation exposure to mists and dusts containing chromium have included nasal tissue damage, perforated septum, ulcerated septum, chrome holes, nosebleed, inflamed mucosa, nasal septal perforation, and nasal septal ulceration (USEPA IRIS, 1998). Exposure to vapors of chromium salts has also been suspected as a cause of asthma, coughing, wheezing, and other respiratory distress in ferrochromium workers.

Despite the consistency of the reported effects from inhalation of chromium contained in dusts and mists, the actual Cr(III) and Cr(VI) exposure levels in many of the studies attributing respiratory effects to chromium were unknown. In addition, data on other confounding factors such as smoking were frequently unavailable. These caveats significantly complicate determination of the potential health effects associated with inhalation exposure to chromium (ATSDR, 2000b).

Although human data examining developmental endpoints are scarce, animal studies have consistently shown that chromium, particularly chromium(VI), is a developmental toxicant. Oral ingestion of chromium (VI) compounds in experimental animals results in significant developmental toxicity. Studies describing the effects observed have been published in the IRIS Toxicological Reviews for both chromium (VI) and chromium (III) as well as from submitted studies to the Agency and are summarized here.

Trivedi et al. (1989) exposed mice to 250, 500, and 1,000 ppm potassium dichromate daily through drinking water during the entire gestational period. The authors reported decreased fetal weight, increased resorptions, and increased abnormalities (tail kinking, delayed ossification of the cranium) in exposed mice. The medium- and high-dose groups registered significant reductions in body weight gain when compared to controls. The most significant finding of the study was the complete absence of uterine implantation in the high-dose group. The 250 and 500 ppm dose groups also showed significant incidences of resorption as compared to controls. The authors observed significant increases in preimplantation and postimplantation losses and dose-dependent reductions in total weight and crown-rump length in the lower dose groups. Additional effects included treatment-related increases in abnormalities in the tail, wrist forelimbs and subdermal hemorrhagic patches in the offspring.

Junaid et al. (1996) exposed female Swiss albino mice to 250, 500, or 750 ppm potassium dichromate in drinking water to determine the potential embryotoxicity of hexavalent chromium during days 6-14 of gestation. No notable changes in behavior or clinical signs were observed in the control or treated dams. Chromium levels in blood, placenta, and fetus increased in a dose-dependent fashion over the course of the study. The authors reported retarded fetal development and embryo- and fetotoxic effects including reduced fetal weight, reduced number of fetuses (live and dead) per dam, and higher incidences of stillbirths and postimplantation loss in the 500 and 750 ppm dosed mothers. Significantly reduced ossification in nasal, frontal, parietal, interparietal, caudal, and tarsal bones was observed in the high-dose group, while reduced ossification in only the caudal bones was observed in the 500 ppm dose group. Based on the body weight of the animals (30 +/- 5 g) and the drinking water ingested by the animals in the 250 ppm dose group (8.0 ml/mouse/day), the dose level in the 250 ppm group can be identified as 67 mg/kg-day. The maternal NOAEL was 63 [22.3] mg/kg/day while the LOAEL was 42.1 mg/kg/day and was based on a decreased gestational body weight. At the lowest dose tested, the incidence of resorptions was increased and a developmental NOAEL was, therefore, not determined.

Kanojia et al. (1996) exposed female Swiss albino rats to 250, 500, or 750 ppm potassium dichromate in drinking water for 20 days 3 months prior to gestation to determine the potential teratogenicity of hexavalent chromium. No notable changes in behavior or clinical signs were observed in the control or treated dams. Chromium levels in blood, placenta, and fetus were significantly increased in the dams of the 500 and 750 ppm dose groups. The authors reported a reduced number of corpora lutea and implantations, retarded fetal development, and embryo- and fetotoxic effects including reduced number of fetuses (live and dead) per dam and higher

incidences of stillbirths and postimplantation loss in the 500 and 750 ppm dosed mothers. Significantly reduced parietal and interparietal ossification was observed in the high-dose group. Based on the body weight of the animals (175 +/- 25 g) and the drinking water ingested by the animals in the 250 ppm dose group (26 ml/mouse/day) the dose level in the 250 ppm group can be identified as 37 mg/kg-day.

Tyl (1991) examined the developmental and maternal effects of daily administration of chromic acid (55.0% a.i.) at dosages of 0, 0.1, 0.5, 2.0 or 5.0 mg/kg/day by gavage in rabbits. Clinical signs of toxicity , including diarrhea, and slow, audible or labored breathing were observed in predominately in the 2.0 and 5.0 mg/kg/day groups. However, these signs did not show a dose-response and were observed in lesser incidence at 5.0 mg/kg/day vs. 2.0 mg/kg/day. However, the incidence of mortality (at 2.0 mg/kg/day, one doe died on gestation day (GD) 28; at 5.0 mg/kg/day, 5 does died (one each on GD 10, 14, and two on GD 15) and the magnitude of decreased body weight gain during the dosing period (average weight loss of 48 grams at 2.0 mg/kg/day, and average weight loss of 140 grams at 5.0 mg/kg/day during gestation days 7-19) were observed to occur in a dose-related fashion at 2.0 and 5.0 mg/kg/day. Food efficiency was also observed to be significantly lower during the dosing period in the 5.0 mg/kg/day dose group. Cesarean section observations were unremarkable in this study at any dose level. No treatment related effects on either fetal malformations or variations were observed.
The Maternal NOAEL = 0.5 [0.12] mg/kg/day and LOAEL = 2.0 [0.48] mg/kg/day (based on the increased incidence of maternal mortality and decreased body weight gain). The Developmental NOAEL = 2.0 [0.48] mg/kg/day and LOAEL > 2.0 [>0.48] mg/kg/day based on the lack of developmental effects at any dose level tested.

By contrast to effects of chromium (VI), effects on development and reproduction from exposure to Cr (III) show either negative results or effects only at high doses. For example, male and female rats treated with 1,806 mg Cr(III) kg/day as Cr(III) oxide 5 days/week for 60 days before gestation and throughout the gestation period had normal fertility, gestational length, and litter size (Ivankovic and Preussman, 1975). Elbetieha and Al-Hamood (1997) examined fertility following chromium chloride exposures in mice. Sexually mature male and female mice were exposed to 1,000, 2,000, or 5,000 mg/L chromium chloride in drinking water for 12 weeks. Exposure of male mice to 5,000 ppm trivalent chromium compounds for 12 weeks had adverse impacts on male fertility. Testes weights were increased in the males exposed in the 2,000 and 5,000 mg/L dose groups, while seminal vesicle and preputial gland weights were reduced in the 5,000 mg/L exposed males. The number of implantation sites and viable fetuses were significantly reduced in females exposed to 2,000 and 5,000 mg/L chromium chloride. Water consumption was not reported precluding calculation of the doses received. However it is evident that adverse effects were observed only at a high dose of Cr (III).

The National Toxicology Program recently conducted a three-part study to investigate oral ingestion of hexavalent chromium in experimental animals (NTP, 1996a,b, 1997). The study included a determination of the potential reproductive toxicity of potassium dichromate in Sprague-Dawley rats, a repeat of the study of Zahid et al. (1990) using BALB/C

mice, and a Reproductive Assessment by Continuous Breeding study in BALB/C mice.
The study in the Sprague-Dawley rat (NTP, 1996a) was conducted in order to generate data in a species commonly used for regulatory studies. Groups of 24 males and 48 females were exposed to 0, 15, 50, 100, or 400 ppm potassium dichromate daily in the diet for 9 weeks followed by a recovery period of 8 weeks. Six male and 12 female rats were sacrificed after 3, 6, or 9 full weeks of treatment or after the full recovery period. Animals were examined for body weights; feed and water consumption; organ weights; microscopic evaluation of the liver, kidney, and ovaries; hematology; histology of the testis and epididymus for Sertoli nuclei and preleptotene spermatocyte counts in Stage X or XI tubules; and chromatin analysis. No treatment-related hematology findings were reported except for slight decreases in MCV and MCH values in the male and female treatment groups receiving 400 ppm potassium dichromate (24 mg/kg-day). While the trends in MCV and MCH were not large and were within the reference ranges, they are consistent with the findings of the companion studies in BALB/C mice and were characterized by the authors as suggestive of a potential bone marrow/erythroid response. The authors considered the 100 ppm (6 mg/kg-day) dose group to be representative of the NOAEL for the study.

The reproductive study in BALB/C mice (NTP, 1996b) was conducted to reproduce the conditions utilized by Zahid et al. (1990) in their examination of comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. Groups of 24 male and 48 female BALB/C mice were exposed to 0, 15, 50, 100, or 400 ppm potassium dichromate in the diet for 9 weeks followed by a recovery period of 8 weeks. Six male and 12 female mice were sacrificed after 3, 6, or 9 full weeks of treatment or after the full recovery period. Animals were examined for body weights; feed and water consumption; organ weights; microscopic evaluation of the liver, kidney, and ovaries; hematology; histology of the testis and epididymus for Sertoli nuclei and preleptotene spermatocyte counts in Stage X or XI tubules; and chromatin analysis. Treatment-related effects included a slight reduction in the mean body weights in the 400 ppm males and the 100 ppm females, a slight increase in food consumption at all dose levels, a slight decrease in MCV and MCH at 400 ppm, and cytoplasmic vacuolization of the hepatocyte at 50, 100 and 400 ppm. None of the effects on spermatogenesis reported by Zahid et al. (1990) were observed in this study. On the basis of the cytoplasmic vacuolization of the hepatocyte in the 50, 100, and 400 ppm dose groups, the authors selected 15 ppm (4 mg/kg-day) as the NOAEL.

Increased resorptions and increased post-implantation loss as well as gross fetal abnormalities were observed in offspring of pregnant mice exposed to potassium dichromate at 57 mg/kg/day in drinking water during gestation (ATSDR, 2000b). At a higher dose of 234 mg/kg/day, no implantations were observed in maternal mice. In a second study in mice, potassium dichromate was administered in the diet for 7 weeks at dose levels of 15.1 and 28 mg/kg/day. Reduced sperm counts and degeneration of the outer layer of the seminiferous tubules was observed at the 15.1 mg/kg/day dose, and morphologically altered sperm was observed at the 28 mg/kg/day dose.

In male rats administered 20 mg/kg/day chromium trioxide for 90 days by gavage, reduced testicular weight, decreased testicular testosterone, and reduced Leydig cell number was observed

(Chowdhury and Mitra, 1995).

Despite the wealth of animal studies on the developmental and reproductive toxicity of chromium VI, there are too few human data with which to make any reliable conclusion regarding the susceptibility of the developing fetus, infants, or children to the toxic effects of chromium VI. The evidence available suggests similar toxic effects in adults and children from ingestion of chromium VI (ATSDR, 2000b).

Hexavalent chromium (Cr VI) is known to be carcinogenic in humans by the inhalation route of exposure. Results of occupational epidemiologic studies of chromium-exposed workers are consistent across investigators and study populations. Dose-response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both Cr(III) and Cr(VI) compounds. Because only Cr(VI) has been found to be carcinogenic in animal studies, however, it was concluded that only Cr(VI) should be classified as a human carcinogen.

Animal data are consistent with the human carcinogenicity data on hexavalent chromiumby the inhalation route. Hexavalent chromium compounds are also carcinogenic in animal bioassays by other routes of exposure, such as: intramuscular injection site tumors in rats and mice, intrapleural implant site tumors for various Cr(VI) compounds in rats, intrabronchial implantation site tumors for various Cr(VI) compounds in rats, and subcutaneous injection site sarcomas in rats (IRIS, 2001). However, these routes of administration are not relevant to exposures of chromium in CCA-treated wood.

Data addressing human carcinogenicity from exposures to Cr(III) alone are not available, and data are inadequate for an evaluation of human carcinogenic potential. Two oral studies located in the available literature (Schroeder et al., 1965; Ivankovic and Preussman, 1975) reported negative results for rats and mice. Several animal studies have been performed to assess the carcinogenic potential of Cr(III) by inhalation. These studies have not found an increased incidence of lung tumors following exposure either by natural routes, intrapleural injection, or intrabronchial implantation (Baetjer et al., 1959; Hueper and Payne, 1962; Levy and Venitt, 1975; Levy and Martin, 1983).

The data from oral and inhalation exposures of animals to trivalent chromium do not support determination of the carcinogenicity of trivalent chromium. IARC (1990) concluded that animal data are inadequate for the evaluation of the carcinogenicity of Cr(III) compounds. Furthermore, although there is sufficient evidence of respiratory carcinogenicity associated with exposure to chromium, the relative contributions of Cr(III), Cr(VI), metallic chromium, or soluble versus insoluble chromium to carcinogenicity cannot be elucidated.

In vitro data are suggestive of a potential mode of action for hexavalent chromium carcinogenesis. Hexavalent chromium carcinogenesis may result from the formation of mutagenic oxidatitive DNA lesions following intracellular reduction to the trivalent form. Cr(VI) readily passes through

cell membranes and is rapidly reduced intracellularly to generate reactive Cr(V) and Cr(IV) intermediates a reactive oxygen species. A number of potentially mutagenic DNA lesions are formed during the reduction of Cr(VI). Hexavalent chromium is mutagenic in bacterial assays, yeasts, and V79 cells, and Cr(VI) compounds decrease the fidelity of DNA synthesis in vitro and produce unscheduled DNA synthesis as a consequence of DNA damage. Chromate has been shown to transform both primary cells and cell lines (ATSDR, 2000b).

Intracellular reduction of Cr(VI) generates reactive chromium V and chromium IV intermediates as well as hydroxyl free radicals (OH) and singlet oxygen. A variety of DNA lesions are generated during the reduction of Cr(VI) to Cr(III), including DNA strand breaks, alkali-labile sites, DNA-protein and DNA-DNA crosslinks, and oxidative DNA damage, such as 8-oxo-deoxyguanosine. The relative importance of the different chromium complexes and oxidative DNA damage in the toxicity of Cr(VI) is unknown.

Hexavalent chromium has been shown to be genotoxic only in the presence of appropriate reducing agents in vitro or in viable cell systems in vitro or in vivo. Hexavalent chromium has been shown to be mutagenic in bacterial systems in the absence of a mammalian activating system, and not mutagenic when a mammalian activating system is present. Hexavalent chromium is also mutagenic in eukaryotic test systems and clastogenic in cultured mammalian cells.

Hexavalent chromium in the presence of glutathione has been demonstrated to produce genotoxic DNA adducts that inhibit DNA replication and are mutagenic (IRIS, 2000). Chromium (III) has also produced positive mutagenic responses in vitro (IRIS, 2000).

Metabolism and Bioavailability

Absorption of chromium by the oral route ranges from essentially zero for the insoluble chromium III compound chromic oxide to 10% for potassium chromate. Absorption through exposure in the diet, in water, or from contaminated soil is consistently low, with values reported in the range of 1-5% (ATSDR, 2000b; USEPA, 1998). Hexavalent chromium can be reduced to the trivalent form in the epithelial lining fluid of the lungs by ascorbate and glutathione as well as by gastric juice in the stomach, which contributes to the low oral absorption. Absorption by the dermal route is also low (1.3% after 24 hours as reported by Bagdon et al., 1991)

Once absorbed, chromium compounds are distributed to all organs of the body without any preferential distribution to any one organ. However, exposures to higher levels of chromium, such as can occur in the chrome plating industry and chrome refining plants, may result in accumulation of chromium in tissues. Witmer et al. (1989, 1991) studied chromium distribution in tissues of rats administered chromium via gavage. In one experiment, the highest dose of sodium chromate [5.8 mg Cr(VI)/kg/day for 7 days] resulted in concentrations of chromium in the tissues in the following order: liver (22 µg chromium/whole organ) > kidney (7.5 µg) > lung (4.5 µg) > blood (2 µg) > spleen (1 µg). These tissues combined retained about 1.7% of the administered dose;

however, some tissues were not analyzed. At the two lower doses administered (1.2 or 2.3 mg/kg/day), very little chromium was detected (<0.5 μg/organ) in the organs analyzed.

Maruyama (1982) studied the chromium content in major organs of mice exposed to potassium dichromate [Cr(VI)] or chromium trichloride ([Cr(III)] for 1 year in drinking water. Groups of mice received 4.4, 5.0 or 14.2 mg Cr(VI)/kg/day or 4.8, 6.1 or 12.3 mg Cr(III)/kg/day. Examination of organs and blood in mice that received Cr(VI) revealed that the liver and spleen had the highest levels of chromium, although some chromium accumulation was observed in all tissues. In mice that received Cr(III), the liver was the only organ with detectable amounts of chromium, and at levels that were about 40-90 times less than in mice that received the Cr(VI) compound. MacKenzie et al. (1958) reported that in rats following the administration of similar concentrations of Cr(VI) as potassium chromate or Cr(III) as chromium trichloride in drinking water for 1 year, tissue levels were approximately 9 times greater in rats that received the Cr(VI) compound, compared to rats that received the Cr(III) compound.

If hexavalent chromium is absorbed, it can readily enter red blood cells through facilitated diffusion, where it will be reduced to the trivalent form by glutathione. During reduction to the trivalent form, chromium may interact with cellular macromolecules, including DNA (Wiegand et al., 1985), or may be slowly released from the cell (Bishop and Surgenor, 1964). Chromium III can be cleared rapidly from the blood but more slowly from tissues, which may be related to the formation of trivalent chromium complexes with proteins or amino acids (Bryson and Goodall, 1983).

The liver is a primary site of chromium metabolism and has been studied in animals. Incubation of Cr(VI) with rat liver microsomes in the presence of the enzyme cofactor nicotinamide adenine dinucleotide phosphate (NADPH) resulted in the reduction of Cr(VI) to Cr(III) (ATSDR, 2000b). Exclusion of the co-factors necessary for the production of NADPH resulted in a large decrease in the reduction of Cr(VI) to Cr (III).

Chromium metabolism can result in the formation of species that interact with deoxyribonucleic acid (DNA). The reduction of Cr(VI) to a Cr(V) intermediate involves a single electron transfer from the microsomal electron-transport cytochrome P-450 system (Jennette 1982). These reactive Cr(V) complexes/ intermediates are relatively unstable and persist for approxim-ately 1 hour *in vitro*. During this time the Cr(V) complexes/ intermediates can interact with deoxyribonucleic acid (DNA), which may eventually lead to cancer. When Cr(VI) interacts with glutathione, Cr(V) complexes and glutathione thonyl radicals were produced, and when Cr(VI) interacts with DNA and glutathione, DNA adducts were formed (Aiyar et al. 1989). The formation of Cr(V) was found to correlate with DNA adduct formation. Following reactions of Cr(VI) with hydrogen peroxide, hydroxyl radicals were produced; the addition of DNA resulted in the formation of an 8-hydroxy guanine adduct and DNA strand breakage.

The elimination of chromium after oral exposure has been studied in both humans and animals. In one study, human volunteers received an acute oral dose of radiolabeled Cr(III) or Cr(VI)

(Donaldson and Barreras 1966). Fecal samples were collected for 24 hours, and urine samples were collected for 6 days and analyzed for chromium. Approximately 99.6% of the Cr(III) compound was recovered in the 6-day fecal sample, while 89.4% of the Cr(VI) compound was recovered. The results of the analysis of the 24-hour urine samples indicated that 0.5% and 2.1% of the administered dose of the Cr(III) and the Cr(VI) compounds, respectively, were recovered in the urine. Other potential routes of excretion include hair, fingernails and breast milk (ATSDR 2000b).

In several studies in which rats and hamsters were fed Cr(VI) compounds, fecal excretion of chromium varied slightly from 97% to 99% of the administered dose, and urinary excretion of chromium, administered as Cr(III) or Cr(VI) compounds, varied from 0.6% to 1.4% of the dose (Donaldson and Barreras 1966, Henderson et al. 1979, Sayato et al. 1980). Following the gavage administration of 13.92 mg chromium/kg/day as calcium chromate for 8 days, the total urinary and fecal excretion of chromium on days 1 and 2 of dosing were <0.5% and 1.8%, respectively (Witmer et al. 1991). The total urinary and fecal excretion of chromium on days 7 and 8 of dosing were 0.21% and 12.35%, respectively. Donaldson et al. (1984), reported that excretion of Cr(III) and creatinine clearance were almost equal suggesting that tubular absorption or reabsorption of chromium in the kidneys was minimal.

Dose-Response Assessment

The process of dose-response assessment as part of a total risk assessment involves describing the quantitative relationship between the exposure to a chemical and the extent of toxic injury or disease. Following the process of hazard identification, in which the available toxicology data is reviewed and selection of NOAELs and LOAELs is made for each study, the reviewed data for a pesticide chemical is presented to a committee of scientists within the Office of Pesticide Programs who reach concurrence on toxicology endpoints that best represent the toxic effects expected from various routes of exposure and durations of exposure. For most pesticide chemicals, the process results in selection of acute and chronic Reference Dose values (which can be used as benchmark values for acute and chronic dietary risk calculations), as well as endpoint values for non-dietary risk assessments involving occupational and/or residential exposures by the oral, dermal, and inhalation routes. Endpoints are selected for non-dietary exposures to represent short-term (1-30 days), intermediate-term (30-180 days), and long-term exposure scenarios, as needed. In addition, incidental oral exposure endpoints are selected for short-term and intermediate term exposure durations to represent ingestion of pesticide chemical residues that may occur from hand-to-mouth behaviors.
In general, toxicity endpoint selection should, to the extent possible, match the temporal and spatial characteristics of the exposure scenarios selected for use in the risk assessment. These endpoints are then used in conjunction with exposure values to calculate risks associated with various types of exposure, depending upon the uses of the pesticide chemical.

Toxicology endpoints for both inorganic arsenic and chromium have been selected for the

residential exposure assessment and are presented below:

Inorganic Arsenic-Endpoint Selection

Acute Reference Dose (RfD)

An acute RfD value was not selected for inorganic arsenic. Inorganic arsenic is not registered for any food uses and there are no existing tolerances. For inorganic arsenic as contained within CCA-treated wood, therefore, an acute RfD is not relevant to the exposures from registered uses.

Chronic Reference Dose (RfD)

The U.S. EPA has published a chronic RfD value for inorganic arsenic (USEPA IRIS, 1998). However, as with the acute RfD, there are no exposure scenarios relevant to the currently registered uses of inorganic arsenic, and specifically the registered uses in CCA-treated lumber. If the Agency determines in the future that an aggregate assessment is needed for calculation of risk from exposure to arsenic in treated lumber and exposure in drinking water and/or food, the chronic RfD value can be utilized.

Short (1-30 days) and Intermediate (30-180 days) Incidental Oral Exposure

Based on the registered use of CCA-treated lumber for fencing and decking materials in residential settings, incidental oral exposure is expected, based on potential ingestion of soil contaminated with arsenic as a result of leaching from wood, and from ingestion of arsenic residues from the palm as a result of direct dermal contact with treated wood. The studies selected for short- and intermediate-term incidental oral exposure are the human case reports of Franzblau and Lilis (Arch. of Envir. Health 44(6): 385-390, 1989) and Mizuta et al. (Bull. Yamaguchi Med. Sch. 4(2-3): 131-149, 1956). The LOAEL of 0.05 mg/kg/day was selected, based on facial edema, gastrointestinal symptoms, neuropathy, and skin lesions observed at this dose level

Franzblau et al., (1989) reported 2 cases of subchronic (2 months) arsenic intoxication resulting from ingestion of contaminated well water (9-10.9 mg/L) sporadically (once or twice a week) for about 2 months. Acute gastrointestinal symptoms, central and peripheral neuropathy, bone marrow suppression, hepatic toxicity and mild mucous membrane and cutaneous changes were presented. The calculated dose was 0.03 - 0.08 mg/kg/day based on a body weight of 65 Kg and ingestion of from 238 to 475 ml water/day.

Mizuta et al. (1956) reported a poisoning incident involving the presence of arsenic [probably calcium arsenate] contained in soy-sauce. The duration of exposure was 2-3 weeks. The arsenic

content was estimated at 0.1 mg/ml. Out of 417 patients, the authors reported on 220 (age not specified for all patients. The age of the 46 paints with age information are ranging from 15 - 69). An early feature of the poisoning was appearance of facial edema that was most marked on the eyelids. Other symptoms presented included multifaceted gastrointestinal symptoms, liver enlargement, upper respiratory symptoms, peripheral neuropathy and skin disorders. In the majority of the patients, the symptoms appeared within two days of ingestion and then declined even with continued exposure. There was evidence of minor gastrointestinal bleeding (occult blood in gastric and duodenal juice). There were abnormalities in electrocardiograms (altered Q-T intervals and P and T waves). These changes were not evident on reexamination after recovery from the clinical symptoms. An abnormal patellar reflex was evident in >50% of the cases. This effect did not return to normal during the course of the investigation.

Based on the consumption of the arsenic in the contaminated soy-sauce, the pattern of soy-sauce consumption and on measured urinary arsenic levels, the authors estimated consumption of arsenic at 3 mg/day. Although the body weight was not reported, the EPA assumes an average body weight of 55 kg in the Asian population. The estimated exposure was, therefore, 0.05 mg/kg/day and was considered the LOAEL. **The LOAEL= 0.05 mg/kg/day (edema of the face; gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms).**

These two case reports are appropriate for both short- and intermediate-term incidental oral endpoints for the following reasons:

1) Symptoms reported in the Mizuta study (gastrointestinal disorders, neuropathy, liver toxicity) occurred after 2-3 weeks of exposure, making this endpoint appropriate for the short-term (1-30 days) exposure period. This study also examined toxicity by the relevant route of exposure (oral).

2) Similar symptoms were observed in the Franzblau study, and are appropriate for the intermediate-term endpoint as they were observed to occur after longer-term (2 months) exposure.

A Margin of Exposure (MOE) of 100 was applied to the NOAEL. This value consists of a 10x factor for intraspecies variation and a 10x factor for the severity of the toxic signs observed at the LOAEL of 0.05 mg/kg/day.

Typically a factor of 3x is applied when extrapolating from a LOAEL to a NOAEL. However, the Health Effects Division Hazard Identification Assessment Review Committee (HIARC) chose a 10x factor for extrapolation, based upon the the severity of the symptoms observed in the Mizuta et al. study and the observation that some of these signs (particularly the neurotoxic effect) were not always reversible even after a short-term exposure. The 10x extrapolation also provides an upper bound for acute toxic effects based on the transient nature of the acute effects. With regard to the 10x factor for intraspecies variation, the HIARC concluded that there was

sufficient variation of recovery within the cohort studied to warrant such a factor.

USEPA Region 8 has also recently published a report on selection of acute and chronic Reference Doses for Inorganic Arsenic, intended to apply to exposures of 1-14 days and 15 days-7 years. The use of the term "reference dose" in the Region 8 report "apply to readily soluble forms of arsenic and are intended to include total oral exposure to inorganic arsenic, that is drinking water, food, and soil. " The report concludes that a NOAEL value of 0.015 mg/kg/day from a study by Mazumder et al (Int. J. Epidem. 27: 871-877) can be used for acute and subchroninc reference dose values, with an uncertainty factor of 1. Alternately, the LOAEL of 0.05 mg/kg/day and an uncertainty factor of 3 (for extrapolation from the LOAEL to the NOAEL) could be selected from this same study. A full factor of 10 was not employed by Region 8 based on the reasoning that a No Effect Level "is likely at an exposure only slightly below the effect level" (USEPA Region 8, 2001). However, this report did not discuss severity or irreversibility of effects observed in the Mizuta et al. report as a factor in selecting the uncertainty factor, which was taken into consideration by the OPP HIARC. Further, the effect observed in the Mazumder et al. study of hyperkeratosis is a result of chronic exposure and not short- or intermediate-term exposure and was thus felt to be inappropriate for determination of short- and intermediate-term incidental oral risk.

Dermal Absorption

Dermal absorption of inorganic arsenic is represented by the study of Wester et al. (Fund. Appl. Toxicol. 20: 336-340, 1993). In this study, the percutaneous absorption of arsenic acid (H_3AsO_4) from water and soil both *in vivo* using rhesus monkeys and *in vitro* with human skin was examined. *In vivo*, absorption of arsenic acid from water (loading 5 µl/cm^2 skin area) was 6.4 ± 3.9% at the low dose (0.024 ng/cm^2) and 2.0 ± 1.2% at the high dose (2.1 µg/cm^2). Absorption from soil (loading 0.04 g soil/cm^2 skin area) *in vivo* was 4.5 ± 3.2% at the low dose (0. 04 ng/cm^2) and 3.2 ± 1.9% at the high dose (0.6 µg/cm^2). Thus, *in vivo* in the rhesus monkey, percutaneous absorption of arsenic acid is low from either soil or water vehicles and does not differ appreciably at doses more than 10 000-fold apart. Wester et al. (1993) also reported that for human skin, at the low dose, 1.9% was absorbed from water and 0.8% from soil over a 24-h period.

The value of 6.4% dermal absorption was chosen based on the use of non-human primates for derivation of this value and the fact that this was a well-conducted study. It is observed in this study that a higher dose on the skin resulted in lower dermal absorption as noted above, but the data in this and other studies suggests sufficient variability in the absorption such that use of the 6.4% dermal absorption value is sufficiently but not overly conservative.

Long-Term Dermal Exposure

While no long-term dermal exposures are expected from residential exposure to arsenic in CCA-treated lumber, long-term dermal exposure is expected in the occupational setting. Thus, for this

exposure scenario, the dose and endpoint selected are the NOAEL of 0.0008 mg/kg/day from the Tseng et al. (1968) study, which examined chronic non -cancer and cancer effects from arsenic exposure through well water in a large cohort in Taiwan.

In Taiwan, Tseng, (1977), Tseng, (1968) [U.S. EPA, 1998] noted that hyperpigmentation, keratosis and possible vascular complications were seen at the LOAEL of 0.17 mg/L, converted to 0.014 mg/kg/day.

The NOAEL was based on the arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. The NOAEL also included estimation of arsenic from food. Since oral arsenic exposure data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg body weight (Abernathy, (1989). Thus, the converted NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day]/55 kg = **0.0008 mg/kg/day**. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng, (1977) of 0.17 mg/L. LOAEL = [(0.17 mg/L x 4.5 L/day)+ 0.002 mg/day]/55 kg = **0.014 mg/kg/day**. Therefore the NOAEL = 0.0008 mg/kg and the LOAEL= 0.014 mg/kg/day (based on hyperpigmentation, keratosis and possible vascular complications)

An MOE of 3 is applied to this risk assessment. A factor of 3 and not 10 is used based on the large sample size of the Tseng study (> 40,000) and is in agreement with the published value and rationale in the 1998 IRIS document on inorganic arsenic.

Relative Bioavailability

The bioavailability of absorbed inorganic arsenic is dependent on the matrix in which it is exposed to. Arsenic in drinking water is in a water-soluble form, and it is generally assumed that its absorption from the gastrointestinal tract is nearly complete. Arsenic in soils, however, may be incompletely absorbed because they may be present in water-insoluble forms or interact with other constituents in the soil. The relative bioavailability of arsenic after it is been exposed (water versus soil) was defined as the percentage of arsenic absorbed into the body of a soil-dosed animal compared to that of animal receiving an single dose of arsenic in aqueous solution.

By carefully comparing data on the urinary and fecal recovery of arsenic in both experimental animals after an oral intravenous dose of sodium arsenate and in humans, the data of Robrts et al. (2001) using the monkey was considered an appropriate study model in evaluating the relative bioavailability of arsenic due to the similarity of monkeys to humans and the similarity in g.i. absorption characteristics. The Roberts et al. study also employed a variety of soil types including soil from a CCA-contaminated site. Therefore, based on the study results of Roberts et al. (2001) **a relative bioavailability of 25% was selected for the oral route**.

Because the dermal absorption of arsenic from water is not statistically different from the absorption from soil (Wester et al., 1993), a dermal relative bioavailability (soil vs. water) of

100% was selected by OPP. In other words, via dermal exposure, the magnitude of absorption of arsenic is equivalent whether the arsenic is in water or soil.

Arsenic - Toxicity Endpoint Selection Summary			
Exposure Scenario	**Dose (mg/kg/day)**	**Endpoint**	**Study**
Acute Dietary	**This risk assessment is not required**.		
Chronic Dietary	**This risk assessment is not required.**		
Short- and Intermediate-Term Incidental Oral	**LOAEL = 0.05** MOE = 100	facial edema; gastrointestinal, upper respiratory, and dermal effects; peripheral neuropathy	Case Reports/Human (Franzblau et al., Mizuta et al)
Short- and Intermediate-term /Dermal	**LOAEL = 0.05** MOE = 100	Same as above	Case Reports/Human (Franzblau et al., Mizuta et al)
Long-term Dermal	**NOAEL = 0.0008** MOE = 3	Hyperpigmentation, keratosis, possible vascular complications	Epidemiology/Human (Tseng et al., 1968)

MOE = margin of exposure
LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level.

Inorganic Chromium Endpoint Selection

Acute Reference Dose (RfD)

An acute RfD value was not selected for inorganic chromium. Inorganic chromium is not registered for any food uses and there are no existing tolerances. For inorganic chromium as contained within CCA-treated wood, therefore, an acute RfD is not relevant to the exposures from registered uses.

Chronic Reference Dose (RfD)

The U.S. EPA has published a chronic RfD value for inorganic chromium (USEPA IRIS, 1998). However, as with the acute RfD, there are no exposure scenarios relevant to the currently

registered uses of inorganic chromium, and specifically the registered uses in CCA-treated lumber. If the Agency determines in the future that an aggregate assessment is needed for calculation of risk from exposure to chromium in treated lumber and exposure in drinking water and/or food, the chronic RfD value can be utilized.

Short-Term (1-30 days) and Intemediate-Term (30-180 days) Incidental Oral Exposure

Based on the registered use of CCA-treated lumber for fencing and decking materials in residential settings, incidental oral exposure to chromium is expected, based on potential ingestion of soil contaminated with chromium as a result of leaching from wood, and from ingestion of chromium residues from the palm as a result of direct dermal contact with treated wood. The study selected for short- and intermediate-term incidental oral exposure is a developmental toxicity study in the rabbit conducted by Tyl and submitted to the Agency under MRID # 42171201. The executive summary is shown below.

In a developmental toxicity study [MRID 421712-01], artificially inseminated New Zealand White rabbits (16 females/dose group) received aqueous chromic acid (55.0%) by gavage once daily on gestation days 7 through 19 at dose levels of 0.0, 0.1, 0.5, 2.0, or 5.0 mg/kg/day in deionized/distilled water.

Clinical signs of toxicity , including diarrhea, and slow, audible or labored breathing were observed predominately in the 2.0 and 5.0 mg/kg/day groups. These signs were observed in slightly higher incidence at the 2.0 mg/kg/day dose level than at the 5.0 mg/kg/day dose level. However, the incidence and temporal occurrence of mortality (at 2.0 mg/kg/day, one doe died on gestation day (GD) 28; at 5.0 mg/kg/day, 5 does died (one each on GD 10, 14, and two on GD 15) and the magnitude of decreased body weight gain during the dosing period (average weight loss of 48 grams at 2.0 mg/kg/day and average weight loss of 140 grams at 5.0 mg/kg/day during gestation days 7-19) were observed to occur in a dose-related fashion at 2.0 and 5.0 mg/kg/day. Overall weight gain was decreased 24% at 2.0 mg/kg/day and 20% at 5.0 mg/kg/day. Food efficiency was also observed to be significantly lower during the dosing period in the 5.0 mg/kg/day dose group. Cesarean section observations were unremarkable in this study at any dose level tested. There were no significant treatment-related effects on the incidence of external, visceral, or skeletal malformations in the offspring in this study.

The Maternal NOAEL = 0.5 [0.12] mg/kg/day and LOAEL = 2.0 [0.48] mg/kg/day (based on the increased incidence of maternal mortality and decreased body weight gain). The Developmental NOAEL = 2.0 [0.48] mg/kg/day and LOAEL > 2.0 [>0.48] mg/kg/day based on the lack of developmental effects at any dose level tested.

The developmental toxicity study in the rabbit was chosen for selection of the short-term and intermediate-term incidental oral exposure endpoint. This study and endpoint is felt to be appropriate for both short- and intermediate-term incidental oral exposures, based on the occurrence of toxic effects after short-term dosing (mortality, clinical signs, weight loss), and

supporting data from the open literature showing similar effects after longer-term exposures at similar dose levels. A study by Zhang and Li (1987) detailed toxic effects observed in 155 human subjects exposed long-term to chromium in drinking water at a concentration of approximately 20 mg/L (USEPA IRIS, 1998), or 0.66 mg/kg/day. These effects included mouth sores, diarrhea, stomach ache, indigestion, vomiting, and elevated white cell count. Although precise concentrations of chromium in the water, exposure durations, and confounding factors were not discussed in this paper, the data suggest gastrointestinal effects at a level of approximately 0.66 mg/kg/day. Thus, the choice of the NOAEL value of 0.5 mg/kg/day from the developmental toxicity study in rabbits (a well-conducted multi-dose animal study) for the incidental oral endpoint is felt to be protective of the gastrointestinal effects observed in humans at a similar dose. The choice of this endpoint is also felt to be protective of the non-lethal effect observed in humans based on a more severe effect observed in animals (i.e. mortality).

Dermal Absorption

For inorganic chromium, a dermal absorption value of 1.3% was selected, based upon the data of Bagdon (1991). The executive summary of this study is presented below.

Sodium chromate (Cr(VI)) was applied to the skin of guinea pigs and the skin permeation was determined by assay of ^{51}Cr content present in the excreta (1.11%) and organs (0.19%) after 24 hours. In this study in guinea pigs, skin penetration of chromium amounted to 1.30% of the applied dose after 24 hours. Using another *in vivo* method, a weighed amount of the agent was patched to the skin of guinea pigs and the concentration followed by determination of the remaining agent at the application site after different intervals. Skin penetration was concentration dependent. The range used was 0.0048 to 1.689 M. Dermal penetration for hexavalent chromium amounted to 2.6% of the applied dose of 0.0175 M/5 hours and 4.0% at 0.261 M/5 hours. At 0.261 M, the skin permeation rate was 700 $m\mu M/cm^2/hr$. This procedure may overestimate skin penetration because chromium present in the skin depot would be calculated as part of the residual test material at the skin's surface.

Short-, Intermediate-, and Long- term Dermal Exposure

The 1998 EPA IRIS document on chromium (VI) states that "chromium is one of the most common contact sensitizers in males in industrialized countries and is associated with occupational exposures to numerous materials and processes.." In addition, it is stated further that "dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis." The relative potency of this effect appears to differ between the (VI) and (III) species of chromium. Bagdon (1991) collected skin hypersensitivity data for trivalent chromium compounds in human subjects and concluded that the threshold level for evoking hypersensitivity reactions from trivalent chromium compounds is approximately 50-fold higher than for hexavalent chromium compounds.Nontheless, it is apparent that both forms of chromium cause hypersensitivity reactions in humans.

It was determined by the Hazard Identification Assessment Review Committee (HIARC) of the Office of Pesticide Programs that quantification of hazard from dermal exposure is not possible for chromium, due to the significant dermal irritation and sensitization observed. Therefore, no endpoints were determined by HIARC for hexavalent chromium from dermal exposures.

Inhalation Exposure (all durations)

Although chromium is not considered a volatile agent when present in soil, inhalation of soil dust contaminated with chromium may present a potential inhalation risk given the significant irritant properties of chromium and the potential for nasal deposition of the chemical after inhalation of contaminated soil dust. The Agency has selected a NOAEL value of 2.4 x 10-4 mg/m^3 taken from the 1998 IRIS update for Cr(VI) using the study of Lindberg and Hedenstierna (Arch Environ Health 38(6):367-374) who observed ulcerations, perforations of the nasal septum and pulmonary function changes in 104 workers (85 males, 19 females) exposed in chrome plating plants at a concentration of 7.14 x 10-4 mg/m^3. The NOAEL value selected is intended to represent an endpoint for use in inhalation risk assessments representative of any duration of exposure.

Relative Bioavailability

As discussed in the inorganic arsenic section, the matrix may plays a role in determining the bioavailability of absorbed inorganic chromium into the body. The relative bioavailability of chromium after it is been exposed (soil versus water) was defined as the percentage of chromium absorbed into the body of a soil-dosed animal compared to that of animal receiving an single dose of chromium in aqueous solution. It is known that either dermal or gastrointestinal absorption efficiency of Cr (VI) is very low (ATSDR, 2000b; USEPA, 1998). There is no study regarding the relative bioavailability of Cr(VI) in soil when compared with in water through either oral or dermal exposure routes. The office of Pesticide Programs (OPP) has chosen a relative bioavailability value (soil vs. water) of 100% for both oral and dermal exposure routes. In other words, via either oral or dermal exposure routes, the magnitude of absorption of chromium is equal if the chromium is in water or in soil.

Summary of Toxicology Endpoints for Chromium (VI)			
Exposure Scenario	**Dose (mg/kg/day) [Cr (VI)]**	**Endpoint**	**Study**
Acute Dietary	**This risk assessment is not required.**		
Chronic Dietary	**This risk assessment is not required.**		
Short- and Intermediate-term Incidental Oral [sodium chromate]	NOAEL = 0.5 [0.12] mg/kg/day MOE = 100	increased mortality and decreased body weight gain in dams at 2.0 mg/kg/day	Developmental toxicity - rabbit (MRID 42171201)
Short-, Intermediate-, and Long-term Dermal		Because dermal irritation and dermal sensitization are the primary concern from dermal exposures, no endpoint was selected for dermal exposure.	
Inhalation (all durations)	NOAEL = 2.4×10^{-4} mg/m^3	ulceration and perforation of the nasal septum; pulmonary function changes	Linberg, E. and Hedenstierna, G. (1983)

[] Conversion to Cr(VI) by using the molar ratio after adjusting to 100% purity. Purity of potassium chromate and potassium dichromate were ≈100%, chromic acid (55% a.i.) in the developmental study.
.MOE = margin of exposure; NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level.

References

Aiyar J, Borges K, Floyd RA, et al. 1989. Role of chromium(V), glutathione thiyl radical and hydroxyl radical intermediates in chromium(VI)-induced DNA damage. Toxicol Environ Chem 22:135-148.

Amdur, MO; Doull, J; Klaassen, CD. (1993) Casarett and Doull's Toxicology. New York: McGraw Hill.

ATSDR (2000a). Toxicological Profile for Arsenic.: U.S. Department of Health and Human Services, Public Health Service.

ATSDR (2000b): Toxicological Profile for Chromium. U.S. Department of Health and Human Services, Public Health Service.

*Author not stated. 1985 Acute Oral Toxicity Study, Bio/dynamics, Inc. Project 5465-84. May 30, 1985. Data Accession No. 26356. Unpublished.

*Author not stated. 1984. Acute Dermal Toxicity Study, Bio/dynamics Inc. Project 5466-84. Nov, 1984. Data Accession No. 26356. Unpublished.

*Author not stated. 1984. Primary Eye Irritation Study, Bio/dynamics, Inc. Project 5468-84. April 24, 1984. Data Accession No. 26356. Unpublished.

*Author not stated. 1984. Primary Dermal Irritation Study, Bio/dynamics, Inc. Project 5467-84. April 18, 1985. Data Accession No. 26356. Unpublished.

Baetjer, AM; Lowney, JF; Steffee, H; et al. (1959) Effect of chromium on incidence of lung tumors in mice and rats. Arch Ind Health 20:124-135.

Bagdon, R.E. and Hazen, R.E. (1991): Skin Permeation and Cutaneous Hypersensitivity as a Basis for Making Risk Assessments of Chromium As a Soil Contaminant. Env. Hlth. Perspec. 92: 111-119.

Bertolero F, Pozzi G, Sabbioni E, et al. 1987. Cellular uptake and metabolic reduction of pentavalent to trivalent arsenic as determinants of cytotoxicity and morphological transformation. Carcinogenesis 8:803-808.

Bishop, C; Surgenor, M, eds. (1964) The red blood cell: a comprehensive treatise. New York: Academic Press.

Bryson WG, Goodall CM. 1983. Differential toxicity and clearance kinetics of chromium(III) or (VI) in mice. Carcinogenesis 4(12):1535-1539.

Chowdhury AR, Mitra C. 1995. Spermatogenic and steroidogenic impairment after chromium treatment in rats. Indian J Exp Biol 33:480-484.

Cohen, Y., Winer, A.M., Creelman, L., and Mabuni, C. (1999): A Critical Assessment of Chromium in the Environment. Critical Rev. in Environmental Science and Technology 29(1): 1-46.

De Flora S, Badolati GS, Serra D, et al. 1987a. Circadian reduction of chromium in the gastric environment. Mutat Res 192:169-174.

Donaldson DL, Smith CC, and Yunice AA. 1984. Renal excretion of chromium-51 chloride in the dog. Am J Physiol 246:F870-F878.

Donaldson RM and Barreras RF. 1966. Intestinal absorption of trace quantities of chromium. J Lab Clin Med 68:484-493.

Federal Register, May 6, 1993, Vol 58, p. 26975, [as cited in Federal Register, Vol 58, No 234/Wednesday, Dec. 8, 1993/Notices, p. 64580-64582]

Fishbein L. 1981. Sources, transport and alterations of metal compounds: An overview. I. Arsenic,beryllium, cadmium, chromium and nickel. Environ Health Perspect 40:43-64.

Franzblau, A. and Lilis, R. 1989. Acute Arsenic Intoxication from Environmental Arsenic Exposure. Archives of Envir. Health 44(6). 385-390.

Freeman, GB., Johnson, J.D., Killinger, J.M., Liao, S.C., Davis, A.O., Ruby, M.V., Chaney, R.L., Lovre, S.C., and Bergstrom, P.D. 1993. Bioavailability of Arsenic in Soil Impacted by Smelter Activities Following Oral Administration in Rabbits. Fundamental and Applied Toxicology 21:83-88

Freeman, G.B., Schoof, R.A., Ruby, M.V., Davis, A.O., Dill, J.A., Liao, S.C., Lapin, C.A., and Bergstrom, P.D. 1995. Bioavailability of Arsenic in Soil and House Dust Impacted by Smelter Activities Following Oral Administration in Cynomologus Monkeys. Fundamental and Applied Toxicology 28:215-222

Gibson DP, Brauninger R, Shaffi HS, et al. 1997. Induction of micronuclei in Syrian hamster embryocells: comparison of results in the SHE cell transformation assay for national toxicology program test chemicals. Mutat Res 392(1-2):61-70.

Groen, K., Vaesen, H.A.G., Klest, J.I.G. deBar, J.L.M., von Ooik, T. Timmerman, A. and Vlug, R.G. 1993. Bioavailability of Inorganic Arsenic from Bog Ore-Containing Soil in the Dog. Environmental Health Perspective 102: 182-184.

Henderson RF, Rebar AH, Pickrell JA, et al. 1979. Early damage indicators in the lung. III. Biochemical and cytological response of the lung to inhaled metal salts. Toxicol Appl Pharmacol 50:123-136.

Hopenhayn-Rich et al., 1998: Lung and Kidney Cancer Mortality Associated with Arsenic in Drinking Water in Cordoba, Argentina. Epidemiology 27: 561-569.

Hopenhayn-Rich et al., 2000: Chronic Arsenic Exposure and Risk of Infant Mortality in Two Areas of Chile. Env. Hlth. Perspec. 108: 667-673, July 2000.

Hueper, WC; Payne, WW. (1962) Experimental studies in metal carcinogenesis--Chromium,nickel, iron, arsenic. Arch Environ Health 5:445-462.

International Agency for Research on Cancer (IARC). (1990) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 49. Some metals and metallic compounds. Lyon, France: World Health Organization.

IRIS. 2000. Chromium VI. Integrated Risk Information System. U.S. Environmental ProtectionAgency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Ivankovic, S; Preussman, R. (1975) Absence of toxic and carcinogenic effects after administrations of high doses of chronic oxide pigment in subacute and long term feeding experiments in rats. Food Cosmet Toxicol 13:347-351.

Jennette KW. 1982. Microsomal reduction of the carcinogen chromate produced chromium(V). J Am Chem Soc 104:874-875.

Junaid M, Murthy RC, Saxena DK. 1996a. Embryo- and fetotoxicity of chromium in pregestationally exposed mice. Bull Environ Contam Toxicol 57:327-334.

Kanojia RK, Junaid M, Murthy RC. 1996. Chromium induced teratogenicity in female rat. ToxicolLett 89:207-213.

Kenyon, E.M. and Hughes, M.F. (2001): A concise review of the toxicity and carcinogenicity of dimethylarsinic acid. Toxicology 160: 227-236.

Kochhar TS, Howard W, Hoffman S, et al. 1996. Effect of trivalent and pentavalent arsenic in causing chromosome alterations in cultured Chinese hamster ovary (CHO) cells. Toxicol Lett 84(1):37-42.

Lerman S, Clarkson TW, Gerson RJ. 1983. Arsenic uptake and metabolism by liver cells is dependent on arsenic oxidation state. Chem Biol Interact 45:401-406.

Larramendy ML, Popescu NC, DiPaolo J. 1981. Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster strains. Environ Mutagen 3:597-606.

Lebow, S. (1996): Leaching of Wood Preservative Components and their Mobility in the Environment- Summary of Pertinent Literature. Gen. Tech. Rep. FPL-GTR-93. Madison, WI: U.S. Department of Agriculture, Forest Service, Forest Products Laboratory, 36 p.

Lee, T-C, et al. (1985): Comparison of arsenic-induced cell transformation, cytotoxicity, mutation, and cytogenetic effects in Syrian hamster embryo cells in culture. Carcinogenesis 6(10): 1421-1426.

Levy, LS; Venitt, S. (1975) Carcinogenic and mutagenic activity of chromium-containing materials. Br J Cancer 32:254-255.

Levy, LS; Martin, PA. (1983) The effects of a range of chromium-containing materials on rat lung. Dye Color Manufacturers Association.

Maruyama, Y.(1982): The health effect of mice given oral administration of trivalent and hexavalent chromium over a long term. Acta Scholae Medicinalis Universitatis in Gifu 31:24-36.

Mass, M.J. et al. (2001): Methylated Trivalent Arsenic Species are Genotoxic. Chem. Res. Toxicol. 14: 355-361.

Mizuta, N, Mizuta, et al. 1956. An Outbreak of Acute Arsenic Poisoning Caused by Arsenic-Containing Soy-Sauce (Shoyu). A Clinical Report of 220 Cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

Moore MM, Harrington-Brock K, Doerr CL. 1997. Relative genotoxic potency of arsenic and its methylated metabolites. Mutat Res 386(3):279-290.

National Research Council: Arsenic in Drinking Water: 2001 Update. September, 2001, National Academy Press, Washington, D.C.

National Toxicology Program (NTP). 1996. Final report on the reproductive toxicity of potassium dichromate (hexavalent)(CAS No. 7778-50-9) administered in diet to SD rats. Dec. 16, 1996. U.S. Department of Commerce, National Technical Information Service, PB97125355.

National Toxicology Program (NTP). 1997a. Final report on the reproductive toxicity of potassium dichromate (hexavalent) (CAS No. 7778-50-9) administered in diet to BALB/C mice. Jan 10, 1997. U.S. Department of Commerce, National Technical Information

Service, PB97125363.

NTP, Public Health Service, U.S. Department of Health and Human Services. (1997) Final report. Potassium dichromate (hexavalent): reproductive assessment by continuous breeding when administered to BALB/c mice in the diet. February 18, 1997. Available from: National Institute of Environmental Health Sciences, Research Triangle Park, NC.

NRC (National Research Council). 1999. Arsenic in Drinking Water. National Academy Press, Washington, D.C.

Oberly TJ, Piper CE, McDonald DS. 1982. Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. J Toxicol Environ Health 9:367-376.

Roberts, S.M.; Welmar, W.R.; Venson, J.R.; Munson, J.W.; and Bergeron. Measurement of Arsenic Bioavailability from Soils Using a Primate Model. Abstract.

Rossman, T.G. et al. (1980): Absence of arsenite mutagenicity in E. coli and Chinese hamster cells. Environ. Mut. 2: 371-379.

Sayato Y, Nakamuro K, Matsui S, et al. 1980. Metabolic fate of chromium compounds. I. Comparative behavior of chromium in rat administered with $Na_2{}^{51}CrO_4$ and ${}^{51}CrCl_3$. J Pharm Dyn 3:17-23.

Schroeder, HA; Balassa, JJ; Vinton, WH, Jr. (1965) Chromium, cadmium and lead in rats: effects on lifespan, tumors, and tissue levels. J Nutr 86:51-66.

Suzuki Y, Fukuda K. 1990. Reduction of hexavalent chromium by ascorbic acid and glutathione with special reference to the rat lung. Arch Toxicol 64:169-176.

Towill, LE; Shriner, CR; Drury, JS; et al. (1978) Reviews of the environmental effects of pollutants. III. Chromium. Prepared by the Health Effects Research Laboratory, Office ofResearch and Development, U.S. Environmental Protection Agency, Cincinnati, OH. Report No. ORNL/EIS-80. EPA 600/1-78-023. NTIS PB 282796.

Trivedi B, Saxena DK, Murthy RC, et al. 1989. Embryotoxicity and fetotoxicity of orally administered hexavalent chromium in mice. Reprod Toxicol 3:275-278.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin, and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40:453-463.

Tseng W-P. 1977. Effects and dose-response relationships of skin cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

USEPA. Relative Bioavailability of Arsenic in Mining Wastes, Region 8, Document Control No. 4500-88-AORH, 1997.

USEPA. Bioavailability of Arsenic and Lead in Environmental Substrates. 1. Results of an Oral Dosing Study of Immature Swine. Superfund/Office of Environmental Assessment, Region 10, EPA 910/R-96-002, 1996.

USEPA Region 8, 2001: Derivation of Acute and Subchronic Oral Reference Doses for Inorganic Arsenic.

U.S. EPA, IRIS, Chromium (VI), 1998; CASRN 18540-29-9, 9/3/1998.

Wiegand, HJ; Ottenwalder, H; Bolt, HM. (1985) Fast uptake kinetics *in vitro* of 51 Cr(VI) by red blood cells of man and rat. Arch Toxicol 57:31-34.

Wester, R.C., Maibach, H.I., Sedik, L. Melendres, J., and Wader, M. 1993. In Vivo and in Vitro Percutaneous Absorption and Skin Decontamination of Arsenic From Water and Soil. Fundamental and Applied Toxicology 20:336-340

Williams, T.W. : Rawlins, B.G.; Smith, B.; and Breward, N. 1998. In-Vitro Determination of Arsenic Bioavailability in Contaminated Soil and Mineral Benefication Waste from Ron Phibun, Southern Thailand: A Basis for Improved Human Risk Assessment. Environmental Geochemistry and Health: 20

Witmer, C.M, Harris R and Shupack SI. 1991. Oral bioavailability of chromium from a specific site. Environ Health Perspect 92:105-110.

Zahid,Z.R., Al-Hakkak ZS, Kadhim AHH, et al. 1990. Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. Toxicol Environ Chem 25:131-136.