A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks

Final Report

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Prepared by:
J. Chen, N. Mottl, T. Lindheimer and N. Cook

U. S. Environmental Protection Agency
Office of Pesticide Programs, Antimicrobials Division

AUTHORS, CONTRIBUTORS, AND REVIEWERS

The National Exposure Research Laboratory of Exposure Assessment and Risk Assessment, Office of Research and Development, and the Antimicrobials Division, Office of Pesticide Programs, was responsible for the preparation of this document. A number of individuals have reviewed and/or have been contributing authors of this report including:

The **Probabilistic Exposure Assessment** portion of this report was developed by the following individuals:

V.G. Zartarian, J. Xue, and H. Özkaynak
U.S. Environmental Protection Agency
Office of Research and Development, National Exposure Research Laboratory

The **Probabilistic Risk Assessment** portion of this report was developed by the following individuals:

J. Chen, N Mottl, T. Lindheimer, and N. Cook
U.S. Environmental Protection Agency
Office of Pesticide Programs, Antimicrobials Division

For General Information Related to This Document Contact:

Norm Cook, Brach Chief
U.S. Environmental Protection Agency
Office of Pesticide Programs, Antimicrobials Division
Risk Assessment and Scientific Support Branch
Mail Code 7510P
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

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TABLE OF CONTENTS:

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICIES

LIST OF ACRONYMS

ACC	American Chemistry Council
AD	Antimicrobials Division
ADD	Average Daily Dose
APVMA	Australian Pesticides & Veterinary Medicines Authority
Ar (V)	Arsenic (V)
As	Arsenic
ATSDR	Agency for Toxics Substances and Disease Registry
AWPA	American Wood-Preserver's Association
AWPI	American Wood Preservers Institute
BF	Bioavailability Factor
CAP	Consumer Awareness Program
CCA	Chromated Copper Arsenate
CCA-C	CCA Type C
CDF	Cumulative Density Function
CDHS	California Department of Health Services
CE	Cumulative Exposure
CFA	Consumer Federation of America
CHAD	Consolidated Human Activity Database
CPSC	Consumer Product Safety Commission
Cr	Chromium
Cr (VI)	Chromium (VI)
Cr (III)	Chromium (III)
CSIS	Consumer Safety Information Sheet
Cu	Copper
DA	Dislodgeable Arsenic
DEC	Department of Environmental Conservation
E	New Exposure
EC	European Commission
EFH	Exposure Factors Handbook
EMRA	Environmental Risk Management Authority
EPA	Environmental Protection Agency
ERDEM	Exposure Related Dose Estimation Model
EWG	Environmental Working Group
FIFRA	Federal Insecticide, Fungicide, Rodenticide Act
FR	*Federal Register*
FQPA	Food Quality Protection Act of 1996
GI	Gastrointestinal
GM	Geometric Mean
GSD	Geometric Standard Deviation
HBN	Healthy Building Network
HED	Health Effects Division, OPP
HIARC	Hazard Identification Assessment Review Committee
IPEMA	International Play Equipment Manufacturers Association
IRIS	Integrated Risk Information System

LADD	Lifetime Average Daily Dose
LD_{50}	Lethal Dose, 50% Kill
LOAEL	Lowest-Observed-Adverse-Effect Level
MCA	Monte Carlo Analysis
MDEP	Maine Department of Environmental Protection
MOE	Margin of Exposure
MOE_{calc}	Calculated MOE
NAS	National Academy of Sciences
NCEA	National Center For Exposure Assessment
NCP	National Contingency Plan
NERL	National Exposure Research Laboratory
NHANES	National Health and Nutrition Examination Survey
NHAPS	National Human Activity Pattern Survey
NOAEL	No-Observed-Adverse-Effect Level
NOIC	Notice of Intent to Cancel
NRC	National Resource Council
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORD	Office of Research and Development
PBPK	Physiologically-Based Pharmacokinetic
pcf	Pounds per cubic foot
PD	Position Document
PDF	Probability Density Function
PMRA	Pest Management Regulatory Agency
PND	Preliminary Notice of Determination
ppm	Parts per million
Pr	Probability
PRA	Probabilistic Risk Assessment
Q_1*	Slope Factor
RAG	Risk Assessment Guideline
RB	Relative Bioavailability
RED	Reregistration Eligibility Decision
RME	Reasonably Maximum Exposed Individual
RPAR	Notice of Rebuttable Presumption Against Registration and Continued Registration
RTI	Research Triangle Institute
SA	Surface Area
SAP	Science Advisory Panel
SCS	Soil Contact Survey
SCTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
SF	Slope Factor
SHEDS	Stochastic Human Exposure and Dose Simulation Model
SHEDS-Wood	Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Scenario
SOPs	Standard Operating Procedures
TC (Dermal)	Transfer Coefficient

TE (Dermal)	Transfer Efficiency
USDA	U.S. Department of Agriculture
USPIRG	U.S. Public Interest Research Group

1.0 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) is aware of increased concerns raised by the general public, municipal and state governments, and state/federal regulatory agencies regarding the safety of young children contacting arsenic and chromium residues while playing on Chromated Copper Arsenate (CCA)-treated wood playground structures and decks. Because of this concern, OPP's Antimicrobials Division (AD), with the recommendation of the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA)'s Scientific Advisory Panel (SAP) and the assistance of the Office of Research and Development (ORD), has conducted a probabilistic exposure assessment entitled the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood). SHEDS-Wood provides exposures reported as average daily doses (ADDs) and lifetime average daily doses (LADDs). Children's exposures may occur through touching CCA-treated wood and CCA-contaminated soil near treated wood structures, mouthing hands after touching CCA-treated wood, and ingesting CCA-contaminated soil.

Since EPA has determined that the arsenic and chromium components of CCA pose the most significant toxicity concerns in comparison to copper, which is not a recognized or suspected carcinogen, AD focused on evaluating both potential adverse short-term (1-day to 1-month) and intermediate-term (1 to 6 months) non cancer risks and the lifetime cancer risks from both total arsenic and chromium as Cr (VI). This was done so in using the exposures modeled in SHEDS-Wood. Some of the key terms used in the SHEDS-Wood probabilistic exposure report are summarized in Table 1-1. It is also important to recognize that risks that are presented in a probabilistic risk assessment (PRA) are defined as feasible detrimental outcome(s) of an activity or action. PRA risks are characterized by two quantities:

- The magnitude (severity) of the possible adverse consequence(s), and
- The likelihood (probability) of occurrence(s) of each consequence(s).

In December, 2003 before the SHEDS-Wood SAP (see Appendix F), EPA released draft reports entitled "A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks (Dang et al., 2003)" and "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks (Zartarian et al 2003)." In 2005, ORD incorporated the SAP exposure recommendations and updated the probabilistic exposure assessment (Zartarian et al., 2005). Using the results of the SHEDS-Wood probabilistic exposure assessment (Zartarian et al., 2005) with some recently updated ORD exposure spreadsheets (see paragraph below), along with the 2003 SAP risk related recommendations, the Antimicrobial Division (AD) has now finalized its draft probabilistic risk assessment (Dang et al., 2003). Ultimately, the purpose of this report is to provide revisions to the OPP draft risk assessment based on comments received as a result of the three SAPs to update risks from the revised ORD SHEDS-Wood exposure assessment (Zartarian et al 2005), utilize the latest toxicological endpoints for CCA (i.e., based on chromium and arsenic)

This document reports children's risks to CCA via multiple routes and pathways, along with the dose estimates; all developed from the SHEDS-Wood document (Zartarian et al. 2005).

Table 1-1. Definitions of Key Terms Used in the SHEDS-Wood Risk Assessment	
Key Term	**Definition**
Population	OPP's primary population of interest for this assessment were children in the United States who frequently contact CCA-treated wood residues and/or CCA-containing soil from public playsets (e.g., at a playground, a school, a daycare center). Children playing on residential playsets were the secondary focus. EPA believes that more young children are exposed to CCA-treated public playsets than residential playsets because children spend more time on public playsets at schools and daycare centers. EPA also believes that children playing on public playsets would encompass a larger population of children. More data were available for public playsets than residential playsets. Further, CPSC and other groups have also focused their review on children exposed to public playsets. SHEDS-Wood also examined a subset of these children who contact CCA-treated wood residues and/or CCA-containing soil from residential playsets and/or residential decks (i.e., at the child's own home or at another home). Results from both groups of children (those who contact public playsets only, and those who contact public and residential playsets) are presented in this report.
Warm vs. Cold Scenarios	The SHEDS-Wood report referred to separate 'warm climate' and 'cold climate' scenarios. The Consolidated Human Activity Database (CHAD) diaries that were used in SHEDS-Wood were missing specific state locator information. As a result, instead of using geographical locations, 'warm climate' and 'cold climate' were simulated by modifying inputs such as surface area of unclothed skin and time spent on playsets and decks. See the text and tables (e.g., Table 12) of Zartarian et al. (2003, 2005) for more details regarding the assumptions for warm vs. cold climates.
With and Without Decks	With or without decks was used to indicate whether or not the population of children examined in the assessment had a residential deck. The term "with deck" was used to indicate that a child was exposed to a residential deck (i.e., at the child's own home or at another home) and a playset. The term "without decks" was used to indicate that a child was exposed to a playset only (Zartarian et al., 2005)
Time Periods	For the CCA assessment presented in this report, three exposure time periods were considered: short-term (represented in SHEDS-Wood by a 15 day averaging time; 1 day to 1 month), intermediate-term (represented in SHEDS-Wood by a 90 day averaging time; 1 to 6 months), and lifetime (6 years exposure over a 75-year lifetime).
Exposure Pathways	There were eight primary exposure pathways considered in SHEDS-Wood: dermal soil contact near decks; dermal residue contact from decks; soil ingestion near decks; residue ingestion from decks (via the wood-to-hand-to-mouth pathway); dermal soil contact near playsets; dermal residue contact from playsets; soil ingestion near playsets; and residue ingestion from playsets (via the wood-to-hand-to-mouth pathway). Dermal exposure was also computed separately for hands and body, and results were aggregated for decks and playsets, as well as between pathways. There are some less common pathways were not included into the CCA risk assessment. As pointed out by CPSC (2003a), it is possible in extreme cases that pre-schoolers may occasionally directly mouth portions of a wood play structure, however this behavior is not likely to be frequent for most playground users. Inhalation exposure to particulates for children that are present during sandblasting of CCA-treated surfaces would also be considered a less common potential pathway. Other potential sources of exposure not included in this assessment or other related CCA risk assessments include child exposures to picnic tables, porch railings and uprights, contact with pets and objects that have contacted treated wood, and CCA residues and soil that are brought indoors from outside.
Soil vs. Residue Exposure	SHEDS-Wood examined ingestion and dermal exposure routes for children from contact with CCA-contaminated soil and wood residues. Soil exposure refers to dermal contact with CCA-contaminated soil and soil ingestion. Residue exposure refers to dermal contact with CCA-treated wood and ingestion for residues from CCA-treated wood via hand-to-mouth contact.

As noted in the previous paragraphs, some of the exposure spreadsheets in the probabilistic exposure assessment have been updated. Subsequent to the release of the SHEDS-Wood exposure assessment (Zartarian et al., 2005); the design of the fluorescent tracer study (Kissel et al., 1998) that was used to estimate skin surface area contact rate in the SHEDS-Wood CCA exposure assessment (Xue et al., 2006; Zartarian et al., 2005, 2006) was found to be inconsistent with the Human Studies Rule. EPA had originally used this data to develop a skin surface area contact rate for the 2005 SHEDS-Wood exposure assessment (Zartarian et al., 2005). An alternative study that was acceptable according to the Human Studies Rule was identified, and ORD reran the original 2005 SHEDS-Wood exposure estimates. With the exception of the skin surface area contact rate, all of the other 40 exposure factors are consistent with the 2005 SHEDS-Wood probabilistic exposure assessment and the differences between the currently calculated exposures and those calculated in 2005 are very minor (see Appendix B for a report of the calculated exposure data). Therefore, Zartarian et al. (2005) was not updated and this current risk assessment was generated. Some of the major findings from the original 2005 probabilistic exposure assessment (Zartarian et al., 2005) include:

- Children who contact playsets only were found to have lower absorbed doses than children who contact both playsets and decks by a factor of 2.

- Warm climate bounding scenarios yielded higher exposure results than cold climate scenarios.
- For children who contact both playsets and decks, the total mean and median arsenic LADDs were both reduced by a factor of 1.3 when hand washing was assumed to occur following exposure.
- Children with pica soil ingestion behavior had about 2-3 times higher absorbed mean doses (totaled over all pathways considered) of arsenic than non-pica children from CCA-treated playsets and decks. The risks estimated for children with pica soil ingestion behavior were greater than those for non-pica children.
- Assuming the mean arsenic dermal absorption rate of 0.01% rather than 3% for children who contact playsets and decks in warm climates, the mean and median arsenic LADDs were 30% and 26% lower, respectively.
- The most significant exposure route for the population of interest for most scenarios was residue ingestion via hand-to-mouth contact, followed by dermal contact, soil ingestion, and dermal soil contact.

It should be noted that the results of this probabilistic risk assessment include combining a probabilistic exposure analysis with single point hazard endpoints because at this time OPP has not developed specific guidance for performing a probabilistic analysis of toxicity endpoints. Risks that arise from the predicted exposures were quantified in this risk assessment and the analyses performed are consistent with current OPP guidance. This risk assessment includes a background chapter on issues related to children's exposure to CCA-treated wood and the reasons that EPA conducted a non-dietary probabilistic assessment (see Chapter 2.0); describes the arsenic and chromium exposures generated by the SHEDS-Wood model (see Chapter 3.0); summarizes the arsenic and chromium toxicity endpoints in a hazard assessment (see Chapter 4.0); characterizes the risks for the exposures generated by the SHEDS-Wood model (see Chapter 5.0); and discusses the uncertainty, strengths, and limitations associated with this risk assessment (see Chapter 6.0). The major changes from the original draft of SHEDS-Wood risk assessment (Dang et al, 2003) are highlighted in the bulleted list below. Specifically, this revised risk assessment:

- Presents risks based on an updated SHEDS-Wood probabilistic exposure assessment (which includes a new skin surface area contact rate exposure factor).
- Incorporates 2001 & 2003 SAP recommendations (see Appendices E & F)
- Considered recommendations of the 2006 SAP meeting on "Studies Evaluating the Impact of Surface Coatings on the Level of Dislodgeable Arsenic, Chromium and Copper from Chromated Copper Arsenate (CCA)- Treated Wood" and does not include the hypothetical risk reduction scenarios for sealants.
- Presents arsenic cancer risks for Kwon et al (2004) data in the Uncertainty Analysis Section, along with an assessment of scenarios in consideration of hand washing and reduced dermal absorption.
- Incorporates a new hexavalent chromium (Cr (VI)) oral cancer slope factor and presents the calculated cancer risks.

In addition, the following appendices are provided and have been updated:

Appendix A	Hazard Identification and Toxicology Endpoint Selection for Inorganic Arsenic and Inorganic Chromium
Appendix B	Risk Spreadsheets
Appendix C	Risk Spreadsheets for Special Scenarios
Appendix D	Comparison of Residue and Soil Risk
Appendix E	Summary of Relative Bioavailability Studies
Appendix F	Summary Table for the SHEDS-Wood December, 2003 SAP Meeting Minutes
Appendix G	Inorganic Hexavalent Chromium (Cr (VI)): Report of the Cancer Assessment Review Committee

The objective of this risk assessment is to present probabilistic risk analysis of the arsenic and hexavalent chromium non cancer and cancer risks to children exposed to CCA-treated playsets and decks. The reader is encouraged to read the complete presentation and discussion of the probabilistic analysis as presented in Chapter 5. This document presents a probabilistic risk characterization, and there are no concluding regulatory statements regarding the percentiles of the distribution or point estimates (e.g., mean**,** 50^{th}, 90^{th}, 95^{th}, etc). Non-cancer Margins of Exposure (MOEs) and cancer risks to children exposed to CCA-treated playsets and decks and/or CCA-containing soil associated with these playsets and decks were calculated from doses generated using OPP/ORD's SHEDS-Wood model for chromium and arsenic. The exposure assessment considered children, ages 1 to 6 years old.[1]

Risks due to possible exposure to Cr (VI) via ingestion of soil were estimated, conservatively, by assuming 10% of total chromium was present as hexavalent chromium (Cr (VI)). For hexavalent chromium, the cancer slope factor (Q1*) used was 0.79 $(mg/kg/day)^{-1}$ and a NOAEL of 0.5 mg/kg/day was used for non-cancer effects.

The cancer slope factor (Q1*) for total arsenic used in this assessment was 3.67 $(mg/kg/day)^{-1}$ (slope factor) for cancer effects and a LOAEL of 0.05 mg/kg/day for non-cancer effects. The arsenic carcinogenic risk is a conservative estimate of the risk because the cancer slope factor is characterized as an upper-bound estimate. Therefore, the true risks to humans are not identifiable; they are not likely to exceed the upper-bound estimates and in fact may be less.

Non cancer risks for both arsenic and chromium were evaluated against OPP's guidance for MOE, for short-term and intermediate-term exposure durations. Lifetime cancer risks from arsenic exposure were compared to EPA/OPP's risk range of 10^{-6}. It is important to note that in the traditional deterministic risk assessment that the Agency conducts, risks are expressed as a single point value. For this type of risk assessment, the variability and uncertainty of the value is not reflected. The exact cancer risk value corresponding to the particular distribution is not presented. A basic understanding of probabilistic risk assessment process is essential to understanding the risks.

[1] Exposure durations modeled were short-term (1 day to 1 month), intermediate-term (1 to 6 months), and lifetime (6 years averaged over 75 years).

In summary, the risks were found to be greater under warm climate conditions than cold climate conditions. Exposure to playsets and decks had higher risks than exposure to playsets alone. Non cancer MOEs for arsenic were found to be above EPA/OPP's guidance MOE of 30 for all exposures, except at the extreme upper end of the distribution. Cr (VI) risks were found to be above the guidance MOE of 100 for all doses. These non cancer MOEs are summarized in the upper portion of Table 1-2. Cancer risks exceeded 10^{-4}, at cumulative percentiles ranging from the 91st for exposure to *CCA-treated playsets and decks in warm climates*, to the 99th for *exposure to playsets only in cold climates*. Across all exposure scenarios, carcinogenic risks were found not to exceed 10^{-6} at cumulative percentiles of the 9th and lower, conversely meaning that at least 91% of the simulated population has risks greater than 10^{-6}. The lower portion of Table 1-2 presents the cumulative percentiles at the three levels 10^{-4}, 10^{-5}, and 10^{-6}.

An analysis comparing the arsenic cancer risks from soil exposure versus residue exposure (i.e., contact with CCA treated wood surfaces only) was conducted for both sources of exposure: playsets alone and playsets with decks. The estimated risks should be viewed as approximations, however, because residue and soil risks were summed across routes at the quartile level and this compounds uncertainties producing inaccuracies. Risks to residues were found to be greater than risk from exposure to soil. Soil only risk for both playset only exposure, and playset and deck exposure exceeded 10^{-5} at the 95th percentile. For contact with playsets only, this difference between soil and residue exposure ranged from a factor of approximately 7 at the 50th percentile to 10 at the 99th percentile. Differences were larger for such exposures resulting from playsets and decks. At the 50th percentile, residue risk for playset and deck exposure was slightly greater than 10^{-5}, and approximately 10^{-4} at the 95th percentile.

Table 1-2. Summary of Risk Assessment Results

Non cancer MOEs for Arsenic and Chromium [a,c]

Source of Exposure	Climate	Duration of Exposure	Arsenic MOE > 30	Chromium MOE > 100
Playset Only	Warm	Short & Intermediate	> 99 th Percentile	None
	Cold			
Playset and Deck	Warm	Short & Intermediate	> 99th Percentile	None
	Cold			

a. Percentiles in this table represent the percent of the simulated population that have MOEs greater than or equal to the guidance MOE.

Cancer Risks for Arsenic [b,c]

Source of Exposure	Climate	Cumulative Percentiles at Specified Risk Levels		
		10^{-6}	10^{-5}	10^{-4}
Playset Only	Warm	2nd	46th	97th
	Cold	9th	69th	99th
Playset and Deck	Warm	< 1st	23rd	91st
	Cold	2nd	48th	98th

b. Percentiles in this table represent the percent of the simulated population that have arsenic risks less than or equal to the stated risk level. In other words, one may conclude that for playsets only, in warm climates, the estimated cancer risk is 1 x 10^{-6} at the 2nd percentile. Based on this, it means that 2% of the population has cancer risks that are predicted to be less than or equal to one in one million chances and the remaining 98% of the population has a potential cancer risk greater than or equal to one in one million chances. See Section 5.0 for more detailed explanation of how to interpret

the results.

c. The simulated population is defined in Table 1.1. It is important to emphasize that the underlying population whose risk is being assessed here is *not* children in general, but is limited specifically to children who frequently contact CCA-treated playsets.

Arsenic Cancer Risks						
Scenario	**Mean**		**Median**		**95th %ile (95th Percentile)**	
	Warm	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**
Playset and Deck	4.2E-05	2.0E-05	2.3E-05	1.0E-05	1.4E-04	6.6E-05
Playset Only	2.2E-05	1.3E-05	1.1E-05	5.4E-06	7.7E-05	4.7E-05

Cancer Risks for Chromium (VI)[a,]

Source of Exposure	Climate	Cumulative Percentiles at Specified Risk Levels		
		10^{-6}	**10^{-5}**	**10^{-4}**
Playset Only	Warm	99.9th	None	None
	Cold	None	None	None
Playset and Deck	Warm	None	None	None
	Cold	None	None	None

a. Percentiles in this table represent the percent of the simulated population that have chromium (VI) risks less than or equal to the stated risk level; e.g., at 10^{-6}, 99.9% of the population have risks less than 10^{-6} and 0.01% have risks greater than 10^{-6}

None- risks are less than 10^{-6} and do not reach the Agencies level of concern.

In 2001, the FIFRA SAP recommended that additional research was needed to evaluate the performance and efficacy of different brands of coatings. As a result, the EPA and the U.S. Consumer Product Safety Commission (CPSC) conducted additional research on the effectiveness of sealants on weathered CCA-treated wood. The sensitivity analysis in the SHEDS-Wood exposure report SHEDS-Wood exposure assessment (Zartarian et al., 2003, 2005) concluded that the concentration of residue at the surface of the wood was a key variable. Both exposure assessments measured the hypothetical impact of sealants on dislodgeable arsenic residues. On November 15, 2006 an SAP meeting entitled "Studies Evaluating the Impact of Surface Coatings on the Level of Dislodgeable Arsenic, Chromium and Copper from Chromated Copper Arsenate (CCA)- Treated Wood" occurred. In this meeting, the SAP elaborated that many uncertainties exist with regard to using surface coating or sealant studies to estimate reduction of dislodgeable arsenic, chromium, and copper residues from the surfaces of CCA-treated wood. The agenda, meeting notes, and supporting documentation on the 2006 SAP meeting are available through the following website link http://www.epa.gov/scipoly/sap/meetings/2006/111506_mtg.htm#minutes

For more information on the SAP review of the uncertainties and limitations of the surface coating studies please refer to the 2006 FIFRA SAP final meeting minutes report which is currently available on the following website link. http://www.epa.gov/scipoly/sap/meetings/2006/november/november2006finalmeetingminutes.pdf

Certain activities and conditions were considered (e.g., hand washing, reducing the dermal absorption rate to 0.01%, and Kwon et. al (2004) residue data (see Table 7-2)[2]), and developed using the SHEDS-Wood exposure model. These are exclusively presented in the uncertainty analysis of the SHEDS-Wood risk assessment. As discussed in this analysis, exposures and risks were lowered by adjusting either the arsenic concentrations, or changing the selected activities of the children based on behavior or exposure. In the hand washing scenario, ORD adjusted the activities modeled for children to simulate the effect of hand washing. The Kwon et. al. (2004) scenario was modeled by using only the Kwon et. al (2004) arsenic hand residue data. This study measured direct dislodgeable arsenic residue from children's hands after playing on CCA-treated playsets. The final scenario used an alternative arsenic dermal absorption from Wester et al. (2003). These activities appear to reduce the arsenic exposure to children and thus risk. Table 1.3 presents the percent differences in the median, mean and upper 95th percentile.

Table 1-3 Lowering of Arsenic Cancer Risks Using Selected Alternative Approaches Presented in the Uncertainty Analysis

Special Scenarios	Median	Mean	Upper 95ile
Playset and Deck			
Baseline (warm climate)	**2.3E-05**	**4.2E-05**	**1.4E-04**
Baseline (cold climate)	**1.0E-05**	**2.0E-05**	**6.6E-05**
Hand washing (warm climate)	**1.7E-05**	**2.8E-05**	**9.2E-05**
0.01% dermal absorption (warm climate)	**1.3E-05**	**2.9E-05**	**1.1E-04**
0.01% dermal absorption (cold climate)	**8.5E-06**	**1.7E-05**	**6.1E-05**
Playset Only			
Baseline (warm climate)	**1.1E-05**	**2.2E-05**	**7.7E-05**
Baseline (cold climate)	**5.4E-06**	**1.3E-05**	**4.7E-05**
Hand washing (warm climate)	**8.2E-06**	**1.9E-05**	**6.8E-05**
0.01% dermal absorption (warm climate)	**7.7E-06**	**1.9E-05**	**6.6E-05**
0.01% dermal absorption (cold climate)	**4.9E-06**	**1.1E-05**	**3.6E-05**
Kwon et al (2004) (cold climate)	**8.4E-07**	**1.3E-06**	**4.0E-06**

Footnotes: Calculated using warm and cold climate scenarios. ORD ran hand washing only run for warm scenario and Kwon et al (2004) was run using only the cold climate scenario.

Note that the Agency analyzed the results of this information in the uncertainty analysis section in order to provide some perspective on the uncertainties and data limitations which are believed to be inherent with these approaches. It should also be noted that the 2005 SHED Wood exposure assessment additionally provided some special analysis of other populations (e.g., pica children, older children) which were also quantitatively assessed in the exposure assessment. These scenarios were not included in this risk assessment but the additional special sensitivities and uncertainties of these scenarios are well captured in the 2005 SHEDS-Wood exposure report.

A qualitative assessment of uncertainty was conducted in this risk assessment. Uncertainty in the risk characterization was a result of the combined uncertainty of the exposure

2 Note the Kwon data exposure analysis was completed by ORD in the fall of 2007 and was not presented in the 2005 SHEDS-Wood exposure report.

assessment generated by SHEDS-Wood and the uncertainty in the toxicological factors. The evaluation of the toxicity values showed that they were at the upper end of the range of a theoretical distribution because they incorporated several conservative assumptions. An in-depth uncertainty and sensitivity analyses of the SHEDS-Wood exposure assessment was performed by Zartarian et al. (2005). For uncertainty, the two (out of six listed) most critical inputs were: transfer efficiency and residue concentration. Sensitivity analysis showed that the most influential variables were: transfer efficiency, residue concentration, fraction of hand mouthed, and amount of hand washing. Total uncertainty in the exposure assessment was estimated at a factor of 3-4.

For carcinogenic risks, it is likely that the uncertainty is asymmetrical around the factor of 3-4 because the slope factor accounts for several conservative assumptions. However, while this was not modeled, there appears to be a greater probability that the risks are lower than reported (lower probability that the risks are to be higher). For non-cancer effects, the uncertainty is also asymmetrical. This is due to the LOAEL and NOAEL being generated from the upper portion of the theoretical distribution. For chromium, there is the added conservative assumption that 10% of total chromium is present as Cr (VI). Taken together with the NOAEL, there is a much greater probability that the Cr (VI) MOEs are greater than those reported (greater MOE means less of a concern).

2.0 INTRODUCTION AND BACKGROUND

2.1 Introduction

The U.S. Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) is aware of increased concerns raised by the general public, municipal and state governments, and state/federal regulatory agencies regarding the safety of children contacting arsenic and chromium residues while playing on Chromated Copper Arsenate- (CCA-) treated wood playground structures and decks. Because of this concern, OPP's Antimicrobials Division (AD), with the recommendation of the Science Advisory Panel (SAP) and the assistance of the Office of Research and Development (ORD), has conducted probabilistic assessments to evaluate potential childhood exposure to arsenic and chromium components of CCA-treated wood in decks, home playsets, public playground structures and contaminated soils commonly found in these settings. This report focuses on the non-dietary assessment of risks from CCA treated wood, specifically the potential health risks to children that may result from contact with CCA-treated wood playsets, decks and CCA-contaminated soil around these structures.

OPP/AD's preliminary approach was reviewed by the SAP in 2001, which used a deterministic exposure assessment methodology for CCA-treated wood. One of SAP's primary recommendations to OPP was that a more comprehensive probabilistic assessment should be developed to examine the exposure scenarios that had been presented in the deterministic assessment in 2001.

OPP requested the assistance of ORD in developing a model to conduct a probabilistic exposure assessment for CCA-treated wood. The Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood), a probabilistic exposure model developed by the National Exposure Research Laboratory (ORD/NERL), was

used to develop the exposure assessment for children exposed to CCA-treated playsets and decks. On August 30, 2002, SHEDS-Wood was presented to the SAP for review and to obtain recommendations from the panel. After incorporation of comments from the second SAP review, a draft document was prepared by ORD entitled *A Probabilistic Exposure Assessment for Children Who Contact CCA-treated Playsets and Decks Using the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood)* (Zartarian et al., 2003). The SHEDS-Wood document provides exposures, reported as average daily doses (ADDs) and lifetime average daily doses (LADDs); it does not report risk estimates. In order to evaluate the risk from SHEDS-Wood, a separate OPP document entitled *A Probabilistic Risk Assessment for Children Who Contact CCA-treated Playsets and Decks*, (U.S. EPA 2003) was prepared. Both the exposure and risk documents were submitted for a third review by the SAP in December, 2003. Since the December 2003 SAP, ORD has revised and enhanced the SHEDS-Wood Model (SHEDS-Wood codes, inputs, and methodology) to incorporate recommendations from the three SAPs.

The purpose of this report is to provide revisions to the OPP draft risk assessment based on comments received as a result of the three SAPs and to update risks from the revised ORD SHEDS-Wood exposure assessment (Zartarian et al 2005). The risk assessment has been revised using the latest toxicological endpoints for CCA (i.e., based on chromium and arsenic) selected by OPP. This document reports children's risks to CCA via multiple routes and pathways, along with the dose estimates; all developed from the SHEDS-Wood document (Zartarian et al. 2005).

This document also provides background information on issues related to children's exposure to CCA-treated wood and the reasons that EPA conducted a non-dietary probabilistic assessment (see below); describes the exposures generated by SHEDS-Wood (see Chapter 3.0); summarizes the arsenic and chromium toxicity endpoints for children used in this risk assessment (see Chapter 4.0); characterizes the risks for the exposures presented in the SHEDS-Wood model (see Chapter 5.0); characterizes risk reduction impacts for the exposures presented in the SHEDS-Wood model (see Chapter 6.0); and discusses the uncertainties, strengths, and limitations of this risk assessment (see Chapter 7.0).

2.2 Background

Chromated Copper Arsenate (CCA) wood preservatives containing chromium (Cr), copper (Cu), and arsenic (As) as pesticidal compounds, protect wood from deterioration. CCA is predominantly used to pressure treat lumber that is intended for outdoor use when constructing a variety of residential landscape and building structures, as well as home, school, and community playground equipment. Children may potentially be exposed to the pesticide residues remaining on the surfaces of the treated wood structures as well as the residues leached into the surrounding soil. EPA is aware of increased concerns raised by the general public and state regulatory agencies regarding the risks as a result of CCA-treated wood for residential applications. The children's risk assessment presented herein evaluates anticipated exposure routes and pathways in consideration of the activity patterns and behaviors of young children near residential playsets, public playsets, and residential decks. Children's exposure may occur through touching CCA-treated wood and CCA-contaminated soil near treated wood structures, mouthing hands after touching CCA-treated wood, and eating CCA-contaminated soil. Since EPA has determined that

the arsenic and chromium components of CCA pose the most significant toxicity concerns in comparison to copper, which is not a recognized or suspected carcinogen, the Agency focused on evaluating potential adverse short-term, intermediate-term, and lifetime exposures and non-cancer/cancer risks to children from arsenic and chromium as Cr (VI). The SHEDS-Wood model developed by ORD was selected by OPP to conduct the probabilistic children's exposure and dose assessment for CCA (Zartarian et al., 2003, 2005). The exposure doses generated by SHEDS-Wood were used in conjunction with toxicity data for arsenic and chromium as Cr (VI) to estimate the risks that are presented in this report.

2.2.1 Regulatory History of CCA

Regulatory actions involving inorganic arsenical wood preservatives, including CCA, have been ongoing for 25 years. An administrative review process was initiated in 1978 to consider whether the registration of certain wood preservative chemicals (pentachlorophenol; coal tar, creosote and coal tar neutral oil; and inorganic arsenicals) should be cancelled or the actual terms modified. A separate Notice of Rebuttable Presumption Against Registration and Continued Registration (RPAR) was issued for each heavy-duty wood preservative under consideration. A RPAR is issued when the Agency determines that a pesticide meets or exceeds any of the risk criteria relating to acute and chronic toxic effects, as set forth under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Registrants then have the opportunity to submit evidence in rebuttal of the Agency's risk presumptions. The RPAR for inorganic arsenicals (43 FR 202) was published on October 18, 1978, along with a supporting Position Document (PD 1). According to the aforementioned document, the risk criteria that were met or exceeded for inorganic arsenicals were: oncogenicity, mutagenicity, and fetotoxic/teratogenic effects. The RPAR generated substantial registrant comments, but these risks remained un-rebutted after the RPAR process.

The Agency issued a Preliminary Notice of Determination (PND), concluding the RPAR process, which was published in the Federal Register of February 19, 1981 (46 FR 13020). This notice, along with the supporting Position Document (PD 2/3), stated the Agency's determination that the wood preservative chemicals continued to exceed the risk criteria and this provided the basis of the RPARs. To reduce the risks, the Agency proposed certain modifications to the terms and conditions of registration, including certain protective clothing requirements, classifying all inorganic arsenical wood preservatives as Restricted Use (available to certified applicators only), and a mandatory program to educate users of treated wood with handling, use and disposal precautions.

The preliminary determinations described above were submitted to the FIFRA SAP and the U.S. Department of Agriculture (USDA) for review. Comments were also solicited from registrants and any other interested persons. The Agency considered the comments received and made modifications to the proposed decision announced in the PND. A public meeting was conducted on April 14, 1983 to allow interested persons to comment on the proposed changes. Their comments were considered in the development of the final determination, which was a Notice of Intent to Cancel (NOIC), published in the Federal Register of July 13, 1984 (49 FR 136), along with a supporting Position Document (PD 4).

Several trade associations and numerous registrants requested hearings to challenge the Agency's determinations in the July 13 NOIC. The Agency published a Federal Register Notice on October 31, 1984 (49 FR 43772), postponing the effective date of the labeling modifications for those registrants who filed applications for amended registration in response to the NOIC. On January 30, 1985, the Agency published an additional Federal Register Notice (50 FR 4269) announcing that persons other than registrants could continue to sell and distribute existing stocks of wood preservative products with existing labeling until further notice. Pre-hearing meetings were held between the Agency and some of the major parties who had requested hearings, during which alternative and mutually acceptable mechanisms for achieving the regulatory goals set forth in the NOIC were discussed. After careful consideration of some of those alternatives, the Agency concluded that certain changes to the July 13, 1984 NOIC were appropriate and consistent with the Agency's goal of protecting the public from unreasonable adverse effects resulting from pesticide use. An amended NOIC, announcing these changes, was published in the Federal Register of January 10, 1986 (51 FR 7). The modifications were mostly minor in scope, with the exception that the previous mandatory Consumer Awareness Program (CAP) was deleted from the labeling requirements. The wood preservative industry agreed to a voluntary CAP to educate consumers on the proper use and precautionary practices for treated wood.

Arsenic, chromium, and chromated arsenical compounds, used as wood preservatives, were evaluated under the Registration Standards Program in 1988. This program was established in order to provide a mechanism for pesticide products having the same active ingredient to be reviewed and brought into compliance with FIFRA. The outcome of the Registration Standard for arsenic, chromium, and chromated arsenical wood preservatives was as follows:

- Classification of inorganic arsenic and hexavalent chromium as Group A carcinogens;
- Acknowledgment that both arsenic and chromium have demonstrated the potential to cause teratogenic/fetotoxic effects through peritoneal exposure;
- Requirement of a reproduction study using a formulated chromated arsenical product to address the teratogenic/fetotoxic effects unless a metabolism study demonstrates that blood levels of chromium and arsenic are not increased above background levels;
- Requirement of metabolism data to assess the bioavailability of chromium and arsenic after exposure to a formulated product;
- Requirement of additional ecological effects and environmental fate data; and
- Reiteration of label restrictions set forth in the prior NOICs.

Currently, the only remaining use of arsenic acid is for wood preservation. The last remaining agricultural use of arsenic acid, as a desiccant on cotton, was voluntarily canceled in 1993 (58 FR 86, May 6, 1993). The voluntary cancellation was enacted following a NOIC issued for the cotton desiccant use of arsenic acid (56 FR 50576, October 7, 1991) due to the cancer risks to workers. The voluntary cancellation allowed the sale of existing stocks until December 31, 2003, after which they could be lawfully disposed of or sold to the wood preservative industry for reformulation or repackaging into registered wood preservative products.

2.2.2 Current Development of CCA Issue

On March 17, 2003 EPA granted the voluntary cancellation and use termination requests affecting virtually all residential uses of CCA-treated wood. Under this action, affected CCA products could not be used after December 31, 2003 to treat lumber intended for use in residential settings. This transition affected virtually all residential uses of wood treated with CCA, including play structures, decks, picnic tables, landscaping timbers, residential fencing, patios, and walkways/boardwalks. This action was proposed in February 2002 by the registrants of CCA pesticide products that are used to treat wood. Phase-out of the residential uses served to reduce the potential exposures and risks from arsenic, a known human carcinogen, thereby protecting human health, especially children's health, and the environment. The current action follows the February 2002 publication of a notice of receipt of voluntary cancellation/use termination requests, which also provided an opportunity for public comments to be submitted to EPA. A notice of the cancellation order was published in the Federal Register on April 9, 2003. Consumers may continue to buy and use the treated CCA wood for as long as it is available, but the transition to using the new generation treatment products is well underway. Until the Agency has evaluated the following uses through the reregistration process, the Agency is deferring any actions involved in the termination requests for: (1) wood used in permanent wood foundations; and (2) wood used in fence posts for agricultural uses. Therefore, these two types of products may continue to be treated with CCA at this time.

The registrations and EPA-approved labels for CCA wood preservatives were voluntarily amended by each registrant to state that, “effective December 31, 2003, CCA may be lawfully used only to treat wood or forest products,” for uses listed on the new label. Subsequently, in December of 2003 and February of 2004, the registrants requested that their registrations and EPA-approved labels be amended. These amendments were approved by the Agency and the resulting label language changed such to limit wood treated for marine construction to brackish or saltwater use (immersion), and members out of water, but subject to saltwater (or brackish water) splash. To accomplish this, the registrants requested voluntary deletion of the use which refers to “members out of water and not subject to salt water splash and not in soil use,” along with the necessary label changes, effective on December 31, 2004.

EPA is working with the registrant community and other stakeholders to ensure that safer, comparable alternatives will become available. EPA is continuing its work on the ongoing comprehensive reevaluation of CCA-treated wood as part of the Agency's effort to re-evaluate older pesticides. This re-evaluation will serve to ensure that they meet current health and safety standards. More information on CCA-treated wood is available at the following EPA website: http://www.epa.gov/oppad001/reregistration/cca/.

The Agency is evaluating CCA under the reregistration process within OPP. Once OPP completes the reregistration review for CCA, the Reregistration Eligibility Decision (RED) document for Chromated Arsenicals will be released to the public. The RED document availability is expected to be announced late 2008. The RED will include a comprehensive assessment of the potential human impacts (preliminary focus on occupational and environmental exposures/risks attributed to the use of CCA-treated wood and related inorganic

chromated arsenical pesticides at the workplace) as well as potential impacts on the environment.

2.2.2.1 CPSC Activities

In June 2001, the U.S. Consumer Product Safety Commission (CPSC) docketed a petition by the Environmental Working Group (EWG) and the Healthy Building Network (HBN) to enact a ban of chromated copper arsenate treated wood for use in playground structures because of potential human health concerns. The playground equipment made with wood treated with CCA is the jurisdictional responsibility of the CPSC and would be subject to the rules of CPSC's Federal Hazardous Substances Act if found to be a hazardous substance. CCA and other pesticides are registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) by the U.S. Environmental Protection Agency (EPA). In March 2003, the EPA granted a request by manufacturers to cancel the registration of CCA for use in wood for most residential structures (e.g., playgrounds, decks, picnic tables, etc.) which was effective December 30, 2003 and thereafter. While this action prohibits the future residential use of wood treated with CCA, it does not address potential exposure to chemical residues (e.g., arsenic) from existing structures made with CCA-treated wood or from structures made with new CCA-treated wood from existing stock supplies that were available to consumers after the cancellation date.

On March 17, 2003, the U.S. Consumer Product Safety Commission (CPSC) staff held a Commission Briefing to respond to the petition from the Environmental Working Group (EWG) and the Healthy Building Network (HBN) to ban the CCA-treated wood being used in playground equipment and to review the safety of CCA-treated wood for general use (CPSC, 2003a). After briefing the Commissioners and the public on CPSC's deterministic risk assessment, CPSC staff recommended denial of the petition based on the actions of EPA (CPSC, 2003a). On November 4, 2003, CPSC voted unanimously that a ban was not necessary because the wood industry no longer uses CCA-treated wood for playsets. CPSC's decision was based on an agreement between CCA manufacturers and the Environmental Protection Agency (EPA) to phase out CCA treatment of wood for most consumer uses by the end of 2003. More information on CPSC's briefing on CCA-treated wood is available at the following website: http://www.cpsc.gov/cpscpub/prerel/prhtml04/04026.html

CPSC staff was concerned about CCA-treated wood in playground equipment because children could potentially be exposed to arsenic. On May 11, 2005 EPA and CPSC released an interim study on the effectiveness of sealants in reducing the amount of that leaches from the treated wood. On November 15, 2006 an SAP meeting entitled "Studies Evaluating the Impact of Surface Coatings on the Level of Dislodgeable Arsenic, Chromium and Copper from Chromated Copper Arsenate (CCA)- Treated Wood" occurred in which sealant studies were reviewed. In the 11/15/06 meeting, the SAP elaborated that many uncertainties exist with regard to using surface coating or sealant studies to estimate reduction of dislodgeable arsenic, chromium, and copper residues from the surfaces of CCA-treated wood. The Agenda, meeting notes, and supporting documentation on the 2006 SAP meeting are available through the following website link http://www.epa.gov/scipoly/sap/meetings/2006/111506_mtg.htm#minutes

For more information on the SAP review of the uncertainties and limitations of the surface coating studies please refer to the 2006 FIFRA SAP final meeting minutes report which is currently available on the following website link.
http://www.epa.gov/scipoly/sap/meetings/2006/november/november2006finalmeetingminutes.pdf

2.2.2.2 Updated International Actions and Activities

European Commission (EC)

The European Commission (EC) published Commission Directive 2003/2/EEC on January 3, 2003. Commission Directive 2003/2/EEC is an amendment to the European Union Commission Directive 76/769/EEC on the marketing and use of dangerous substances. Commission Directive 2003/2/EEC became effective on June 30, 2004 and restricted the use of CCA-treated wood to very specific circumstances in all of the 25 EC countries. The EC countries include Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, The Netherlands, and The United Kingdom.

The EC amendment restricts the marketing and use of both the CCA chemical as well as timber treated with CCA, and also applies to imported treated wood and waste wood reuse. Commission Directive 2003/2/EC states that arsenic compounds may not be used "in the preservation of wood. Furthermore, wood so treated may not be placed on the market." The only exception is wood to be used in industrial installation where "the structural integrity of the wood is required for human or livestock safety and skin contact by the general public during its service life is unlikely." It should be noted that the EC regulations do not apply to CCA-treated wood that is already in service. Background information is available at the following website: http://europa.eu.int/comm/enterprise/chemicals/legislation/markrestr/index_en.htm

Commission Directive 2003/2/EC specifically prohibits the following uses of CCA-treated wood:

- in residential or domestic construction, regardless of the purpose;
- in any application where there is a risk of repeated skin contact;
- in marine waters;
- for agricultural purposes other than for livestock fence posts and structural uses;
- in any application where the treated wood may come into contact with; and,
- intermediate or finished products intended for human and/or animal consumption.

Commission Directive 2003/2/EC was based on the results of a risk assessment that was generated by the European Commission Enterprise Directorate General through which the following unacceptable risks were identified:

- risks to children playing on CCA-treated timber play equipment;
- environmental risks from combustion and disposal (including leaching from landfills and to aquatic organisms); and,
- health risks from use of CCA-treated timber, (DEFRA, 2003)

The European Communities' Scientific Committee for Toxicity, Ecotoxicity, and the Environment (SCTEE) evaluated the risk assessment and found that no threshold exists for the carcinogenic effects of arsenic. The SCTEE could not establish the arsenic-related risks stemming from landfill disposal of CCA-treated timber. Disposal of this sort of timber is currently classified as a hazardous waste by the EC, and therefore the SCTEE concluded that it was appropriate to attempt to reduce the production of CCA-treated timber as much as possible, because it is likely to cause serious harm (SCTEE, 2003).

The current regulatory status of CCA treated wood is expected to change in the near future because the remaining uses of arsenic in wood preservation are also subject to the Biocidal Product Directive 98/8/EC. This Directive was adopted in 1998 and addresses placement of biocidal products on the market. All EC member countries are required to make necessary arrangements to monitor whether or not biocidal products placed on the market comply with the requirements of Directive 98/8/EC. Directive 98/8/EC aims to harmonize the European market for biocidal products and their active substances while providing a high level of protection for humans, animals, and the environment. A review of all the active substances used in biocidal products marketed prior to May 14, 2000 is currently being performed under the regulatory framework of Directive 98/8/EC. Industry is required to notify the EC of all substances they intend to defend during this review process and for which of those that they intend to submit data so that they can remain on the market at the close of the review process. The only arsenic compound that has been submitted under the notification process to date is diarsenic pentaoxide (CAS No. 1308-28-2) which is used as a wood preservative. However, the company that submitted the notification subsequently withdrew its submission from the review program. It is anticipated that wood preservatives containing arsenic as the active substance is no longer going to be used as of September 1, 2006. Further information is available at: http://europa.eu.int/comm/environment/biocides/index.htm

Canada

Health Canada's Pest Management Regulatory Agency (PMRA) and the U.S. EPA have been jointly re-evaluating CCA for use as a preservative for wood. While Health Canada has not yet concluded that CCA-treated wood poses any unreasonable risk to the public or the environment; Health Canada believes that any reduction in the levels of potential exposure to arsenic is desirable since arsenic is a known human carcinogen. Current risk assessment methods have been employed in Canada's reevaluation of CCA, which includes consideration of worker exposure along with emphasized focus on sensitive sub-populations such as children who may come in contact with treated wood.

Canada's Pest Management Regulatory Agency has reached an agreement with industry on the proposed transition of significantly decreasing the use of CCA-treated wood at residential sites. The wood treatment industry in Canada stopped treating wood with CCA for use in

residential applications on December 31, 2003. Existing structures built from CCA-treated wood were not affected by this action. CCA-treated wood is still available for industrial uses. The PMRA agreement is identical to the voluntary label changes for CCA-treated wood that were proposed by the U.S. EPA. Canada's Consumer Safety Information Sheet on CCA-treated wood can be found at http://www.ptw-safetyinfo.ca/cca.htm and a Fact Sheet on CCA-treated wood can be found at http://www.pmra-arla.gc.ca/english/pdf/fact/fs_cca-e.pdf

Australia

In Australia, CCA preservative use is approved and regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA). In March 2003, the APVMA announced the review of the registrations of timber treatment products containing arsenic, and approval of labeling associated with those products. The levels of dislodgeable residues on CCA-treated lumber are presumably higher than what was previously thought, and this has prompted concerns related to exposure to the human population. Concerns were also raised that environmental contamination may occur near sites where timber is treated with CCA along with disposal sites of CCA-treated timber. The aims of the review were to examine the potential for adverse public health effects arising from the use of CCA or arsenic trioxide timber treatments, the potential for adverse environmental effects from the use and disposal of these products, and the adequacy of instructions and warnings on product labels. The technical assessments are detailed in a document entitled *The Reconsideration of Registrations of Arsenic Timber Treatment Products (CCA and Arsenic Trioxide) and Their Associated Labels* available at: http://www.apvma.gov.au/chemrev/arsenic.shtml. .

On March 2005, the Australian Pesticides & Veterinary Medicines Authority (APVMA) announced that it is moving to phase out uses of copper chrome arsenate (CCA) timber treatments for which the safety of the population is questionable. The news release is available at http://www.apvma.gov.au/media/mr0501.shtml

According to APVMA Principal Scientist, Dr David Loschke, certain residential uses of CCA would be phased out over a 12 month period to the end of March 2006 but the existing structures would not be dismantled. The actions that the APVMA is taking to manage the risk of exposure to arsenic from CCA timber treatments are consistent with those taken recently by other leading regulatory agencies in Europe, the USA and Canada.

The regulatory report is available on the APVMA website. Among the proposed outcomes of the review include those:

- Use sites on the product labels are specifically defined such that uses of CCA timber treatment products are not permitted for timber intended for use as garden furniture, picnic tables, exterior seating, children's play equipment, patio and domestic decking, and handrails.

- Specific statements are found on the product label to require that each piece of timber be clearly identified as having been treated with CCA (except specific circumstances where supplied and therefore marked as a pack).

- CCA timber treatment products are declared restricted chemical products (RCP) 1 in the public interest. Supply and use will be restricted to persons with special skills and knowledge achieved through authorized training. It will also be an RCP requirement that supply be restricted to treatment plants that comply with the specified Australia / New Zealand Standards.

- Registrants are required to submit specific worker exposure data to address concerns associated with arsenic and chromium (VI).

More details are available at http://www.apvma.gov.au/chemrev/arsenic_summary.pdf

New Zealand

New Zealand commissioned research on public health risks related to CCA, particularly around homes and playgrounds (EMRA, 2003a; APVMA, 2003). The New Zealand Environmental Risk Management Authority (ERMANZ) found that the extent of any risk to public health arising from CCA remains unclear, but is considering further investigation into the possible environmental and occupational health risks arising from CCA. Based on an internal review of public health risks (ERMANZ) has decided against a reassessment of registrations of CCA. However, ERMANZ is currently reviewing labeling procedures, disseminating public health information on CCA, assessing alternatives to CCA, etc. For public CCA-treated playsets, ERMANZ is not taking action on existing facilities. However, the government is working with schools on ways to reduce exposure to CCA (e.g., using coatings) on publicly-maintained playsets (ERMANZ, 2003b). Information is available on the Department of Environment and Conservation (NSW) website at:
http://www.environment.nsw.gov.au/licensing/qaswood.htm

Table 2-1 summarizes international regulatory actions and activities related to CCA. The table provides the information by international community, activity, and website source.

Table 2-1. International Regulatory Actions and Activities Related to CCA

International Community	Summary of Action and Activities		Website Source
USA	EPA CCA is currently undergoing reregistration review by EPA. EPA granted the voluntary cancellation and use termination requests affecting virtually all residential uses of CCA-treated wood. Under this action, affected CCA products cannot be used after December 31, 2003, to treat lumber intended for use in most residential settings. EPA provides public health information on arsenic in pressure treated wood and provides safety recommendations for homeowners and additional information on their website. EPA will complete the reregistration review for CCA, and the Reregistration Eligibility Decision (RED) late 2008	CPSC On March 17, 2003, CPSC held a Commission Briefing to respond to the petition from the Environmental Working Group (EWG) and the Healthy Building Network (HBN). After briefing the Commissioners and the public on their deterministic risk assessment, CPSC deferred their decision on the petition pending final EPA action. CPSC and EPA are conducting parallel studies employing similar methodologies to evaluate the ability of surface coatings to mitigate exposure and published a report of their findings through December 2004. CPSC provides public health	http://www.epa.gov/oppad001/reregistration/cca/ http://www.cpsc.gov http://www.cpsc.gov/cpscpub/prerel/prhtml04/04026.html http://www.cpsc.gov/library/foia/foia05/os/ccamitig.pdf

Table 2-1. International Regulatory Actions and Activities Related to CCA			
International Community	**Summary of Action and Activities**		**Website Source**
		information on arsenic in pressure treated wood and provides safety recommendations for homeowners and additional information on their website.	
Europe	The European Commission (EC) published Commission Directive 2003/2/EEC on January 3, 2003 restricting the use of CCA-treated wood to very specific circumstances in all of the 25 EC countries (i.e., Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, The Netherlands, and The United Kingdom). Commission Directive 2003/2/EC specifically prohibits use of CCA-treated wood in residential or domestic construction, whatever the purpose; in any application where there is a risk of repeated skin contact; in marine waters; for agricultural purposes other than for livestock fence posts and structural uses; and, in any application where the treated wood may come into contact with intermediate or finished products intended for human and/or animal consumption. The European Communities' Scientific Committee for Toxicity, Ecotoxicity, and the Environment (SCTEE) evaluated the risk assessment and concluded that is was appropriate to reduce the production of CCA-treated timber as much as possible because it is likely to cause serious harm. The currently regulatory status of CCA treated wood is expected to change in the near future because the remaining uses of arsenic in wood preservation are also subject to the Biocidal Product Directive 98/8/EC, which addresses placement of biocidal products on the market. It is anticipated that wood preservatives containing arsenic as the active substance will no longer be used as of September 1, 2006.		http://europa.eu.int/comm/enterprise/chemicals/legislation/markrestr/index_en.htm http://europa.eu.int/comm/environment/biocides/index.htm
Canada	Health Canada's Pest Management Regulatory Agency (PMRA) and the U.S. EPA have been working together on the revaluation of CCA for use as a preservative for wood. Health Canada believes that any reduction in the levels of potential exposure to arsenic is desirable and a revaluation has been completed since. Canada's Pest Management Regulatory Agency (PMRA) has reached an agreement with industry on the proposed transition away from the use of CCA-treated wood at residential sites. The wood treatment industry in Canada stopped treating wood with CCA for use in residential applications on December 31, 2003. Existing structures built from CCA-treated wood were not affected by this action. CCA-treated wood is still available for industrial uses.		http://www.pmra-arla.gc.ca/english/pdf/fact/fs_cca-e.pdf
Australia	In Australia, CCA preservative use is approved and regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA). In March 2003, the APVMA announced the review of the registrations of timber treatment products containing arsenic, and approval of labeling associated with those products because of health concerns associated with contact with dislodgeable residues on CCA-treated lumber. Concerns were also raised that environmental contamination may occur near sites where timber is treated with CCA and where timber is disposed of. The results of the review are detailed in a document entitled *The Reconsideration of Registrations of Arsenic Timber Treatment Products (CCA and Arsenic Trioxide) and Their Associated Labels* (APVMA 2005). One of the significant conclusions of the review was that product labels be revised such that uses of CCA timber treatment products are not permitted for timber intended for use as garden furniture, picnic tables, exterior seating, children's play equipment, patio and domestic decking, and handrails		http://www.apvma.gov.au/chemrev/arsenic.shtml
New Zealand	New Zealand commissioned research on public health risks related to CCA, particularly around homes and playgrounds. Based on an internal review of public health risks, the New Zealand Environmental Risk Management Authority (ERMANZ) has decided against a reassessment of registrations of CCA. However, ERMANZ is currently reviewing labeling procedures, disseminating public health information on CCA, assessing alternatives to CCA, etc. For public CCA-treated playsets, ERMANZ is not taking action on existing facilities. The government is working with schools on ways to reduce exposure to CCA (e.g., using coatings) on publicly-maintained playsets.		http://www.environment.nsw.gov.au/licensing/qaswood.htm

2.2.2.3 Updated State Actions and Activities

In 1987, the California Department of Health Services (CDHS), Health and Welfare Agency, conducted a research study entitled, *Evaluation of Hazards Posed by the Use of Wood Preservatives on Playground Equipment*, and made recommendations to the Legislator for the State of California (CDHS, 1987). As a result of the findings and recommendations of that report, a new law was signed into effect in September 1987 (Div. 20 of the California Health and Safety Code, §25930.10.7) (Spease, 2002). The law stated that:

- State funds could not be used to purchase wooden playground or recreational equipment that may have been treated with arsenic (unless treated in accordance with AWPA standard C-17), pentachlorophenol or creosote;
- State funds may not be used for maintenance of the wooden playground or recreational equipment in question; and
- People installing any such structures must seal the structures with a non-toxic, non-slip sealer at the time of installation, and reseal the structure every two years.

Maine legislators approved the Nation's first ban on the sale of wood treated with arsenic on June 4, 2003. The bill states "that beginning April 1, 2004, Maine lumber dealers can no longer sell arsenic-treated lumber for use in residential construction" (Edgecomb, 2003). Additionally, retailers are prohibited from purchasing arsenic-treated wood for most residential uses (mid-September 2003). Additionally, the Maine Department of Environmental Protection (MDEP) was expected complete a market evaluation of remaining uses. The Maine Bureau of Health also developed informational brochures to educate consumers by January 1, 2004, on what homeowners should know about hazards, and methods for reducing exposures with sealants. By January 1, 2005, the MDEP had developed plans to restrict the disposal of arsenic-treated wood (Our Stolen Future, 2003).

In New York, Section 37-0109 of the New York State Environmental Conservation Law makes it illegal for schools and public playgrounds to have playground equipment constructed from pressure treated lumber that contains CCA. The law requires that existing playground equipment be sealed to stop CCA from leaching or escaping from the wood, and to cover the ground to protect children from arsenic that may have leached to the soil. The Department of Environmental Conservation (DEC) has published information on the dangers and hazards to public health and the environment from the use of CCA-treated lumber. The DEC has also compiled and published a list of less toxic materials that may be used on playgrounds as an alternative to CCA-treated lumber. Lastly the DEC has compiled and published information on non-toxic methods and materials that are available to seal playground structures with CCA wood and to cover the ground (Healthy Schools Network, 2003).

Recently, North Carolina's Department of Environment and Natural Resources has modified section 15A NCAC 18A.2831 which is sub-titled ANIMAL AND VERMIN CONTROL. This new amendment serves to include restrictions on CCA treated wood. This amendment was effective as of August 2, 2007. This law states that decks, fences, playground equipment and any other products constructed or installed after September 1, 2006 shall not be

constructed with CCA treated wood. The amendment also indicates that the only time that use of CCA-treated wood will be allowed is when it is for an approved use listed on the CCA product label and allowed under the US EPA Supplemental Guidance on Interpretation of Revised Chromated Copper Arsenate (CCA) Wood Preservative Label. If there are areas that are considered to be accessible to children, such as decks, playgrounds, or recreational equipment and have been constructed prior to January 1, 2005, all of the structure shall be sealed using oil-based, semi-transparent sealant; oil-based clear stain; or a water-based clear stain applied at least once every two years. This regulation also applies to any use sites that EPA may allow uses of CCA-treated wood. Once these identified areas have been sealed, according to law this sealing process will need to occur at intervals no less than two years. For the initial sealant application and in cases when more than 2 years has elapsed since the previous sealant application, any soil located under the structure will need to be removed and replaced with similar material. This new material will need to be at least four inches of soil, gravel, sand, sod, or other vegetation. If this is not possible then it will be necessary to make sure that the area under regulation is made inaccessible (NCDENR, 2007).

Other state agencies such as the Connecticut Department of Public Health, the Massachusetts Department of Public Health, the Florida Department of Environmental Protection, and the Minnesota Department of Health have been actively investigating issues related to pressure-treated playground equipment. These agencies have provided public health information on arsenic in pressure-treated wood, as well as safety recommendations for homeowners (see websites listed in Table 2-2). These recommendations include:

- sealing CCA-treated structures (decks and playsets) every two years with oil-based stain;
- preventing exposure to pressure-treated wood and dust;
- washing hands after playing on wooden playground equipment;
- inspecting structures for decay;
- suggesting alternatives to CCA-treated pressure treated wood;
- not placing food, drink or paper products on pressure treated wood;
- never burning treated wood;
- limiting use of under deck areas where arsenic may have accumulated in the soil;
- not using treated wood on indoor surfaces; and
- not using CCA-treated wood for wood chips or mulch.

Table 2-2 presents a summary of state regulatory activities and actions related to CCA. The table provides the information by state, summary of actions and activities, and website source.

Table 2-2. State Regulatory Actions and Activities Related to CCA

State	Summary of Actions and Activities	Website Source
California	In 1987, the California Department of Health Services (CDHS), Health and Welfare Agency conducted a research study entitled, *Evaluation of Hazards Posed by the Use of Wood Preservatives on Playground Equipment* and made recommendations to the Legislator in the State of California (CDHS, 1987). As	http://www.dhs.ca.gov

Table 2-2. State Regulatory Actions and Activities Related to CCA		
State	**Summary of Actions and Activities**	**Website Source**
	a result of the findings and recommendations of the report, a new law was signed into effect in September 1987 (Div. 20 of the California Health and Safety Code, §25930.10.7). Legislation required that publicly-maintained wooden playground or recreation equipment be treated with a certain formulation of CCA. This legislation also required that existing publicly-maintained wooden playground/recreation structures made with arsenic-treated wood be sealed with a non-toxic and non-slippery sealant every two years. CDHS provides public health information on arsenic in pressure-treated wood, safety recommendations for homeowners, as well as additional information on their website.	
Connecticut	The Connecticut Department of Public Health provides public health information on arsenic in pressure treated wood, safety recommendations for homeowners, as well as additional information on their website.	http://www.ct.gov/dph
Florida	Proposed legislation would prohibit the public use of CCA-treated wood in playground structures and associated ground covers that are constructed or contracted for by October 1, 2003. It would require that existing publicly-maintained wooden playground/recreation structures made with arsenic treated wood be sealed with a non-toxic and non-slippery sealant every two years. Florida Department of Environmental Protection provides public health information on arsenic in pressure-treated wood, safety recommendations for homeowners, as well as additional information on their website.	http://www.dep.state.fl.us
Maine	Legislature approved a bill that states "beginning April 1, 2004, Maine lumber dealers can no longer sell arsenic-treated lumber for use in residential construction." Additionally retailers are prohibited from purchasing arsenic- treated wood for most residential uses (mid-September 2003). The Maine Department of Environmental Protection (MDEP) must complete a market evaluation of remaining uses. The Maine Bureau of Health must develop informational brochures by January 1, 2004, on what homeowners should do know about hazards, and methods for reducing exposures with sealant. By January 1, 2005, the MDEP must develop plans to restrict the disposal of arsenic treated wood.	http://janus.state.me.us/legis/ros/lom/lom121st/10Pub451-500/Pub451-500-96.htm http://www.maine.gov/dep
Massachusetts	The Massachusetts Department of Environmental Protection provides public health information on arsenic in pressure-treated wood and safety recommendations for homeowners on their website.	http//:www.mass.gov/dph/
Minnesota	In Minnesota, a bill has been introduced that would	http//:www.health.state.mn.u

Table 2-2. State Regulatory Actions and Activities Related to CCA		
State	**Summary of Actions and Activities**	**Website Source**
	ban the use and sale of CCA in the state. A second Minnesota bill would require that schools that use CCA-treated products seal the wood every two years (Environmental Health Perspectives, 2001). Minnesota Department of Health provides public health information on arsenic in pressure treated wood, safety recommendations for homeowners, as well as additional information on their website.	s
New York	In New York, Section 37-0109 of the New York State Environmental Conservation Law makes it illegal for schools and public playgrounds to construct playground equipment from pressure-treated lumber that contains CCA. The law requires that previously installed playgrounds be sealed to stop CCA from leaching or escaping from the wood, and to cover the ground to protect children from arsenic that may have leached to the soil. The New York Department of Environmental Conservation provides public health information on arsenic in pressure-treated wood, safety recommendations for homeowners, as well as additional information on their website.	http//:www.dec.ny.gov http://www.dec.ny.gov/chemical/8790.html
North Carolina	North Carolina has made it illegal for any structures built after 9/1/2006 to contain CCA treated wood. The only allowed use of CCA is any approved use listed on the CCA product label and allowed under the US EPA Supplemental Guidance on Interpretation of Revised Chromated Copper Arsenate (CCA) Wood Preservative Label. Areas that are considered to be accessible to children and have been constructed prior to January 1, 2005 will need to be sealed every two years. This required sealing also applies to any use sites that EPA may allow uses of CCA-treated wood. Re-sealing will need to occur at intervals no less than two years. At the initial sealant application and in cases when more than 2 years has elapsed since the previous sealant application, any soil located under the structure will need to be removed and replaced at least four inches of soil, gravel, sand, sod, or other vegetation. If this is not possible then it will be necessary to make sure that the area under regulation is made inaccessible.	http://www.deh.enr.state.nc.us/ehs/images/rules/t15a-18a.28.pdf

2.2.3 Use Profile of CCA

CCA preservatives protect wood from deterioration that can result from a variety of insects, fungi, and rot organisms. There are currently 26 CCA-containing wood preservative products registered with the EPA. CCA is used for pressure-treated lumber that is intended for outdoor use in constructing a variety of residential landscape and building structures, as well as

home, school and community playground equipment. However, it should be noted that EPA has granted the voluntary cancellation and use termination requests of CCA-treated wood. The labels for the three CCA-containing preservatives that contained the non-pressure treatment uses were effectively canceled via a 6(f) notice on May 16, 2003. A final cancellation order was issued on May 28, 2003 for Osmose Special K-33 Preservative (EPA Registration 3008-21), Hollow Heart Concentrate (EPA Registration 75341-1) and Osmoplastic SD Wood Preserving Compound (EPA Registration 75341-7). The cancellation of these three products resulted in pressure treatment being the only allowable use for CCA-containing preservatives. CCA-treated wood, predominantly of Southern yellow pine, represents the majority of pressure-treated dimensional lumber marketed to the general consumer via lumberyards/hardware stores and other retailers. In some cases, CCA-treated lumber is recycled into wood chips which are stained, then sold to consumers as landscape mulch. Major commercial installations include utility poles, highway railings, roadway posts/barriers, bridges, bulkheads, and pilings. Industry cites advantages of CCA-treated wood over other pressure-treated wood, including superior durability, low-odor, and dry "non-oily" surfaces which can be painted or sealed.

There are three formulations of CCA, each containing varying ratios of arsenic pentoxide, chromic acid, and cupric oxide. CCA treatment solutions are typically classified by the American Wood-Preservers' Association (AWPA) as either type A, B, or C, with CCA type C (CCA-C) being the formulation most commonly used for pressure treating dimensional lumber for residential applications. AWPA's P5 Preservative Standard requires CCA-C composition to be 34.0% arsenic pentoxide (As_2O_5), 47.5% chromic acid (CrO_3), and 18.5% cupric oxide (CuO) (AWPA, 1998).

After pressure treatment and fixation, arsenic and chromium can be retained in the wood from 0.25 to 2.50 pounds per cubic foot (pcf), and this is based on the retention of CCA-C in wood following AWPA treatment standards. Typical retention levels achieved depend on the intended applications of the treated lumber. Lower retention values are required for plywood, lumber, and timbers used for above-ground applications (0.25 pcf), and for ground or freshwater contact uses (0.40 pcf). Higher retention levels are required for load bearing wood components, such as pilings, structural poles, and columns (0.60 - 0.80 pcf). The highest levels are required for wood foundations and saltwater applications (up to 2.50 pcf).

Nationwide, approximately 70% of single family homes have existing pressure-treated decks and porches, and approximately 14% of public playground equipment is constructed with treated wood. Based on current data from the American Chemistry Council (ACC), approximately 34% of CCA treated wood was used for decks and less than 1% was used in playground equipment (Zartarian et al., 2003; CPSC, 2003b). The potential for exposure to pesticide residues remaining on the surfaces of the existing aged treated wood structures, as well as to the residues leached into the surrounding soil may pose child health hazard concerns.

2.2.4 Overview of CCA Chemistry

CCA contains chromium (Cr), copper (Cu), and arsenic (As), each of which contributes to the wood-preservative properties of the compound. Copper acts as a fungicide in the CCA formulation and the arsenic protects against insect damage. Chromium, in the form of chromic acid, acts as a fixative (binding agent), whereby the Cr, Cu, and As metal ions present in the wood are fixed to the wood fibers. Most of the information presented in this overview has been extracted from U.S. EPA (2001b).

Metals go through various changes in environmental compartments such as soil, water, plants, and animals. The speciation of metals depends on sorption, desorption, redox reactions in soil and water, precipitation reactions, complexation reactions, etc. (Lebow, 1996). The different species of arsenic and chromium vary in their ability to be absorbed into the body and metabolized within the body, and differ in their toxicological profiles. Therefore when assessing the exposures to these chemicals, it is important to consider the species of arsenic or chromium present in soils that surround CCA-treated wood as well as what is found at the surface of the treated wood itself.

2.2.4.1 Speciation

The FIFRA SAP (FIFRA SAP, 2001) noted that there is no reliable evidence on either the presence or absence of Cr (VI) in dislodgeable residues on treated wood surfaces. However, since that meeting, more studies have indicated that Cr (III) is the primary component on treated wood surfaces. The FIFRA SAP also noted that some measurable Cr (VI) probably exists in certain soils, but it is unlikely to be 100 percent of the total chromium present. One approach recommended by FIFRA SAP in evaluating the hazards of chromium in the soil was to utilize an estimate of 5 to 10 percent (or more conservatively 25 to 50 percent) Cr (VI).

More recent studies have indicated that Cr (III) is the primary component in CCA pressure-treated wood surfaces of existing decks and playground structures (RTI International, 2003 (cited as ACC, 2003b in SHEDS-Wood Report); Cooper, 2003; Nico et al., 2003) and in the air of treatment plants (ACC, 2002). In fact, RTI International (2003) found that Cr (VI) was not detected in 142 of 145 wood surface dislodgeable residue samples taken; Cr (VI) was not detected in any of the samples from existing aged decks, and only trace amounts of this chemical were detected in the newly treated woods in the remaining samples. The registrants of CCA conducted a CCA treatment plant worker exposure study in 1999 (ACC, 2002). This study indicated that the Cr (VI) in the air was undetectable (based on the sensitivity of the limit of detection of Cr (VI) used in that study). Nico et al. (2003) found that chromium and arsenic in CCA-treated wood were consistent between samples of fresh treated wood and aged wood, and between treated wood and dislodgeable residue. The Nico et al. (2003) report indicated that a "chemical complex" type of matrix was formed between As-Cr-Wood. However, the Nico et al. (2003) report did not quantify the matrix type of CCA-treated wood and the free metal forms of arsenic and chromium.

2.2.4.2 Fixation

After undergoing pressure treatment with CCA wood preservative, the chromium, copper and arsenic penetrate into the wood and become bound or fixated to the wood. The term, fixation, refers to the series of chemical reactions that take place after the wood has been pressure treated with CCA. These reactions render the CCA less likely to leach from the wood during service. The use of metal oxides in CCA formulations has been shown to aid in the fixation process. Fixation precedes the actual action of CCA to act as a wood preservative. The CCA penetration/fixation process preserves and protects the wood from pest attack. The absorption and fixation of CCA occur in the cellulosic and lignin components of the wood (Kartal and Lebow, 2000). Since lignin is thought to be a primary binding site for chromium to form chromium-lignin complexes, the use of woods with increased lignin content may result in improved treatment. Softwood species, which have high lignin content often, perform better than hardwoods in terms of preservative treatment. Studies have shown that all of the three metals are able to be fixed into the wood structure.

The initial reaction of fixation is the absorption of the CCA preservative into the cellulosic and lignin components of the wood. A second reaction occurs which converts Cr (VI) to Cr (III). This second reaction continues for a period of several hours to a few days. The reduction of Cr (VI) to Cr (III) is important in the formation of insoluble complexes in CCA-treated wood. Additionally, Cr (III) is less toxic than Cr (VI). The third reaction involves the conversion of copper arsenate in the wood to basic copper arsenate with an arsenic valence state of +5. The complete fixation reaction may even take several months. Studies with treated pine have indicated that the copper and arsenic components of the CCA metals are “fixed” more rapidly than chromium. Some researchers have concluded that the fixation process is complete when the presence of Cr (VI) is no longer detected in the leachate or compensate of the treated wood. Cooper (2003) conducted research on CCA fixation using existing data and noted that virtually all of the chromium injected into the wood during the treating process is eventually reduced to low toxicity Cr (III) and there is no evidence that Cr (VI) is produced as a result of the oxidation of Cr (III) in the wood. The completion of the fixation process can be from a few days to a several months, depending on the ambient temperature of treatment plants.

2.2.4.3 Leaching

The fixation process binds much of the chromium, copper, and arsenic into the wood fibers; however, some of the metals will not be “fixed” and will remain “free” on the surface of the treated wood. These will be susceptible to dislodging through washing off or by physical contact with other objects, including humans who have physical contact with the wood. The fixated metals can also slowly be leached from the treated wood by water.

Playground equipment constructed with treated wood can be in the form of many different types of items including swing sets, climbing bars, etc. The chromium, copper, and arsenic in/on the treated wood can be leached from the wood so that the metals fall vertically onto the soil under the equipment and leach laterally into the soil from the vertical pieces of treated wood that have contact with the playground soil. Metals also leach from ground-contact horizontal pieces of CCA-treated wood fabricated into playsets and related structures. Playground equipment may also have mulch placed under the equipment, and the mulch will receive leachate from the treated equipment pieces. Children playing on such equipment can be exposed to the CCA leachates either through contact with the CCA-treated wood or through

contact with soil or mulch that is found either under the equipment or immediately adjacent to the equipment.

A large amount of data is available regarding the leaching of chromium, copper, and arsenic from treated wood (Lebow, 1996). Much of the data are from studies that are not directly applicable to leaching from playground equipment. Some of the available data that are most applicable to playground equipment and decks constructed of CCA-treated wood are summarized below.

Leaching of chromium, copper, and arsenic from treated wood in an aqueous medium, which is most likely to simulate the playground use (where rainfall occurs), appears to be most rapid from freshly treated wood and is in the order of Cu > As > Cr. The release rate is also higher under acidic conditions; this would mean that leaching would be faster in the areas of the United States that have acid rain, such as the northeastern states. One study has shown that the leaching process from treated wood is aided by slow or drizzling rain rather than heavy showers. Leaching rates are generally lowest in wood that has been kiln-dried at high temperatures.

Most of the leaching from treated wood appears to take place in the first few days after treatment, but continues slowly over time (Lebow, 1996). Leaching rates depend on the size of the wood, type of wood, and on the fixation process. CCA leaches from hardwood more than soft wood. Pressure treated red pine leaches more than lodgepole pine and Douglas fir. A scheme has been proposed in the literature for the long-term leaching mechanism of CCA from wood: reversible disassociation of ion-exchanged metals and their redistribution to the wood surface and their loss; and physical or biological decay of the wood.

No leaching information was found to address the question of whether CCA metals leach from treated wood as copper or copper arsenate, or as complexes with inorganic or organic ligands, or as derivatives of wood-metal moieties or as water soluble extracts. Water mobility for the metal ions from CCA depend on many factors which give rise to a number of pathways. The metals can diffuse through the soils as complexes, simple salts or free ions, or can percolate through soils as insoluble substances.

Little data were found to estimate the level of CCA residues in soil or mulch under playground equipment constructed of treated wood. A Canadian study evaluated wooden play structures consisting mostly of CCA-treated lumber of various dimensions constructed in a range of designs and were up to ten years old (Riedel et al., 1991). The structural elements were comprised of beams and planks fastened together. Poles were cut and used to form rungs, ramps and ladders. Treated wood pieces were used to construct tower-like structures and to connect to swings, slides, ladders or horizontal monkey bars. Some structures incorporated hut-like shelters. Treated wood pieces were placed in vertical, horizontal and angled positions. Some structures were coated with an oil-based stain which had worn off in some areas. The ground under the structures and surrounding the structures generally consisted of a layer of sand at least 25 centimeters deep which is replaced or replenished from time to time. The sand is carried onto the structures and contributes to the abrasion and wear of the treated wood pieces.

Sand and soil samples were taken from under each of the treated playground structures

and a control soil sample was taken at a distance of ten meters (33 feet) from the treated playground structure. The sand samples were taken at similar locations under each structure; at the bottom of a slide, next to a support post, at the bottom of a support post holding the main structure, and underneath a wooden platform or underneath a structure approximately one meter from the wooden post. The samples were all collected in the fall with cloudy weather. The soil samples were stored in plastic bags and taken to the laboratory for analyses and were oven dried and analyzed using inductively coupled plasma mass spectrophotometry for total nitric acid soluble arsenic (not speciated). Neither chromium nor copper were analyzed in the sand and soil samples.

The background levels of arsenic present in the control sand samples were generally less than 0.3 parts per million (ppm). The authors of the paper reported that the average arsenic residue level from samples taken from below the treated structures was 3.0 ppm with a range of 0.032 - 9.6 ppm. However, sand samples taken from other areas around the playground structures showed arsenic residues ranging from 0.13 ppm to 113.5 ppm under a structure or next to a post. It should be noted that arsenic residues in sand sampled next to a treated post were less than 10 ppm except for one playground, which generated the 113 ppm value. That study showed significantly higher sand residues than the other playground studies.

There is no explanation for this difference, but it could be due to reasons such as samples being taken near newly treated and replaced wood posts. However the playground where arsenic residues were highest was ten years old and constructed of wood that had been stained, but the stain had worn off. Additionally, sand had been placed under the structures and leaching from wood posts into the sand may be more rapid and spread further from the post than would be the case for arsenic leaching into a clay soil. It could also be argued that if wood mulch rather than sand had been placed under the playground structures that, because of the surface area to weight relationship for this organic material, any arsenic residues leaching from treated wood could result in even higher arsenic residues. Overall based on the results of the study, there did not appear to be a correlation between residue levels in the sand under and around the playground structures and whether the equipment had been stained or painted, or was left unsealed.

There are also data available showing soil residue levels that occur under wooden decks that have been constructed from CCA-treated wood. Children can play in the soil under and around a treated deck. While the deck data may exaggerate residue levels in soil compared to what would be expected under playground equipment, the data show that the level of CCA metals in soil under treated wood structures was greater than the background level of the metals in soil from the study location and show residue levels in soil where children could play.

In one study conducted by Stilwell and Gorny (1997), soil samples from under seven decks that had been constructed from CCA-treated wood were analyzed. Chromium levels ranged as high as 154 ppm under the treated decks and averaged 43 ppm, whereas, the control soils had an average of 20 ppm of chromium. Arsenic levels ranged as high as 350 ppm under the treated decks and averaged 76 ppm, whereas, the control soils had an average of 3.7 ppm of arsenic. No data are available for mulch under the treated deck, but residues in mulch may even be higher because of the surface area weight relationship of mulch. The same study showed that those decks that had been coated tended to show a lesser degree of leaching of CCA metals.

However, the degree of leaching from a deck that had been coated or sealed would most likely be dependent on the coating product used and on the age of the coating. The same study also showed that the age of the deck was a factor in the leachate residues found under the treated deck, with the older deck showing higher soil residues under the treated deck. This study does not reflect the soil CCA residue levels that could occur under treated playground equipment, but the generalization can be made that CCA residues in soil under treated playground equipment will be higher than soil background levels of the CCA metals in the surrounding area. The residue data from this study do not speciate the metals but determine total copper, chromium, and arsenic.

Lateral and vertical migration of CCA metal residues can also occur from vertical pieces of the playground equipment that have contact with the soil. In a study conducted by DeGroot et al. (1979), treated southern pine wooden stakes were placed in sandy soil, and the lateral and vertical migration of CCA metal residues were measured after 30 years. Both arsenic and chromium residues leached into the top six inches of a soil core, arsenic as high as 108 ppm and chromium as high as 25 ppm. Some increase in arsenic levels, but not chromium levels, was seen in the six- to twelve-inch core. In the twelve- to eighteen-inch core, there did not appear to be any increase in the arsenic and chromium level. In soils which have a high clay or organic content, metal leaching would be expected to be lower because of the metal binding to the soil particles. Lateral movement of residues in the soil surrounding the stakes appeared to be limited to the zero- to three-inch area surrounding the treated stakes. Based on the findings in this and other studies, CCA metal residues are not likely to leach from vertically-placed wood structures placed in contact with the soil to depths greater than twelve inches from the structure or to lateral distances of greater than three inches from these treated wood pieces.

In another study conducted in Florida with CCA-treated decks (Townsend et al., 2001), nine decks were studied (one deck could not be confirmed as treated with CCA). The decks were located in Gainesville, Miami, and Tallahassee and sampling was conducted in 1999. The decks varied in age from two to nineteen years old. A grid was set up under each deck before sampling where soil samples were collected. Surface samples, from the top inch of soil, and soil core samples, of approximately seven inches in depth, were taken. Soil control samples were also taken at locations away from the grid. The soil samples were digested and analyzed for total arsenic, copper, and chromium. Analyses were performed using an atomic absorption spectrophotometer. This method determines the total metal residue level and does not speciate the metals.

Arsenic residues were found in the soil beneath all of the CCA-treated decks. The average surface arsenic level was 39 ppm and the maximum level under one deck was 217 ppm. The maximum arsenic residue found under any of the other decks was 88 ppm. The maximum arsenic residues present in soil core samples were detected in the top two inches, but were also present at levels of approximately 2-20 ppm over the depth range of two to eight inches. Control arsenic values average 1.5 ppm.

The average surface copper residue found in the soil beneath all of the CCA-treated decks was 40 ppm and the maximum level found from under one deck was 216 ppm (soil from the same deck that generated high arsenic levels). The maximum copper residue found in soil under

the remaining decks was 156 ppm. The maximum residues present in soil core samples were generally higher than what was found in the top few inches of soil, and were also higher than those levels in control samples.

The surface chromium residues found in the soil beneath the treated decks averaged to be 34 ppm; and the maximum detected value was 198 ppm (this maximum was detected in the soil that had been collected from the deck that generated high arsenic levels). The maximum chromium residue found in soil samples was 114 ppm. The average control level was 9.8 ppm, and average chromium levels of up to 11.7 ppm were reported at collection depths of 4.5 inches.

The soils under the CCA-treated decks are described as ranging from beach sand to being dark in color with a sponge-like consistency. It was also found that a high percentage of volatiles were given off during analysis. This latter observation seems to support that the soils have a high organic content. The site with the highest arsenic level was characterized as having relatively high volatile solids, and this correlation can also be found in five of the nine deck sites. The lowest arsenic residues were found at sites with low volatile solids content (Townsend et al., 2001). This study indicates that CCA-treated decks increase arsenic, copper, and chromium levels in soil beneath treated decks.

Based on the available information from both CCA-treated playground equipment and decks, it appears that the primary source of soil exposure to children that play on playground equipment constructed of CCA-treated wood or play under treated decks will occur from the leaching of CCA metal residues from horizontal pieces onto the soil. Maximum residue levels would likely be less than 200 ppm arsenic, copper, and chromium, and, on the average, would be less than 50 ppm for each of the metals. Maximum residues of arsenic would likely occur in sandy soil under treated wood. However, if an organic material such as wood mulch with a high surface to weight relationship were placed under CCA-treated playground equipment, residues of the metals could be absorbed and retained in the material and followed with slow leaching from the mulch. All three of the leaching studies described above are suitable to show that residues of copper, chromium, and arsenic leach from treated wood onto the soil under playground equipment and decks constructed of treated wood. Additional studies would be desirable, which reflect the use of CCA-treated wood in playground equipment, specifically, studies designed to sample soils beneath/adjacent to CCA-treated playground structures from different (representative) geographic regions of the United States.

2.2.4.4 Environmental Fate

Many studies in the recent literature (Lebow, 1996; Stilwell and Gorny, 1997; Stilwell, 1998; Townsend et al., 2001; Osmose, 2000) report data regarding leaching of CCA into soils. These studies support that the three metals, copper, chromium and arsenic are not expected migrate large distances (twelve inches vertically and three inches laterally) from the treated wood structure. Some studies have shown that the contamination level is elevated in the soil compared to the natural background levels of these metals. Such studies support that metals can be persistent in the soils, particularly on the soil surfaces, and can result in environmental exposure. The metals show various speciation characteristics in soils, depending on the types of soil.

The metals migrating into water bodies can result in aqueous contamination. Metals also show a tendency to speciate in water, and various species will be present in water depending on the pH of water as well as the salinity. If water is highly acidic, the leaching rates and amounts of leachates will be expected to increase. Generally, in soil and water, the amounts of metals released are in the order of Cu > As > Cr. In some recent cases it has been shown that the order of release rates is: As > Cu > Cr. In all cases, the amounts of chromium released are the least of the three metals

Numerous studies on bioaccumulation in various aquatic organisms have also been carried out over a period of time. A number of these aquatic species have shown a degree of bioaccumulation, and toxic effects have been observed. The studies were conducted under varying conditions and very few studies reported depuration rates.

An overall robust fate assessment cannot be made at this time, as the studies were conducted under different laboratory or field conditions that were not standardized. Hence, while at this time the exposure and hazards of these metals on humans, plants, and aquatic organisms can be determined, a complete fate assessment is not possible.

2.2.5 CCA Use and Potential Exposures to Components of CCA

The Agency is aware of potential exposure concerns to arsenic and chromium components of CCA-treated wood that has been used to build decks and playground structures, along with contaminated soils commonly found in these settings. During the pressure treatment of wood, CCA undergoes a fixation process where it initially is absorbed into the cellulosic and lignin structures of the wood. Chromium in the form of Cr (VI) attaches itself to the 'carboxylic groups' of the cellulosic structure and converts into Cr (III). Copper arsenate converts into basic copper arsenate. In pressure-treated wood, arsenic leaches to the surface of the wood mostly as As (V), but there may be some As(III). Chromium leaches mostly as Cr (III); however, trace amounts of Cr (VI) may also be present. Copper is present as Cu (II) (U.S. EPA, 2001b).

Of the components in CCA, copper does not pose significant toxicity concerns compared to arsenic and chromium. Copper is an essential nutrient that functions as a component of several enzymes in humans, and the toxicity of copper in humans involves consumption of water contaminated with high levels of copper (U.S. EPA, 2001b). Because of the relatively low toxicity of copper, the Agency did not conduct an exposure/risk assessment for copper. For chromium, hazard data clearly show that Cr (VI) demonstrates more significant toxicity than Cr (III). Thus, the Agency believed that it would not be credible to apply Cr (VI) toxicity endpoints to Cr (total) residue results to assess incidental ingestion and dermal exposures in children. Since the Agency has not identified any endpoints of concern for Cr (III), the short-term intermediate-term and lifetime risks to Cr (III) are not presented.

2.2.6 Probabilistic Risk Assessment (PRA) versus Deterministic Risk Assessment

A probabilistic assessment (i.e., using SHEDS-Wood) was conducted to evaluate exposure to CCA (Zartarian et al., 2003, 2005). A probabilistic exposure assessment uses

probability distributions for one or more variables in an exposure equation in order to quantitatively characterize variability and/or uncertainty. A Monte Carlo Analysis (MCA) is perhaps the most widely used probabilistic method. MCA uses computer simulations to combine multiple probability distributions in exposure or risk equations. In contrast, a deterministic assessment uses point estimates for each of the variables in the exposure algorithm. The result is a single estimate of exposure dose. The output of a probabilistic assessment is a probability distribution of exposures that reflects the combination of the input probability distributions. If the input distributions represent variability, then the output distribution can provide information on variability in the population of concern. The input/output uncertainties of this assessment are discussed in Zartarian et al. (2003, 2005). If the input distributions reflect uncertainty, then the output distribution can provide information about uncertainty in the estimate. Information from SHEDS-Wood can be used in combination with toxicity data to form a probabilistic risk assessment (PRA). The PRA can be used to make statements about the likelihood of exceeding a risk level of concern, given the estimated variability in elements of the risk equation. Since the results of point estimate methods generally do not lend themselves to this level of risk characterization (e.g., quantitative uncertainty assessment), the PRA can provide unique and important supplemental information that can be used in making risk management decisions. Table 2-3 summarizes the key differences between deterministic and probabilistic risk assessment methods. This table clearly supports why a probabilistic risk assessment was conducted in assessing the risks from CCA-treated deck and playground equipment.

Table 2-3. Comparison of Deterministic and Probabilistic Risk Assessments

Category	Deterministic Risk Assessment	Probabilistic Risk Assessment
Data Input	Pesticide concentrations and potential exposure factors are expressed as single point estimates.	Takes into account all available information and considers the probability of an occurrence.
Risk Estimates	Expressed as a single point value. The variability and uncertainty of the value is not reflected.	Expressed as a distribution of values, with a probability assigned to each value. Distribution reflects variability and can provide risk manager with information helpful to determine what particular range of the risk estimate distribution most closely represents real life scenarios.
Resources	Less time and not resource intensive, calculation is relatively simple, but provides little information about the proportion of the population receiving the estimated exposure.	May require more time and resources for seeking credible software to use for specific site.
Methods	Useful for screening method - easily described.	More complicated for risk manager who may need time to understand the methodology.
Risk Communication	Single point risk estimates are often viewed as “the answer”; public perception may be misled.	Communication of uncertainty in the risk assessment can help to build trust among stakeholders.

Table 2-3. Comparison of Deterministic and Probabilistic Risk Assessments		
Category	**Deterministic Risk Assessment**	**Probabilistic Risk Assessment**
Uncertainties	Qualitative; importance of variability is sometimes lost.	Provide quantitative information and a more comprehensive characterization of variability associated with in input parameters.
Regulatory Concern	Does not quantify the probability that the risk estimate exceeds a regulatory level of concern.	Can identify the data gaps for further evaluation/data collection and can use wider variety of site-specific information.
Data Analysis	May not utilize all available data for characterizing variability and uncertainty in risk estimates; provides fewer incentives for collecting better and credible information	Complete use of available data when defining inputs to the risk equation; and can provide more comprehensive characterization of variability in risk estimates.
Sensitivity Analysis	Only limited to dominant exposure pathways and chemical of concern	Can identify the exposure variables, probability models, and model parameters that influence the estimates of risk.

EPA recognizes that there are many parameters that affect the level of potential exposure and that each of these parameters may vary. Probabilistic (e.g., Monte Carlo) techniques are capable of using multiple data sets which reflect the variability of parameters to produce estimates of the distribution of potential exposures. OPP has identified a number of data sets that contain information on the variability of parameters affecting the levels of exposure to CCA residues experienced by children as a result of their playground activities.

Children playing on decks and playgrounds that are built out of CCA pressure treated wood can be exposed to arsenic and chromium residues on wood surfaces and soils via oral and dermal routes. OPP has considered four proposed exposure scenarios individually in their previous assessment; however, to more comprehensively assess risks to children from exposure to arsenic as a result of contact with wood and soil found at CCA treated decks and playgrounds. All four of the scenarios must be considered concurrently, and PRAs present the most flexible tool for this type of consideration. The advantages of conducting a probabilistic risk assessment are as follows:

- PRAs more comprehensively address the distributions and variability of multiple sets of data in both inputs and outputs;
- PRAs offer more in depth analysis of uncertainty for both inputs and outputs;
- PRAs present the most flexible tool to examine combined activities concurrently; (e.g., for residential exposure, children may be exposed to residues from playsets decks, and soil concurrently);
- PRAs allow for more subsets of data (e.g., warm or cold environments, hand washing, bathing, etc.) and allow the user to separate the data and consider different exposure considerations;
- PRAs characterize more of the statistical uncertainties and special sensitivities for

certain population groups (e.g., pica children);

- PRAs may show the actual shape of the composite distribution. For example, the actual distributions of the data may be lognormal instead of normal distribution;
- PRAs account for covariance between variables. The variance of the product could be inflated if there is a positive correlation between the variables;
- PRAs show the influence of a particular data set on the exposure, and graphically depict the data;
- PRAs show the distributional quartiles;
- PRAs use sophisticated software that can reproduce the calculation quickly and accurately;
- PRAs allow for a comprehensive sensitivity analysis that can identify the exposure variables, probability models, and model parameters that influence risk; and
- PRAs more accurately quantify the upper bound high-end percentile of total risk to more accurately help the risk managers make decisions based on the data.

2.2.7 EPA and OPP Regulatory Approach to PRA

Agency policy is that risk assessments should be conducted in a tiered approach, proceeding from simple to more complex analyses as the risk management situation requires (Agency Policy Document, 5/15/97)(U.S. EPA, 1998a). More complex analyses require greater resources, and probabilistic assessments can represent high levels of complexity. In a deterministic assessment, exposure is expressed as a single value, which could represent an upper-bound scenario or a central tendency. If a deterministic analysis, based on conservative assumptions, leads to risk estimates that are below levels of concern, then there is no need to refine risk assessments with more complex techniques (U.S. EPA, 1998a). However, if a conservative deterministic assessment leads to estimates above the level of concern, more sophisticated risk assessments may be warranted.

Probabilistic techniques offer a higher level of sophistication. In contrast to deterministic techniques, probabilistic risk assessments more fully considers ranges of values regarding potential exposure, and then weighs possible values by their probability of occurrence. Individual input values used to generate a point estimate are replaced by a distribution reflecting a range of potential values; a computer simulation then repeatedly selects individual values from each distribution to generate a range and frequency of potential exposures. In accordance with Agency policy at this current time, such techniques will not be considered for dose-response evaluations of toxicological data (U.S. EPA, 1998a), but are limited to exposure assessments.

3.0 EXPOSURE ASSESSMENT

Note: This chapter only provides a summary of the SHEDS-Wood exposure doses used for the risk assessment. For the detailed probabilistic SHEDS-Wood exposure assessment please refer to Zartarian et al. (2005), *A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks*, Final Report, February, 2005.

SHEDS-Wood, a probabilistic exposure model developed by ORD, was used to generate

the exposure assessment for CCA. The exposure assumptions, pathways, exposure routes, algorithms, and methodologies for this model are explained in detail in an exposure report prepared by ORD and OPP. ORD released the final report on EPA's website on Sept 27, 2005 (A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks, dated Feb 2005). http://www.epa.gov/heasd/sheds/CCA_all.pdf (Zartarian et al, 2005). In addition, supplemental guidance on the SHEDS Wood model was also published (Zartarian et al, 2006 and Xue et al., 2006) in 2006 by ORD.

This exposure chapter presents an updated version of original exposure chapter that is in the preliminary draft report entitled "A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks (dated November 10, 2003). http://www.epa.gov/scipoly/sap/meetings/2003/december3/shedsprobabalisticriskassessmentnov03.pdf

A general introduction to the exposure assessment approach in this model is described in the narrative below. It should be noted that subsequent to the release of the ORD SHEDS assessment (Zartarian et al, 2005), the Human Studies Rule was published. As a result, the Kissel (1998) study which was used to develop the skin surface area contact rate in SHEDS was deemed inappropriate to cite. ORD updated the SHEDS exposure data by using a new contact rate from the NHEXAS MN study (ethics of study also under review). Thus, the exposure doses presented in Zartarian et al. (2005) have all been updated by ORD in December 2007 and the exposure values although close are no longer relevant for this risk assessment. This chapter discusses this change and also includes the new ORD exposure spreadsheets updated in December 2007 (Appendix C) and the revised calculation of risks (Chapter 5.0).

SHEDS-Wood evaluates child exposures based on four scenarios: dermal contact with CCA-treated wood and CCA-contaminated soil near treated wood structures, mouthing hands after touching CCA-treated wood, and ingesting CCA-contaminated soil. SHEDS-Wood was used to evaluate potential short-term, intermediate-term, and lifetime exposures to arsenic and chromium. The potentially exposed population for this assessment are children in the United States who contact CCA-treated wood and/or CCA-containing soil from public playsets (e.g., at a playground, a school, a daycare center). A subset of these children was also assumed to contact CCA-treated wood residues and/or CCA-containing soil from residential playsets (i.e., at the child's own home or at another home) and/or residential decks (i.e., at the child's own home or another home). This population was selected because of the particular focus by CPSC and other groups on playground playsets in conjunction with EPA's focus on estimating the risk to children from various primary sources of CCA-treated wood that children may contact (U.S. EPA, 2003a).

Two bounding estimate climate scenarios (warm throughout the year and cold throughout the year) were considered, as well as three exposure time periods: short-term (one day to one month), intermediate-term (one month to six months), and lifetime (6 years over a 75 year lifetime). SHEDS-Wood calculated the predicted exposure and dose to arsenic and chromium using age and gender representative time-location activity data for 1-6 year old children.

It should be noted that an adjustment was made to SHEDS-Wood chromium ADDs/LADDs. Chromium ADDs calculated by SHEDS-Wood represent only total chromium (e.g., combination of Cr (III) and Cr (VI)). The Agency and the FIFRA SAP were concerned that assessing total chromium doses would overestimate the exposure. The FIFRA SAP was asked by OPP for information to differentiate chromium species found in CCA dislodgeable residues on wood surface and species. Some panel members suggested that 5 to 10% of total chromium could be used to represent Cr (VI) (U.S. EPA, 2001b). OPP agreed that 10% would be conservative enough and decided to use this estimate in the risk assessment. Therefore, for total chromium in soil, OPP adjusted the ADDs by multiplying by 0.10 (10%) to account for Cr (VI) speciation. In addition, OPP only assessed soil exposures. As previously mentioned in Chapter 2.0 (Introduction and Background) along with Chapter 4.0 (Hazard Assessment), wood surface residue exposure doses for Cr (VI) were not assessed in this assessment. EPA has supplemented this chapter by providing lifetime average daily doses (LADDs) since a new cancer slope factor was developed.

Adjustment of the Skin Surface Area Contact Rate in SHEDS

Because of EPA Human Subjects Review Board issues with the fluorescent tracer study (Kissel et al., 1998) that was used to estimate skin surface area contact rate in the SHEDS-Wood CCA exposure assessment (Xue et al., 2006; Zartarian et al., 2005, 2006), OPP requested ORD to develop an alternative approach for estimating this exposure factor as part of OPP's final CCA risk assessment based on the SHEDS-Wood exposure estimates. Thus, the following equation was developed for use in revised SHEDS-Wood CCA exposure estimates:

HAS=1-(1-avgArea)^H_freq,

where:

HAS = Hand contact rate (fraction) during 20 minutes
avgArea: averaged contact area of skin per contact
H_freq: frequency of contact during 20 minutes

For the H_freq term, hand-to-playset contact information from videotapes of four 5-7 year-old children (Natalie Freeman, personal communication) in the NHEXAS MN Children's Study (Freeman et al., 2001) was used instead. The duration of the videotape activities for the four children ranged from 14 to 49 minutes. Left hand-to-playset contact frequency ranged from 13-52 contacts during videotaping, and right hand-to-playset contact frequency ranged from 13-55 contacts during videotaping. For the avgArea term, 20% hand surface area was assumed for a given hand-to-playset contact (best estimate in the absence of available data). These assumptions lead to HAS=0.99, 0.98, 0.88 and 0.50 for the 4 sets of NHEXAS MN children's videotapes. Using these 4 points, a triangular distribution (0.5, 0.9, 0.99) was developed for a hand-to-surface contact rate (1/20 min). Furthermore, it was assumed that unclothed non-hand skin has 25% the contact rate as the hands, which leads to a triangular distribution (0.5/4, 0.9/4, 0.99/4) for the non-hand body-to-surface contact rate.

A simulation of 1000 individuals for the hand and body triangular distributions was

conducted, and the two sets of 1000 numbers were fitted into beta distributions: Beta(10,2.5) for hand-to-surface contact rate per 20 minutes and Beta(42,166) for body-to-surface contact rate per 20 minutes. Table 3.1 presents summary statistics of contact rate (fraction) by hand and body for children, using the original SHEDS-Wood inputs based on Kissel et al. 1998 and the new inputs based on the playset videography data. Figure 3-1 shows the CDFs for the hand- and body- to surface contact rates using the original and revised estimates. All the exposure assumptions used in SHED-Wood are summarized in Table 3-2.

Table 3-1 Summary Statistics of Contact Rate (fraction) by Hand and Body for Children

body part	n	mean	STD	min	p50	max
hand (new)	1000	0.8	0.11	0.32	0.82	0.99
body (new)	1000	0.2	0.03	0.13	0.2	0.29
hand (old)	1000	0.74	0.12	0.31	0.75	0.97
body (old)	1000	0.17	0.08	0.01	0.16	0.49

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Fraction of children with a CCA-treated home playset [-]		point (0.08)						Agency-derived estimate based on personal communications with IPEMA. CFA. USPIRG
Average fraction of residential outdoor time a child plays on/around a CCA-treated residential playset (on days when the child plays on/around a CCA-treated residential playset) [-]	WARM	beta (1.1.0.36)	0.753	0.275	0.870	0.588	0.981	based on CHAD diary data
	COLD	beta (1.3.0.34)	0.793	0.249	0.905	0.669	0.988	"
Average #days/yr children play on/around a residential CCA-treated playset [days/yr]	WARM	point (126)						Agency-derived estimate based on SCS-II play day data and rain day assumptions
	COLD	point (54)						"
Average fraction of non-residential outdoor time a child plays on/around a CCA-treated public playset (on days when the child plays on/around a CCA-treated public playset)[-]	WARM	beta (1.1.0.36)	0.753	0.275	0.870	0.588	0.981	based on CHAD diary data
	COLD	beta (1.3.0.34)	0.793	0.249	0.905	0.669	0.988	"
Average #days/yr children play on/around a CCA-treated public playset [days/yr]	WARM	point (126)						Agency-derived estimate based on SCS-II play day data and rain day assumptions
	COLD	point (54)						"
Fraction of time a child plays on/around a CCA-treated playset is on the playset itself versus on the ground near the playset [-]		beta (12.35.12.12)	0.505	0.0990	0.505	0.436	0.573	Agency-derived estimate

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment Continued).

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Fraction of children who have a CCA-treated residential deck [-]		point (0.5)						Shook and Eastin (1996); U.S. Census (2000)
Average fraction of residential outdoor time a child plays on/around a CCA-treated residential deck (on days when the child plays on/around a CCA-treated residential deck) [-]	WARM	beta (1.1.0.36)	0.753	0.275	0.870	0.588	0.981	based on CHAD diary data
	COLD	beta (1.3.0.34)	0.793	0.249	0.905	0.669	0.988	"
Average #days/yr children play on/around a CCA-treated residential deck [days/yr]	WARM	point (126)						Agency-derived estimate based on SCS-II play day data and rain day assumptions
	COLD	point (54)						"
Fraction of time a child on/around a CCA-treated home deck is on the deck versus on the ground near the deck [-]		beta (39.2.4.3)	0.901	0.0448	0.907	0.875	0.934	Agency-derived estimate
Soil arsenic concentrations near CCA-treated playsets ($C_{soil,playset}$) [mg/kg]	WARM	lognormal (29.97.1.643)	33.9	17.9	30.0	21.4	41.9	Solo-Gabriele et al. (2001)
	COLD	lognormal (1.6.3.68)	3.74	7.90	1.60	0.663	3.85	Riedel et al. (1991)
Soil chromium concentrations near CCA-treated playsets ($C_{soil,playset}$) [mg/kg]	WARM	lognormal (32.38.1.88)	39.5	27.7	32.4	21.1	49.6	Solo-Gabriele et al. (2001)
	COLD	lognormal (6.7.3.9)	16.9	39.2	6.69	2.67	16.8	Doyle and Malaiyandi (1992)
Wood surface arsenic residues on CCA-treated playsets ($SR_{wood,playset}$) [µg/cm^2]	WARM	lognormal (0.228.2.24)	0.316	0.304	0.228	0.133	0.394	ACC (2003b)
	COLD	lognormal (0.258.1.97)	0.325	0.249	0.258	0.163	0.407	ACC (2003b); CPSC (2003a,b)*

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment Continued)

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Fraction of children who have a CCA-treated residential deck [-]		point (0.5)						Shook and Eastin (1996); U.S. Census (2000)
Average fraction of residential outdoor time a child plays on/around a CCA-treated residential deck (on days when the child plays on/around a CCA-treated residential deck) [-]	WARM	beta (1.1.0.36)	0.753	0.275	0.870	0.588	0.981	based on CHAD diary data
	COLD	beta (1.3.0.34)	0.793	0.249	0.905	0.669	0.988	"
Average #days/yr children play on/around a CCA-treated residential deck [days/yr]	WARM	point (126)						Agency-derived estimate based on SCS-II play day data and rain day assumptions
	COLD	point (54)						"
Fraction of time a child on/around a CCA-treated home deck is on the deck versus on the ground near the deck [-]		beta (39.2.4.3)	0.901	0.0448	0.907	0.875	0.934	Agency-derived estimate
Soil arsenic concentrations near CCA-treated playsets ($C_{soil,playset}$) [mg/kg]	WARM	lognormal (29.97.1.643)	33.9	17.9	30.0	21.4	41.9	Solo-Gabriele et al. (2001)
	COLD	lognormal (1.6.3.68)	3.74	7.90	1.60	0.663	3.85	Riedel et al. (1991)
Soil chromium concentrations near CCA-treated playsets ($C_{soil,playset}$) [mg/kg]	WARM	lognormal (32.38.1.88)	39.5	27.7	32.4	21.1	49.6	Solo-Gabriele et al. (2001)
	COLD	lognormal (6.7.3.9)	16.9	39.2	6.69	2.67	16.8	Doyle and Malaiyandi (1992)
Wood surface arsenic residues on CCA-treated playsets ($SR_{as,playset}$) [µg/cm^2]	WARM	lognormal (0.228.2.24)	0.316	0.304	0.228	0.133	0.394	ACC (2003b)
	COLD	lognormal (0.258.1.97)	0.325	0.249	0.258	0.163	0.407	ACC (2003b); CPSC (2003a,b)*

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment Continued)

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Chromium residue-skin transfer efficiency ($TE_{surface}$) [-]	WARM	lognormal (0.106,2.33)	0.152	0.155	0.106	0.0599	0.187	ACC (2003b) warm weather data. dividing hand load data by wood load data
	COLD	lognormal (0.140,2.45)	0.209	0.234	0.140	0.0764	0.256	ACC (2003b) cold weather data (hand wipe divided by wood wipe)
Fraction of total body (non-hand) skin surface area that is unclothed ($F_{unclothed\ body}$) [-]	WARM	beta (3,6.7)	0.309	0.141	0.295	0.202	0.402	U.S. EPA (2002) for % total SA by body part: Wong et al. (2000) for assumed % of body part exposed to soil: O'Rourke(2003) for clothing scenarios
	COLD	point (0.05)						assumed only face exposed other than hands: Wong et al. (2000)
Fraction of hand skin S.A. contacting residues per time ($F_{contact\ res.\ hand}$) [per 20 min]		beta (10, 2.5)	0.80	0.11	0.82	0.73	0.88	Freeman et al., 2001
Fraction of unclothed body (non-hand) skin S.A. contacting residues per time ($F_{contact\ res.\ body}$) [per 20 min]		beta (46, 166)	0.20	0.03	0.20	0.18	0.22	Freeman et al., 2001
Fraction of hand skin S.A. contacting soil per time ($F_{contact\ soil\ hand}$) [per 20 min]		beta (10, 2.5)	0.80	0.11	0.82	0.73	0.88	Freeman et al., 2001.

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment Continued)

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Fraction of unclothed body (non-hand) skin S.A. contacting soil per time $(F_{soilskin,soilbody})$ [per 20 min]		beta (46. 166)	0.20	0.11	0.20	0.18	0.22	Freeman et al.. 2001
Daily soil ingestion rate (IR_{soil}) [mg/day]	Typical child	lognormal (31.4). <500 mg/day	80.6	80.5	29.8	11.9	73.4	Stanek and Calabrese (2000): Stanek et al. (2001)
	Pica child	lognormal (31.4). >500 mg/day	962.	758.	735.	590.	1046.	ATSDR (2001)
Soil-skin adherence factor $(Adh_{soil-skin})$ [mg/cm^2]		lognormal (0.11.2)	0.140	0.109	0.110	0.0688	0.175	Holmes et al. (1999): Kissel et al. (1996)
Fraction of hand surface area mouthed per mouthing event $(F_{hand-mouth})$ [-]		beta (3.7.25)	0.129	0.0615	0.120	0.0834	0.165	Leckie et al. (2000) data for frequency of mouthing events for different surface area categories. and assuming each finger 10% of hand. surface area palm mouthed 25%. 1 partial finger 5%
Frequency of hand-mouth activity per hour (N_{hm}) [-]		Weibull (0.73.6.93)	8.45	11.75	4.21	1.27	10.86	Leckie et al. (2000): Zartarian et al. (1998): Reed et al. (1999): Tulve et al. (2002)
Average # of hand-washing events per day [#/day]		lognormal (3.74.2.63)	5.96	7.43	3.73	1.95	7.17	Wong et al. (2000): Tsang and Klepeis (1996): Freeman et al. (2001): Kissel (2003)
Hand-washing removal efficiency (F_{hw}) [-]		beta (32.22)	0.593	0.0662	0.594	0.548	0.638	Wester et al. (1993)
Bathing removal efficiency (F_{bath}) [-]		beta (17.1.5.1)	0.770	0.0874	0.778	0.715	0.834	Wester et al. (1993)

Table 3-2 Summary of SHEDS-Wood Input Values and Selected Variability Distributions for CCA Exposure and Dose Assessment Continue)

SHEDS-Wood Input Variable for CCA Assessment	Scenario	Selected Variability Distribution	Mean	Stdev	Median	p25	p75	Comments
Hand-to-mouth dermal transfer fraction ($F_{hm\text{-}ramov}$) [-]		beta (14.5,4.1)	0.780	0.0935	0.790	0.721	0.849	based on triangular using Camann et al. (1995) data; Lewis (2003) personal communication; and 100% as min, mode, and max
Dermal absorption rate for arsenic residues ($AbsR_{dermal,res}$) [1/day]		beta (50,1611)	0.0301	0.0042	0.0299	0.0272	0.0328	Wester et al. (1993); FIFRA SAP (2001)
Dermal absorption rate for arsenic in soil ($AbsR_{dermal,soil}$) [1/day]		beta (50,1611)	0.0301	0.0042	0.0299	0.0272	0.0328	Wester et al. (1993); FIFRA SAP (2001)
Dermal absorption rate for chromium residues ($AbsR_{dermal,res}$) [1/day]		point (0.01)						FIFRA SAP (2001)
Dermal absorption rate for chromium in soil ($AbsR_{dermal,soil}$) [1/day]		point (0.01)						FIFRA SAP (2001)
GI absorption rate for arsenic residues ($AbsR_{ingest,res}$) [1/day]		beta (4.7,12.5)	0.273	0.105	0.264	0.197	0.341	ACC (2003c)
GI absorption rate for chromium residues ($AbsR_{ingest,res}$) [1/day]		point (1.0)						FIFRA SAP (2001)
GI absorption rate for arsenic in soil ($AbsR_{ingest,soil}$) [1/day]		beta (11.4,13)	0.467	0.0989	0.466	0.398	0.535	ACC (2003d)
GI absorption rate for chromium in soil ($AbsR_{ingest,soil}$) [1/day]		point (1.0)						FIFRA SAP (2001)

Notes for Table 3-2

(1) “Child” and “children” refer to children 1–6 years old in the United States who contact CCA-treated wood residues and/or CCA-containing soil from public playsets (e.g., at a playground, a school, a daycare center), at a minimum. A subset of these children also contacts CCA-treated wood residues and/or CCA-containing soil from residential playsets (i.e., at the child’s own home or at another child’s home) and/or residential decks.

(2) Playing “around” a wood structure (i.e., playset or deck) is defined as play within 2 feet of the structure, since that is the distance in which CCA-contaminated soil has been identified.

(3) A non-residential location refers to CHAD locations where it is assumed that a public CCA-treated playset may be present.

(4) The variability distributions are parameterized as follows:

Lognormal (a, b) indicates a lognormal distribution with geometric mean exp(:) = a and geometric standard deviation exp(F) = b. Under a logarithmic transformation, this is a normal (:, F) distribution.

Beta (a, b) indicates a beta distribution with minimum=0 and maximum=1, with PDF given by $f(x) = x^{a-1} (1-x)^{b-1} ' (a+b) / ('(a) '(b))$, for $0<= x <=1$.

Weibull (a,b) indicates a Weibull distribution with shape parameter ‘a’ and scale parameter ‘b’. The PDF is $f(x) = a\, b^{-a}\, x^{a-1}\, \exp[(-x/b)^{a}]$

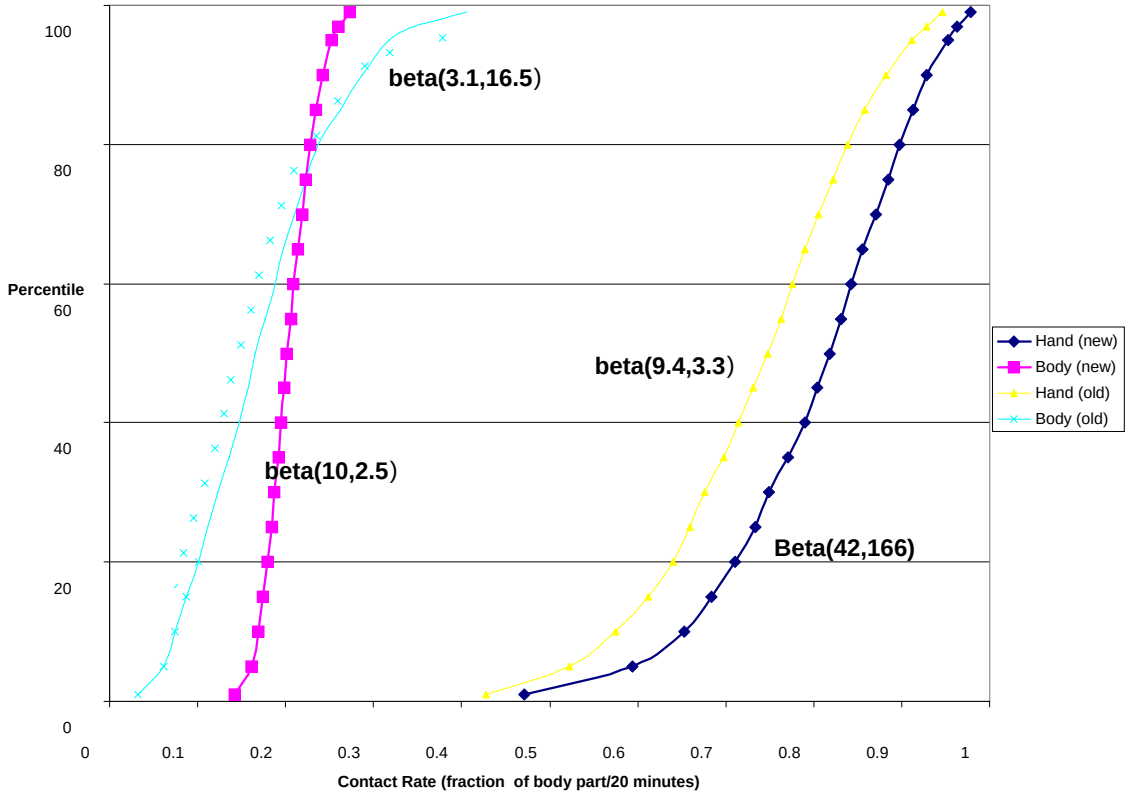
No statistical population parameters are provided for variables that are set to point values.

(5) A point estimate means that the same number is used for all persons in the simulation.

(6) “Agency-derived best estimate” means that no data were available and the best professional judgment of the exposure assessors was used.

(7) In combining CPSC and ACC data for the transfer efficiency and deck residues in the cold climate scenario, only data from phase 3 of the CPSC study was used since it applied similar methods to collect data as the ACC study (sample size 348). There are 32 observations in the CPSC study and those data were merged with data collected from Pennsylvania for the cold weather climate scenario. No statistically significant difference was found between the distributions for the maximum dermal loading, deck residue concentration, and transfer efficiency variables.

Figure 3-1. Contact rate on playsets by children by hand and body



Tables 3-3 through 3-8 summarize the total average daily doses and lifetime average daily doses (ADD/LADD) exposure doses for arsenic and chromium used in the risk characterization (see Chapter 5.0) chapter. Appendices B-D provide the updated model runs for SHEDS-Wood.

Table 3-3. Arsenic ADDs (mg/kg/day) - Playsets and Decks[a]

Time Frame[b]	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	1.4E-04	6.7E-05	6.3E-05	2.8E-05	5.1E-04	2.5E-04	1.1E-03	5.5E-04
Intermediate	1.4E-04	7.4E-05	6.7E-05	3.1E-05	5.1E-04	2.6E-04	1.1E-03	7.7E-04

a. The ADD's represent the mean, median, 95%ile, and 99%ile total doses for both warm and cold climate residue and soil data for playsets and decks.
b. Time frame considers short-term (1 day to 1 month) and intermediate-term (1-6 months) exposures.

Table 3-4. Chromium (Cr (VI)) ADDs (mg/kg/day) - Playsets and Decks[a,b]

Time Frame[c]	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	5.1E-07	9.7E-08	1.2E-07	1.4E-08	2.0E-06	3.8E-07	7.0E-06	1.3E-06
Intermediate	4.1E-07	8.7E-08	1.1E-07	1.6E-08	1.6E-06	3.5E-07	4.4E-06	1.2E-06

a. The exposure doses represent soil ingestion exposure only for Cr (VI).
b. The ADD's represent the mean, median, 95%ile, and 99%ile total doses for both warm and cold climate soil ingestion data for playsets and decks.
c. Time frame considers short-term (1 day to 1 month) and intermediate-term (1-6 months) exposures.

Table 3-5. Arsenic ADDs (mg/kg/day) - Playsets Only[a]

Time Frame[b]	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	1.0E-04	5.1E-05	3.9E-05	1.3E-05	3.6E-04	2.0E-04	1.1E-03	5.9E-04
Intermediate	8.3E-05	4.0E-05	3.2E-05	1.3E-05	3.0E-04	1.6E-04	9.3E-04	3.9E-04

a. The ADD's represent the mean, median, 95%ile, and 99%ile total doses for both warm and cold climate residue and soil data for playsets only.
b. Time frame considers short-term (1 day to 1 month) and intermediate-term (1-6 months) exposures.

Table 3-6. Chromium (Cr (VI)) ADDs (mg/kg/day) - Playsets Only[a,b]

Time Frame[c]	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	5.2E-07	8.6E-08	1.1E-07	8.2E-09	2.1E-06	3.5E-07	6.6E-06	1.5E-06
Intermediate	4.7E-07	8.1E-08	9.2E-08	8.7E-09	2.1E-06	3.7E-07	5.8E-06	1.3E-06

a. The exposure doses represent soil ingestion exposure only for Cr (VI).
b. The ADD's represent the mean, median, 95%ile, and 99%ile total doses for both warm and cold climate soil ingestion data for playsets only.
c. Time frame considers short-term (1 day to 1 month) and intermediate-term (1-6 months) exposures.

Table 3-7. Arsenic LADDs (mg/kg/day)[a]								
Scenario	**Mean**		**Median**		**95%ile**		**99%ile**	
	Warm	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**
Playset and Deck	1.1E-05	5.5E-06	6.3E-06	2.8E-06	3.7E-05	1.8E-05	8.2E-05	3.7E-05
Playset Only	6.0E-06	3.4E-06	3.1E-06	1.5E-06	2.1E-05	1.3E-05	4.2E-05	3.6E-05

a. The LADDs represent the mean, median, 95%ile, and 99%ile total doses for playsets and decks and playsets only in warm and cold climates.

Table 3-8. Chromium VI LADDs (mg/kg/day) [a]								
Scenario	**Mean**		**Median**		**95%ile**		**99%ile**	
	Warm	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**
Playset and Deck	2.9E-08	8.4E-09	1.1E-08	1.9E-09	1.2E-07	3.9E-08	2.3E-07	7.9E-08
Playset Only	5.8E-09	5.8E-09	1.2E-08	1.0E-09	1.4E-07	2.4E-08	3.3E-07	8.8E-08

a The LADDs represent the mean, median, 95%ile, and 99%ile total doses for playsets and decks and playsets only in warm and cold climates.

4.0 HAZARD ASSESSMENT

The purpose of the hazard assessment is to identify available evidence regarding the potential for the chemical of concern to cause adverse effects to the potential receptor (individual) and to provide, where possible, an estimate of the relationship between the extent of exposure to the chemical of concern and increased likelihood and/or severity of the adverse effects.

For non cancer toxic effects, available toxicology data are reviewed and no-observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) are developed for each study. Subsequently, the reviewed data for the chemical of concern are presented to a committee of scientists within OPP who reach concurrence on toxicology endpoints that best represent the toxic effects expected from various routes of exposure and durations of exposure. Endpoints are selected for non-dietary exposures to represent short-term (1-30 days), intermediate-term (30-180 days), and long-term (greater than 180 days) exposure scenarios, as needed. In addition, incidental oral exposure endpoints are selected for short-term and intermediate-term exposure durations to represent ingestion of the chemical of concern 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 chemical of concern.

For carcinogenic effects of a chemical, a slope factor (SF), also know as potency factor, is derived. Slope factors are developed based on a dose-response curve for carcinogenicity of the specific chemicals. The slope factors are developed from human and animal studies and are designed to be health protective. The SF is used to estimate an upper-bound probability of an individual developing cancer as a result of exposure to a potential carcinogen. Carcinogens with EPA-derived slope factors are also given an EPA weight-of-evidence classification, whereby, potential carcinogens are grouped according to the likelihood that the chemical is a human carcinogen, depending on the quality and quantity of carcinogenic potency data for a given chemical.

For the current CCA risk assessment, arsenic and chromium were considered as the primary chemicals of concern. The current policy, Conditions for Acceptance and associated principles are not intended to apply to dose-response evaluations for human health risk assessments until this application has been studied further (Agency Policy Document, 5/15/1997) (U.S. EPA, 1997a). Currently, OPP does not have the Guidance to perform the probabilistic analysis of toxicity endpoints.

For this risk assessment, OPP used the endpoints developed by U.S. EPA. These endpoints were developed using guidance provided by the FIFRA SAP (U.S., EPA, 2001c). As stated in the Agency Policy Document, 5/15/97 (U.S. EPA, 1998a), "For human health risk assessments, the application of Monte Carlo and other probabilistic techniques has been limited to exposure assessments in the majority of cases. The current policy, Conditions for Acceptance and associated guiding principles are not intended to apply to dose-response evaluations for human health risks assessment until this application of probabilistic analysis has been studied further." Currently, OPP does not have guidance available to perform the probabilistic analysis of toxicity endpoints. According to Agency policy, endpoints used in assessments should be consistent with the exposure of concern (acute, subchronic, chronic), and should be those selected by the HED Hazard Identification Assessment Review Committee (HIARC), or selected in accordance with the *Draft Toxicology Endpoint Selection Process: A Guidance Document*, presented to the SAP in February 1997. Thus, point estimates have been used to characterize toxicity for the CCA risk assessment. Toxicology endpoints for both inorganic arsenic and chromium have been selected for the residential exposure assessment and are presented in Sections 4.1 and 4.2, respectively. Summary tables are provided in Section 4.3.

It also should be noted that the studies from Ginsberg (2003) and other researchers, and the recent work on early-life exposures by ORD in the *Draft Final Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2003a) and *Supplemental Guidance for Assessing Cancer for Environment Assessment* (U.S. EPA, 2003b), discussed the criteria for assessing early-life exposure. A discussion of early-life exposures to arsenic is presented in Section 4.4. In addition, a brief discussion of the relative bioavailabilities and dermal absorption values of arsenic and chromium in surface residues and soil are presented in Sections 4.5 and 4.6, respectively.

4.1 Arsenic

Based on the registered use of CCA-treated lumber for fencing and decking materials in residential settings, both incidental oral and dermal exposures are expected. The studies selected for short- and intermediate-term incidental oral exposure were the human case reports of Franzblau and Lilis (1989) and Mizuta et al. (1956). The oral LOAEL of 0.05 mg/kg/day was selected, based on facial edema, gastrointestinal symptoms, neuropathy, and skin lesions observed at this dose level. A Margin of Exposure (MOE) of 30 should be applied to the oral LOAEL. This value consists of a 10x factor for intraspecies variation and a 3x factor for extrapolating from a LOAEL to a NOAEL observed at the LOAEL of 0.05 mg/kg/day (see Appendix A).

Since there were no appropriate dermal studies, the same studies selected for short- and intermediate-term incidental oral exposure were selected for short- (1-30 days) and intermediate- (30-180 days) term dermal exposure scenarios (see Appendix A). OPP did not develop an exposure

assessment for long-term exposures (see Zartarian et al., 2003, 2005). Thus, the oral LOAEL of 0.05 mg/kg/day was selected for dermal exposures, based on facial edema, gastrointestinal symptoms, neuropathy, and skin lesions observed at this dose level. The dermal absorption factor approach used in this assessment does not use a point estimate but uses a range of reported values from the Wester et al. (1993) study which was recommended by the FIFRA Scientific Advisory Panel (U.S. EPA, 2001c). The same MOE of 30 was also selected for dermal exposure. No long-term incidental oral or dermal exposures are expected from residential exposure to arsenic in CCA-treated lumber. At the advice of the SAP, EPA decided not to quantify inhalation exposure to metals since such exposure would be minimal (U.S. EPA, 2001c).

For this risk assessment, an oral cancer slope factor of 3.67 $(mg/kg/day)^{-1}$ was used. This value is based on the Agency's risk assessment associated with inorganic arsenic in drinking water presented in 2000 (U.S. EPA, 2001e, personal communication with Andrew Schulman). It is consistent with the slope factor used by the Office of Water for the arsenic MCL. See Appendix A for more details and discussion regarding the carcinogenic slope factor used. Following the risk assessment associated with inorganic arsenic in drinking water, which was presented in 2000, EPA asked the National Research Council (NRC) to meet again to: (1) review EPA's characterization of potential human health risks from ingestion of inorganic arsenic in drinking water; (2) review the available data on the carcinogenic and non cancer effects of inorganic arsenic; (3) review the data on the metabolism, kinetics and mechanism(s)/mode(s) of action of inorganic arsenic; and (4) identify research needs to fill data gaps. In 2001, NRC published an update to the 1999 NRC report (NRC, 1999) and concluded that: (1) arsenic-induced bladder and lung cancers still should be the focus of arsenic-related cancer risk assessment; (2) southwestern Taiwan data are still the most appropriate for arsenic-related cancer risk assessment; and (3) present modes of action data are not sufficient to depart from the default assumption of linearity. However, the 2001 NRC update made specific recommendations with respect to the overall cancer risk estimates.

The Agency incorporated the NRC's recommendations, and in September 2005 EPA scientists presented the proposed approach in the dose response assessment of cancer effects for inorganic arsenic to the Science Advisory Board (SAB). Linear dose response was selected for inorganic arsenic-induced bladder and lung cancer. The SAB Committee released its final report in 2007 and indicated that the proposed approaches for dose response modeling for the inorganic arsenic cancer assessments is supported by the available information. SAB Concluded southwestern Taiwan data still remain the appropriate dataset for cancer risk. Inorganic arsenic has the potential for a highly complex mode of action in causing different forms of cancer. Indirect genotoxicity suggests a threshold, but studies do not show where the threshold might be or the shape of the dose-response curve at low dose levels. SAB (U.S. EPA 2007) concluded that using of linear model until more is learned about the pharmacokinetics and pharmacodynamics in the causing different forms of cancer in human population.

4.2 Chromium

For chromium, hazard data clearly show that Cr (VI) demonstrates more significant toxicity than Cr (III). During the pressure treatment of wood, CCA undergoes a fixation process where it is initially absorbed into the cellulosic and lignin structures of the wood. Chromium, in the form of Cr (VI), attaches itself to the 'carboxylic groups' of the cellulosic structure and converts into Cr (III)

(U.S. EPA, 2001c). More recent studies by the ACC and RTI International indicate that Cr (III) is the main component in CCA pressure-treated wood (RTI International, 2003; Nico et al., 2003; Cooper, 2003). Based on the non-detectable results of Cr (VI) in the CCA-treated wood in the Cooper (2003) and RTI International (2003) studies, the Agency felt that it was not credible to assign Cr (VI) toxicity endpoints to total Cr surface residue results since evidence indicates that most of the Cr wood surface residues in wood are primarily Cr (III). Therefore, OPP did not assess the risks from incidental ingestion exposures in wood surface residues for children in this assessment. However, the Agency felt that it would be appropriate to assess soil ingestion exposure to Cr (VI) (dermal toxicity endpoints were not identified for Cr (VI)). Therefore, toxicity information to assess soil ingestion exposures to Cr (VI) was required. As discussed in the Exposure Chapter (3.0), the total chromium doses from SHEDS-Wood for soil ingestion were multiplied by 0.10 (10%) to estimate a Cr (VI) equivalent dose. This was done for both short- and intermediate-term chromium doses. Toxicity endpoints for Cr (VI) were then applied to the Cr (VI) equivalent doses to evaluate Cr (VI) risks.

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. The study selected for short- and intermediate-term incidental oral exposure was a developmental toxicity study in the rabbit conducted by Tyl et al. (1991) and submitted to the Agency under MRID #42171201 (see Appendix A for details regarding this study). Based on the Tyl et al. (1991) study, a maternal NOAEL of 0.5 mg/kg/day and a LOAEL of 2.0 mg/kg/day were selected as the short- and intermediate-term toxicity endpoints, based on the increased incidence of maternal mortality and decreased body weight gain (see Appendix A for a complete description of the studies utilized to develop the toxicity endpoints). An MOE of 100 was assigned by OPP for this endpoint (Chen and McMahon, 2007).

The U.S. EPA (1998b) IRIS document on Cr (VI) states that "chromium is one of the most common contact sensitizer in males in industrialized countries and is associated with occupational exposures to numerous materials and processes." In addition, it further states that "dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis." It was determined by the OPP HIARC that quantification of hazard from dermal exposure is not possible for chromium, due to the significant dermal irritation and sensitization observed. EPA selected Concentration of Concern for Dermal Sensitization (CCDS) of 92 ng Cr (VI)/cm^2 and MOE of 1 for assessing the potential risk associated with dermal sensitization for hexavalent chromium on a treated wood surface (McMahon. 2006). However, chromium on the CCA treated playground treated equipment and decks are expected to be already converted into trivalent chromium. Therefore, the dermal sensitization potential of chromium is not evaluated in this risk assessment.

The members in the October 23-25, 2001, FIFRA SAP meeting agreed that the Agency should not consider the inhalation route of exposure for chromium in the risk assessment.

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Program (OPP) classified hexavalent chromium, Cr (VI), as **"Likely to be Carcinogenic to Humans"** based on the presence of oral mucosa and tongue tumors in male and female rats and tumors of the small intestine in male and female mice in the NTP cancer study at

doses that were adequate, but not excessive, to assess carcinogenicity. There is clear evidence that Cr (VI) is mutagenic and sufficient evidence supporting a mutagenic mode of carcinogenic action. The decision is also qualitatively supported by human epidemiological data which indicates an association between exposure and increased stomach tumor incidence. A potency factor of 0.79 $(mg/kg/day)^{-1}$ based on combined adenomas and/or carcinoma incidence of the small intestine (duodenum, jejunum or ileum) in female mice as reported in the NTP two year mouse cancer study was established (Brunsman, 2008). The Office of Pesticide Programs (OPP) decision of establishing the oral slope factor and a mutagenic mode of action for hexavalent chromium was based on the best science available. OPP has briefed other EPA program offices on this decision. OPP recognizes, however, that other program offices are in the process of re-evaluating the existing oral carcinogenicity toxicity information for hexavalent chromium including the Integrated Risk Information System (IRIS). The Agency has announced that hexavalent chromium is one of the candidates to be re-evaluated in the 2008 IRIS agenda (*Federal Register* (Volume 72, Number 245, pp 72715-72719). Thus, OPP acknowledges that the cancer risk assessment and characterization in this document may not necessarily represent other EPA program office assessments when their review processes are completed, particularly if new facts or information arise.

4.3 Summary Tables

All the selected non-cancer toxicological endpoints used for arsenic are summarized in Table 4-1. Table 4-2 presents the toxicological endpoints for Cr (VI). For child exposures in this assessment, only the incidental ingestion and dermal exposure pathways were considered.

Table 4-1. Toxicological Endpoints for Assessing Exposures/Risks to Arsenic (V)

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Incidental Short- and Intermediate- Term Oral [a]	LOAEL= 0.05 MOE = 30	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al. (1989) and Mizuta et al. (1956)
Dermal Short- and Intermediate-Term [a,b]	LOAEL= 0.05 MOE = 30	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al. (1989) and Mizuta et al. (1956)
Carcinogenicity - Oral Ingestion (Oral and Dermal Risks)	Q_1* = 3.67 $(mg/kg/day)^{-1}$	Internal organ cancer (liver, lung and bladder)	Chronic epidemiological oral study on humans

Note:

[a] MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level.

[b] The dermal absorption factor approach used in this assessment does not use a point estimate but uses a range of reported values from the Wester et al. (1993) study which was recommended by the FIFRA Scientific Advisory Panel. The dermal absorptions are incorporated into the SHEDs-Wood model.

Table 4-2. Toxicological Endpoints for Assessing Exposures/Risks to Chromium (VI)			
EXPOSURE SCENARIO	**DOSE (mg/kg/day)**	**ENDPOINT**	**STUDY**
Incidental Short- and Intermediate- Term Oral [a]	NOAEL= 0.5 MOE = 100	Increased mortality and decreased body weight gain in dams at 2.0 mg/kg/day.	Developmental/Rabbit Tyl et al. (1991)
Dermal Short- and Intermediate-Term [b]	Because dermal irritation and dermal sensitization are the primary concern through the dermal exposure route, no toxicological end-point is selected for use in assessing dermal exposure risks to chromium for systemic effects.		
Carcinogenicity - Oral Ingestion (Oral and Dermal Risks)	Q_1* = 0.79 $(mg/kg/day)^{-1}$	Female Mice - Small Intestine (Duodenum, Jejunum or Ileum) adenomas and/or carcinomas combined	NTP two year mouse cancer study (2007)

Note:

[a] MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level.

[b] An oral NOAEL is used for the toxicity endpoint for soil ingestion. Dermal absorption factor of 1% is incorporated into SHEDS-Wood model.

4.4 Early-Life Exposures

Ginsberg (2003) mentions that for "a vast majority of chemicals that have cancer potency estimates on IRIS, the underlying database is deficient with respect to early-life exposures." Ginsberg (2003) concluded that based on the results of his study "short-term exposures in early life are likely to yield a greater tumor response than short-term exposures in adults, but similar tumor response when compared to long-term exposures in adults." The risk attributable to early-life exposure often appears modest compared with the risk from lifetime exposure. It can be about 10-fold higher than the risk from an exposure of similar duration occurring later in life (Ginsberg, 2003).

EPA released the *Final Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). This document mentions the need to address early-life exposures from carcinogens. In addition, ORD has also published the *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b). U.S. EPA (2003b) presents an approach for assessing cancer susceptibility from early-life exposure to carcinogens.

4.4.1 Arsenic

Much toxicity data are available on arsenic; however, the data needed to account for an accurate representation of early-life exposure to arsenic appears to be insufficient. For example, the National Resource Council (NRC, 2001) reports that "few studies of the effects of arsenic on reproduction and development had been published" (NRC, 2001). NRC also concluded "that although a large amount of research is available on arsenic's mode of action, the exact nature of the carcinogenic action is not clear" (NRC, 2001). Finally, NRC concluded that inorganic arsenic and its metabolites have been shown to induce chromosomal alterations and large deletion of mutations, but not point mutations.

Although there is some new evidence indicating that exposure to arsenic from drinking water during pregnancy may be associated with decreased birth weights of newborns (Hopenhayn, 2003) and may increase the cancer incidence of the child in the later stage of life (Waalkes, 2003), the data needed to account for an accurate representation of early-life exposure of arsenic appears to be insufficient (NRC, 2001). However, because the cancer slope factor used in this cancer risk assessment is derived from the epidemiology study using the Southwestern Taiwan data, it is generally believed that the sensitive population exposed to inorganic arsenic through drinking water during the most sensitive period of time is already included in the exposed population. In addition, Science Advisory Board (SAB) concluded "based on available data, it is still not clear whether children differ from adults with regard to their sensitivity to the carcinogenic effects of arsenics." Therefore, an adjustment factor does not appear to be appropriate to apply to the cancer risk assessment associated with arsenic exposure. This conservative assumption is applied to this risk assessment only.

4.4.1 Chromium

It is concluded that children are likely to have an elevated cancer risk to hexavalent chromium (Cr VI) based on the following toxicological evidence. Cr (VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos (Ref?). In addition, Cr (VI) can also penetrate cellular membranes and interact with intracellular mechanisms leading to mutations (EPA, 2005). Based on the potential of Cr (VI) to induce tumors by a mutagenic mode of action, OPP's Cancer Assessment Review Committee (CARC) concluded that the age dependent adjustments factors (ADAFs) should be applied for cancer risk assessments associated with children exposure to hexavalent chromium (Kidwell, 2008). Further guidance and interpretation of ADAFs in early life cancer risk assessment can be found in EPA's Final guidelines for carcinogen risk assessment - Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (EPA, 2005)
The guideline proposed ADAFs are:

- Risk during the first 2 years of life (where the ADAF = 10);
- Risk for ages 2 through < 16 (ADAF = 3); and
- Risk for ages 16 until 70 years (ADAF = 1).

According to EPA's guideline, the 10-fold and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. It is important to emphasize that these adjustments are combined with corresponding age-specific estimates of exposure to assess cancer risk. Under the situation, it is difficult to differentiate the exposure pattern for children from age 1 to 6 for children playing around playground equipment. Thus, as a conservative approach the ADAF of 10 is applied to all children exposure evaluated in this assessment for ages 1 to 6. This conservative approach is for this risk assessment only.

4.5 Relative Bioavailability

The absorption of a chemical of concern is dependent on the matrix to which it is exposed. It is generally assumed that the absorption of the chemical of concern from the gastrointestinal tract is nearly complete. The toxicological endpoints were selected based on the administered dose, not the absorbed dose. However, when the chemical is in a different matrix, it may have a different absorption rate because it may be present in water-insoluble forms or interact with other constituents in the matrix. The relative bioavailability of the chemical of concern, after it is exposed (water vs. soil), was defined as the percentage of the chemical of concern absorbed into the body of a soil-dosed animal compared to that of an animal receiving a single dose of the chemical of concern in an aqueous solution.

The issue of arsenic and chromium relative bioavailability has already been discussed in the October 23-25, 2001, FIFRA SAP Meeting (see comments in Appendix F). The recommendations of the FIFRA SAP for both arsenic and chromium have been incorporated into the SHEDS-WOOD document to develop ADDs and LADDs (Zartanian et al., 2003). A summary of relative bioavailability studies for arsenic is presented in Appendix E.

Arsenic

Zartarian et al. (2003, 2005) used data from ACC (2003a; 2003b) to determine the relative bioavailability for arsenic in the matrix of concern (either CCA-treated wood surface residue or soil collected from areas around CCA-treated wood) vs. arsenic in water. According to Zartarian et al. (2003, 2005), the ACC data were fitted in SHEDS-Wood to a beta distribution, with a mean relative bioavailability of 0.273 (27.3%) for CCA-treated wood surface residue vs. arsenic in water. For arsenic in soil collected from an area close to CCA-treated wood, Zartarian et al. (2003, 2005) fitted the ACC (2003a) data to a beta distribution, with a mean relative bioavailability of 0.476 (47.6%).

Chromium

Zartarian et al. (2003, 2005), per FIFRA SAP (U.S. EPA, 2001c) recommendations, assumed a relative bioavailability of 100% for both chromium surface residues and soil vs. chromium in water.

4.6 Dermal Absorption

Arsenic

Although OPP reported a point estimate for dermal absorption from Wester et al. (1993) in the hazard assessment (see Appendix A), the dermal absorption factor approach used in the Zartarian et al. (2003, 2005) probabilistic exposure assessment, and in this risk assessment, used a range of reported values from Wester et al. (1993). The distribution of values selected from SHEDS-Wood is described in more detail in the SHEDS-Wood probabilistic assessment (Zartarian et al., 2003). It should be noted that the approach used in SHEDS-Wood was consistent with the recommendations of the FIFRA Scientific Advisory Panel (U.S. EPA, 2001c). Wester et al. (1993) *in vivo* results with monkeys ranged from 2.0% to 6.4%. In the OPP 2001 deterministic assessment, OPP used 6.4% and

later also used this for the occupational risk assessment in the reregistration document. The 2001 SAP recommended a value in the range of 3%." For the SHEDS-Wood probabilistic exposure assessment, ORD fit a triangular distribution to the Wester et al. (1993) data (Zartarian et al., 2003, 2005). Zartarain et al. (2003, 2005) also indicated that "It was important to note that because of dermal removal processes (hand washing, bathing, and hand mouthing), the modeled daily absorption rate is lower than the user-specified value. For a 3% per day input, the actual amount absorbed is predicted at about 1% per day. This is consistent with the SAP 2001(U.S. EPA, 2001c) comment that the 2%-3% from the monkey studies may be too high because of real-world removal processes from skin noted above" (Zartarian et al., 2003, 2005).

Chromium

As noted in Section 4.2, dermal irritation and dermal sensitization are still the primary concern for the dermal exposure route. The FIFRA SAP noted that "it is unlikely that sufficient chromium could penetrate the skin and enter the circulation to cause systemic effects from dermal exposure. Skin penetration for chromium is estimated to be 1%. It is usually assumed that the contribution to systemic effects from dermal exposure is not likely to be significant relative to oral exposure."

5.0 RISK CHARACTERIZATION

5.1 Introduction

The objective of the risk characterization was to integrate toxicity data (see Chapter 4.0) with the results of the exposure assessment (Chapter 3.0) to evaluate potential human health impacts to children who are exposed to arsenic and chromium residues while playing on or near CCA-treated wood playgrounds and decks. Children can be exposed to arsenic and chromium residues via hand-to-mouth ingestion and dermal absorption of residues that may be present on the treated wood or in the surrounding soil. This chapter presents the incremental risks from exposure to CCA-treated wood and does not address risks from exposure to all sources of arsenic and chromium in the environment. The probabilistic exposure assessment (Zartarian et al., 2003, 2005) used for this risk assessment was specific for exposure to surface residues from treated wood and surrounding soils.

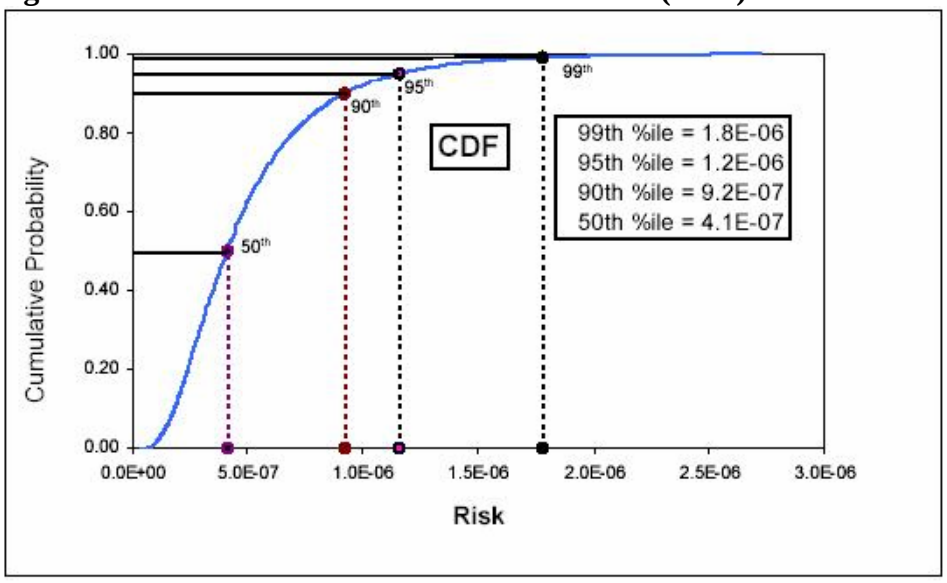
This chapter presents a probabilistic risk characterization. Distributions were used for input variables of the exposure dose algorithm, and the output of the exposure assessment is a distribution of risks across all members of the population. This exposure distribution was combined with toxicity data to provide a risk distribution for members of the exposed population. A hypothetical example of a cumulative distribution function for cancer risk is shown in Figure 5-1. The x-axis of Figure 5-1 represents the excess lifetime cancer risk level and the y-axis represents the cumulative probability of the cancer risk level within the hypothetical population. The figure also shows various landmarks along the distribution curve, such as the 50^{th}, 90^{th}, 95^{th} percentiles, etc. For example, in Figure 5-1, the 95^{th} percentile corresponds to a cancer risk of 1.2E-06 and the 50^{th} percentile corresponds to a cancer risk of 4.1E-07 (U.S. EPA, 2001d).

Risks due to exposure to CCA-treated wood were evaluated for non cancer and cancer effects. Cancer risk refers to the probability of increased cancer incidence resulting from exposure to

proven or suspected carcinogenic chemicals. The magnitude (severity) of a possible adverse consequence for cancer risk is generally expressed in scientific notation (e.g., an individual excess lifetime cancer risk of 1 in 10,000 is represented as 1 x 10-4 or 1E-04, cancer risk of 1 in 100,000 is represented as 1E-05, and cancer risk of 1 in a million is 1E-6). The impact of carcinogenic chemicals was assessed by combining chemical-specific estimates of doses and toxicity values (slope factors) and comparing the estimated risks to specified risk levels.

Non cancer effects were evaluated by calculating the ratio of the NOAEL or the LOAEL to the projected or estimated intake (i.e., dose). The resulting value is termed the Margin of Exposure, or MOE. Typically, the larger the MOE, the more unlikely it is that a non cancer adverse effect would occur. It was cautioned by some of the 2001 SAP Panel members that when the calculated MOE is below the acceptable MOE, it does not necessarily indicate that health effects will occur. The presence or absence of health effects should not be drawn solely on whether there calculated MOEs exceed the acceptable MOEs (U.S. EPA, 2001c). EPA has established a guidance MOE value of 30 for arsenic and 100 for chromium (Cr (VI)) to account for the uncertainties associated with the toxicity data and other factors. Specific to this assessment, arsenic risks were evaluated for non cancer and cancer effects and Cr (VI) risks were evaluated for non cancer effects only.

Figure 5-1: A Cumulative Distribution Function (CDF) for Cancer Risks



The interpretation of results in this risk assessment is somewhat unique. In traditional risk assessments, the intent is to inform risk managers whether or not a pre-established health effects threshold is exceeded. For example, in traditional cancer risk assessment, 1 x 10^{-6} is considered by OPP as the threshold of concern for residential scenarios. If this risk is exceeded, the risk manager then decides which remedial or mitigation measures are to be implemented to reduce the risks to an acceptable level. The intent and nature of this present probabilistic risk assessment is slightly different. The goal of this risk assessment is to present the SAP with the calculated arsenic cancer risks to children (ages 1-6) that are exposed to CCA-treated playsets and decks, through using a probabilistic risk analysis. It also identifies methods (e.g., hand washing) which can reduce the arsenic cancer risks to children. However, there are no concluding statements regarding the

percentiles of the distribution or point estimates (e.g., mean**,** 50^{th}, 90^{th}, 95^{th}, etc) at which risk management decisions will be made.

A probabilistic risk assessment (PRA) is characterized by two quantities:

- the magnitude (severity) of the possible adverse consequence(s), and
- the likelihood (probability) of occurrence of each consequence.

Consequences are expressed as potential cancer risks and the likelihood of occurrence are expressed as probabilities. Figure 5-2 illustrates an estimate of the probability of occurrence of a potential arsenic cancer effect associated with particular risk level of concerns (e.g., cancer risk of 1E-4, 1E-05, and 1E-06) for CCA. A PRA that quantifies variability can be used to address the question, "What is the likelihood (i.e., probability) that risks to an exposed population will exceed 1E-06, 1E-05 and 1E-06?"

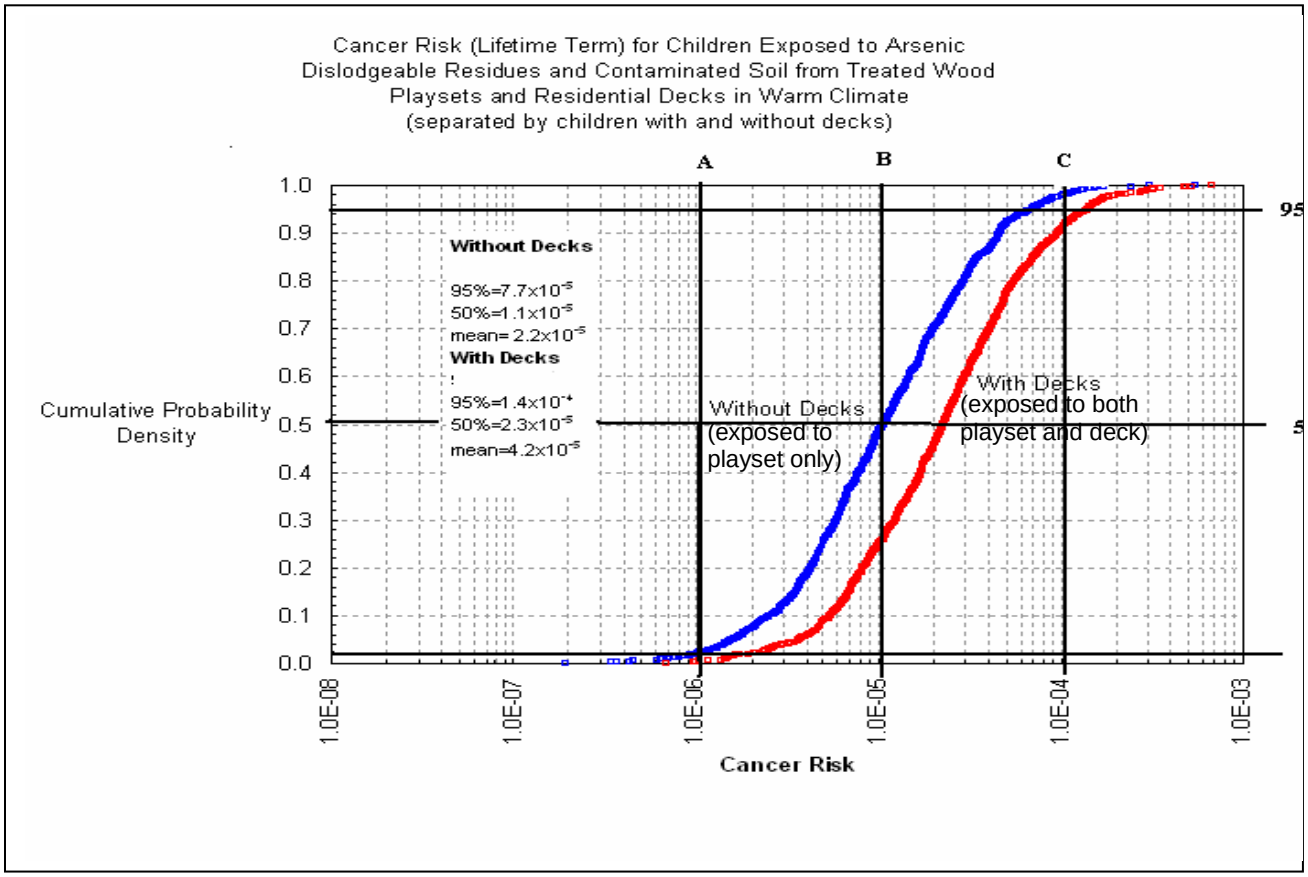
It is important to note that in the traditional deterministic risk assessment that the Agency conducts, risks are expressed as a single value. Typically the Agency expresses cancer risk "as the risk exceeds the target level of 1E-6." For this type of risk assessment, the variability and uncertainty of the value is not reflected. The estimated cancer risk value corresponding to the particular distribution is not presented. Discussions of the value of probabilistic risk assessments vs. deterministic risk assessments are presented in the end of Chapter 2 (see section 2.2.6 and table 2.3). A basic understanding of probabilistic risk assessment process is essential to understanding the risks.

Figure 5-2 depicts the probabilistic cancer risks for children exposed to CCA-treated wood in warm climates. Additionally, the model considered contaminated soil from treated wood. It is concluded from Figure 5-2 that predicted cancer risks exceed 1×10^{-6} for children ages 1-6 at the 2^{nd} percentile (%ile) of the simulated population (point A). This means that under warm climate conditions, 98% of the simulated populations of children have cancer risks that exceed 1×10^{-6} when playing on CCA-treated play sets. These values are summarized in Table 1-2 under the scenario of play set only, warm climate at the 10^{-6} risk level. Similarly at point B, approximately 50% of the simulated populations have a risk of 1×10^{-5} (actual cancer risk is 1.1×10^{-5}) when exposed to playset only and at point C approximately 5% of the simulated populations have a risk exceeding 1×10^{-4} (i.e. the actual cancer risk is reported as 7.7×10^{-5}).

Finally, at point C (7.7 E-05 risk level at 95th% ile) it represents the population of children (ages 1-6) exposed to CCA-treated with play sets and decks. The estimated distribution for variability in risk across the target population (e.g. children age 1-6 exposed to CCA treated playsets in warm climates) indicates that approximately 5% of the individuals exposed under these circumstances have a risk exceeding 1×10^{-4}. The exact value presented in Table 5-1.

For brevity, Table 5-2 presents a summary of the results of the figures presented in the rest of the chapter.

Figure 5-2



Footnote *: Without deck (blue line) represents simulated population assuming contact with playsets only (absence of deck at primary residence). With decks (red line) represents the simulated population assumed to play on playsets and decks (deck is located at the primary residence).

Results

Non cancer margins of exposure (MOEs) and cancer risks were generated based on exposure doses calculated by the SHEDS-Wood model, as summarized in Chapter 3 of this document and the selected toxicological endpoint doses described in Chapter 4 of this document. Exposure doses were generated for the following:

- Two exposure routes – dermal and oral;
- Three durations – short (1 day to 1 month); intermediate (1-6 months); and lifetime (6 years averaged over 75 years);
- Two sources of exposure – play set (e.g. without decks), and play set and deck (e.g., with decks);
- Two climates – warm and cold; and
- Two chemicals – arsenic and chromium.

- One population – children (ages 1-6 years).

Table 5-1 presents a summary of the risk assessment results for non cancer and cancer risks. This table indicates which exposure conditions exceed specified risk levels. The summary is presented according to exposure scenario (i.e., source of exposure, climate, and duration of exposure for non carcinogens). For the non cancer effects of arsenic, estimated MOEs were found to be greater than the guidance MOE of 30 for all exposures at the 99.4th percentile. For non cancer effects of chromium (VI), none of the exposure scenarios evaluated had estimated MOEs below the target MOE of 100, and therefore were not of concern.

Cancer risks from arsenic and chromium (VI) were compared to three levels of risk: 10^{-6}, 10^{-5}, and 10^{-4} (e.g., excess lifetime risk of one per 1 million, one per 100 thousand, or one per 10 thousand). Values reported in Table 5-1 are cumulative probabilities above which the respective risk level has been exceeded. For example, for exposure to play sets only in a warm climate the risk level of 10^{-6} was exceeded at the 2nd percentile; or in other words 98% of the SHEDS-Wood simulated population had risks that exceeded 10^{-6} (e.g., excess lifetime risk of one per 1 million). Cancer risks were found to be higher for the warm climate scenario than the cold climate scenario, reflecting the increased exposure in a warm climate. For cold climate, the 10^{-6} risk level was exceeded across all exposure scenarios at the very low end (i.e., less than the 9th percentile) of the cumulative probability distribution. For play sets and decks, the 10^{-6} risk level was exceeded at <1st percentile for exposure to play sets and decks in a warm climate and at the 2nd percentile in a cold climate. See Table 5-1 for risks at the 10^{-6}, 10^{-5} and 10^{-4} levels for warm and cold climates. The difference versus warm and cold climate populations is more pronounced at the 10^{-5} level.

As noted at the 10^{-5} risk level the SHEDS simulated population risk percentile differences were also more pronounced for children playing on play sets alone versus playing on play sets and decks. For example, for the warm climate scenario for play sets, risks at the10^{-5} level occurred at the 46th percentile (e.g. 46% of the population had risk levels less than 10^{-5} and 54% of the population had levels greater than 10^{-5}). For the warm climate scenario for play sets and decks, risks at the10^{-5} level occurred at the 23rd percentile (e.g. 23% of the population had risk levels less than 10^{-5} and 77% of the population had levels greater than 10^{-5}).

Table 5-1. Summary of Risk Assessment Results

Non cancer MOEs for Arsenic and Chromium

Source of Exposure	Climate	Duration of Exposure	Arsenic MOE > 30	Chromium MOE > 100
Play set Only	Warm	Short & Intermediate	> 99th Percentile	None
	Cold			
Play set and Deck	Warm	Short & Intermediate	> 99th Percentile	None
	Cold			

Cancer Risks for Arsenic[a]

Source of Exposure	Climate	Cumulative Percentiles at Specified Risk Levels		
		10^{-6}	10^{-5}	10^{-4}
Play set Only	Warm	2nd	46th	97th
	Cold	9th	69th	99th
Play set and Deck	Warm	< 1st	23rd	91st
	Cold	2nd	48th	98th

a. Percentiles in this table represent the percent of the simulated population that have arsenic risks less than or equal to the stated risk level; e.g., at 10^{-6}, 2% of the population exposed to playsets only in warm climates have risks less than 10^{-6} and 98% have risks greater than 10^{-6}.

Cancer Risks for Chromium (VI)[a]

Source of Exposure	Climate	Cumulative Percentiles at Specified Risk Levels		
		10^{-6}	10^{-5}	10^{-4}
Play set Only	Warm	99.9th	None	None
	Cold	None	None	None
Play set and Deck	Warm	None	None	None
	Cold	None	None	None

a. Percentiles in this table represent the percent of the simulated population that have chromium (VI) risks less than or equal to the stated risk level; e.g., at 10^{-6}, 99.9% of the population have risks less than 10^{-6} and 0.01% have risks greater than 10^{-6}.
None- risks are less than 10^{-6} and do not trigger what the Agency would consider a level of concern in a typical cancer assessment.

The remainder of this chapter presents the detailed results of the risk characterization. Non-cancer MOE results are presented in Section 5.2 and cancer risks results are presented in Section 5.3.

5.2 Non Cancer Effects

Non cancer effects were evaluated by calculating the ratio of the NOAEL or LOAEL to the projected or estimated intake (i.e., dose). The resulting value is termed the margin of exposure (MOE). The larger the MOE, the more unlikely it is that a non cancer adverse effect would occur. EPA has established an acceptable MOE value of 30 for arsenic and 100 for chromium (Cr (VI)) to account for the uncertainties associated with the toxicity data and other factors. When the calculated MOE is below the acceptable MOE, it does not necessarily mean that health effects will occur. EPA uses the MOE approach in a screening level capacity only. That is, firm conclusions on the presence or absence of health effects should not be drawn solely on whether the calculated MOEs exceed the acceptable MOEs. For arsenic, the LOAEL used was 0.05 mg/kg/day and the target MOE was 30. For Cr (VI), the NOAEL used was 0.5 mg/kg/day and the guidance MOE was 100. The equation for this calculation was:

MOE = NOAEL or LOAEL / ADD

Where:

NOAEL = No-Observed-Adverse-Effect Level (mg/kg/day)
LOAEL = Lowest-Observed-Adverse-Effect Level (mg/kg/day)
ADD = Average Daily Dose (mg/kg/day)

Tables 5-2 and 5-3 present the MOEs for children who play on outdoor CCA-treated play sets only. The MOEs are calculated based on different exposure durations (short-term and intermediate) and climates (warm and cold). The mean, median, 95th percentile, and 99th percentile of the distributions are presented in this section. Please note that the values displayed under the mean heading are the MOEs estimated using the mean ADDs, and not an estimate of the mean of the MOEs. Table 5-2 presents the arsenic MOEs for exposure to play sets only. The cold climate conditions were found to have a larger MOE than for the warm climate conditions. For all conditions, the MOEs were found to be substantially greater (minimum factor of 2) than the guidance MOE of 30. Table 5-3 presents the MOEs for Cr (VI) for the same scenarios. All the chromium MOEs were found to be at least two orders of magnitude above the target MOE of 100.

Table 5-2. Arsenic Non cancer MOEs - Play set Only

Time Frame	Arsenic (guidance MOE = 30)							
	LOAEL of 0.05 mg/kg/day							
	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	497	988	1,293	3,767	140	247	44	85
Intermediate	601	1,246	1,557	3,832	165	313	54	129

Table 5-3. Chromium (Cr (VI)) Non cancer MOEs - Play set Only

Time Frame	Chromium (VI) (guidance MOE = 100)							
	LOAEL of 0.5 mg/kg/day							
	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	9.6E+05	5.8E+06	4.7E+06	6.1E+07	2.4E+05	1.4E+06	7.6E+04	3.3E+05
Intermediate	1.1E+06	6.1E+06	5.4E+06	5.8E+07	2.4E+05	1.4E+06	8.6E+04	3.9E+05

The non cancer MOEs for exposure to both play sets and decks are presented in Table 5-4 for arsenic and Table 5-5 for chromium. The results for the exposure to arsenic were similar to those for play sets alone. The MOEs for all exposures were found to be greater than the guidance value of 30. Cold climate conditions had higher MOEs (i.e., lower doses) than warm climate conditions. None of the MOEs for chromium (Table 5-5) were below the guidance value; even at the 99th percentile, these MOEs were orders of magnitude above the guidance MOE of 100.

Table 5-4. Arsenic Non cancer MOEs - Play set and Deck

Time Frame	Arsenic (guidance MOE = 30)							
	LOAEL of 0.05 mg/kg/day							
	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	367	744	795	1,768	98	199	45	91
Intermediate	359	680	750	1,626	98	193	45	65

Table 5-5. Chromium (Cr (VI)) Non cancer MOEs - Play set and Deck								
Time Frame	Chromium (VI) (guidance MOE = 100)							
	LOAEL of 0.5 mg/kg/day							
	Mean		Median		95%ile		99%ile	
	Warm	Cold	Warm	Cold	Warm	Cold	Warm	Cold
Short	9.9E+05	5.2E+06	4.3E+06	3.5E+07	2.5E+05	1.3E+06	7.1E+04	3.8E+05
Intermediate	1.2E+06	5.8E+06	4.5E+06	3.1E+07	3.0E+05	1.4E+06	1.1E+05	4.1E+05

Short-term MOEs

Arsenic risk cumulative density functions and probability density functions (CDFs/PDFs) were plotted for all exposure scenarios. Short-term duration (i.e., 1 day to 1 month) risks are shown in Figure 5-3 for warm climate conditions and in Figure 5-4 for cold climate conditions. Each figure presents risks from exposure to play sets only (without decks) and play sets and decks (with decks). Probabilistic short-term MOE distributions and risk levels are presented in Table 5-6 for warm climates and Table 5-7 for cold climates for arsenic risks with play sets and decks, and play sets only. MOEs for play sets and decks and play sets only were found to be less than 30 only above the 99^{th} percentile.

Chromium (VI) probabilistic short-term MOE distributions and risk levels (soil ingestion only) for children with play sets and decks, and play sets only in warm and cold climates are presented in Tables 5-8 and 5-9, respectively. All MOEs are >100 for all climate conditions and scenarios.

Intermediate-term MOEs

Arsenic risk PDFs/CDFs were plotted for all exposure scenarios. Intermediate duration (i.e., 1 to 6 months) risks are shown in Figure 5-5 for warm climate conditions and Figure 5-6 for cold climate conditions. Each figure presents risks from exposure to play sets only, and play sets and decks. Probabilistic intermediate-term MOE distributions and risk levels are presented in Table 5-10 for warm climates and Table 5-11 for cold climates for arsenic risks for both play sets and decks, and play sets only scenarios. MOEs were found to be less than 30 only above the 99^{th} percentile for warm climate exposures for play sets and decks together. MOEs were above 30 for all cold climate exposures.

Chromium intermediate-term MOEs and risk levels (soil ingestion only) for children with play sets and decks, and play sets only at warm and cold climates are presented in Tables 5-12 and 5-13, respectively. All MOEs were found to be greater than 100 for both climate scenarios.

Figure 5-3

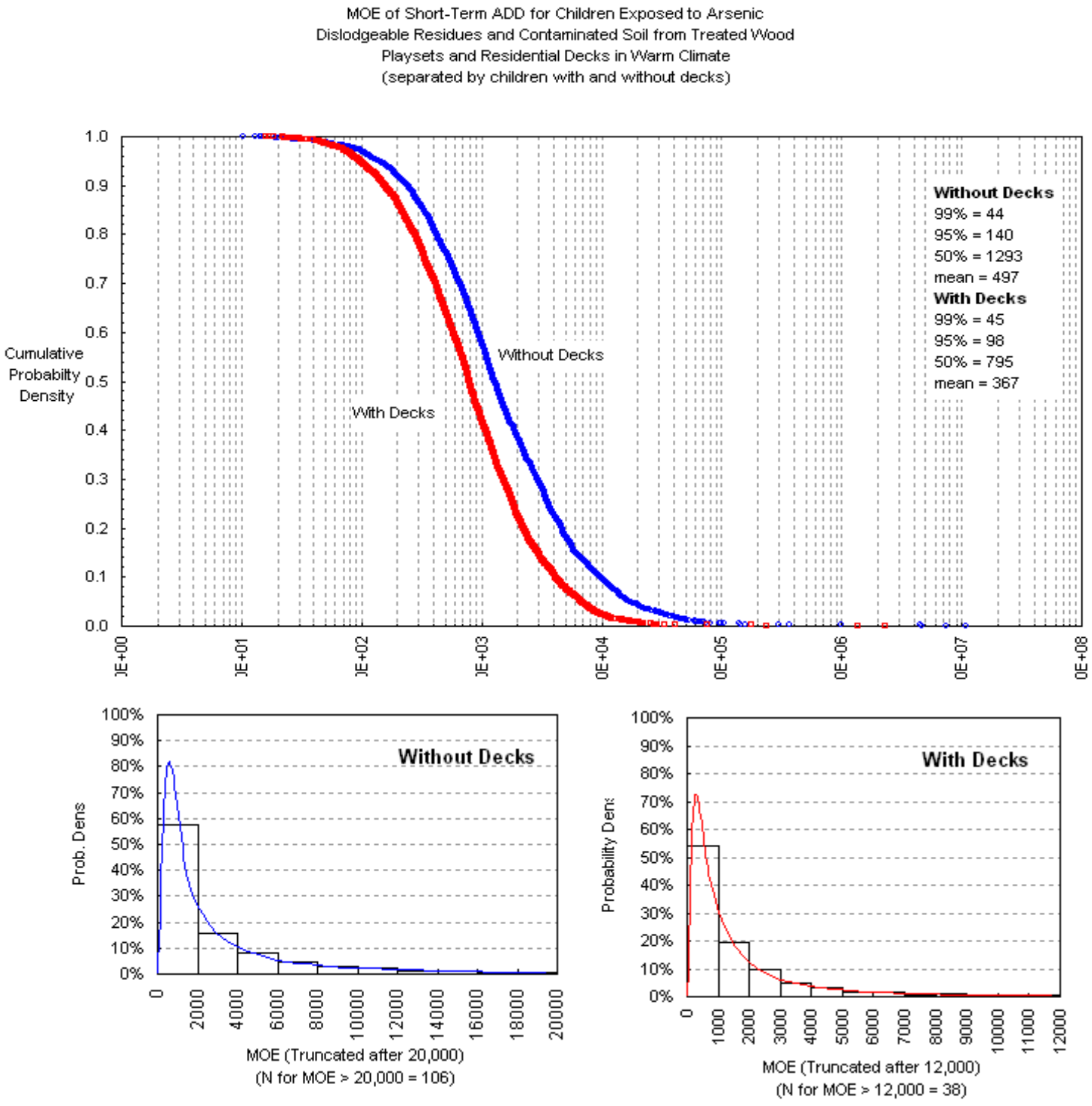

MOE of Short-Term ADD for Children Exposed to Arsenic
Dislodgeable Residues and Contaminated Soil from Treated Wood
Playsets and Residential Decks in Warm Climate
(separated by children with and without decks)
Cumulative Probability Density
Without Decks
With Decks
Without Decks
99% = 44
95% = 140
50% = 1293
mean = 497
With Decks
99% = 45
95% = 98
50% = 795
mean = 367
Prob. Dens
MOE (Truncated after 20,000)
(N for MOE > 20,000 = 106)
Probability Dens
MOE (Truncated after 12,000)
(N for MOE > 12,000 = 38)

Figure 5-4

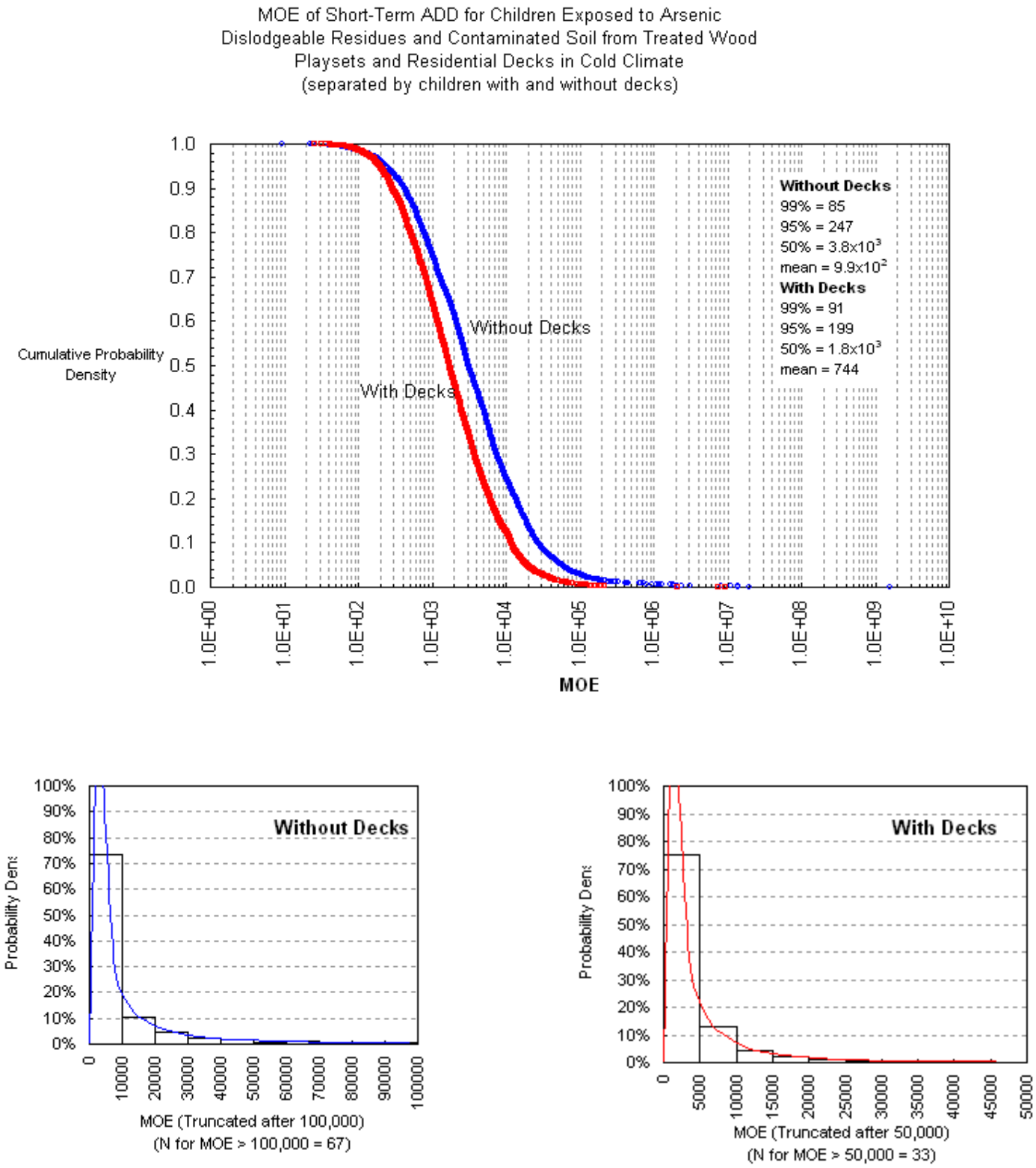

MOE of Short-Term ADD for Children Exposed to Arsenic
Dislodgeable Residues and Contaminated Soil from Treated Wood
Playsets and Residential Decks in Cold Climate
(separated by children with and without decks)
Cumulative Probability Density
Without Decks
With Decks
Without Decks
99% = 85
95% = 247
50% = 3.8x10^3
mean = 9.9x10^2
With Decks
99% = 91
95% = 199
50% = 1.8x10^3
mean = 744
MOE
Without Decks
MOE (Truncated after 100,000)
(N for MOE > 100,000 = 67)
With Decks
MOE (Truncated after 50,000)
(N for MOE > 50,000 = 33)

Table 5-6. Probabilistic Short-Term MOE Distributions and Risk Levels for Children Exposed to Arsenic in Warm Climate (Based on Short-term ADDs from SHEDS-WOOD)

Play set Only

Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level
			MOE = 30
99	1.1E-03	44	
95	3.6E-04	140	
90	2.1E-04	243	
50	3.9E-05	1.3E+03	
10	5.0E-06	1.0E+04	
5	2.9E-06	1.7E+04	
1	8.0E-07	6.3E+04	
minimum dose	0.0E+00	N/A	
99.4	1.67E-03	30	

Note: Percentiles include cases where dose = 0

Play set and Deck

Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level
			MOE = 30
99	1.1E-03	45	
95	5.1E-04	98	
90	3.2E-04	156	
50	6.3E-05	795	
10	1.2E-05	4.1E+03	
5	7.4E-06	6.8E+03	
1	2.9E-06	1.7E+04	
minimum dose	2.2E-08	2.3E+06	
99.6	1.7E-03	30	

Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.

Table 5-7. Probabilistic Short-Term MOE Distributions and Risk Levels for Children Exposed to Arsenic in Cold Climate (Based on Short-term ADDs from SHEDS-WOOD)			
Play set Only			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level
			MOE = 30
99	5.9E-04	85	
95	2.0E-04	247	
90	1.1E-04	452	
50	1.3E-05	3.8E+03	
10	5.6E-07	8.9E+04	
5	0.0E+00	N/A	
1	0.0E+00	N/A	
minimum dose	0.0E+00	N/A	
99.8	1.7E-03	30	
Note: Percentiles include cases where dose = 0			
Play set and Deck			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level
			MOE = 30
99	5.5E-04	91	
95	2.5E-04	199	
90	1.7E-04	293	
50	2.8E-05	1.8E+03	
10	3.9E-06	1.3E+04	
5	2.1E-06	2.3E+04	
1	0.0E+00	N/A	
minimum dose	0.0E+00	N/A	
99.9	1.7E-03	30	
Note: Percentiles include cases where dose = 0			
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.			

Table 5-8. Probabilistic Short-Term MOE Distributions and Risk Levels for Children Exposed to Chromium (VI) in Warm Climate (Soil Ingestion Only)

Play set Only

Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 100**
99	6.6E-06	7.6E+04	
95	2.1E-06	2.4E+05	
90	1.2E-06	4.2E+05	
50	1.1E-07	4.7E+06	
10	1.0E-08	4.9E+07	
5	4.6E-09	1.1E+08	
1	8.9E-10	5.6E+08	
minimum dose	2.6E-11	1.9E+10	
>99.9	5.0E-03	100	

Note: Percentiles include cases where dose = 0

Play set and Deck

Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 100**
99	7.0E-06	7.1E+04	
95	2.0E-06	2.5E+05	
90	1.1E-06	4.5E+05	
50	1.2E-07	4.3E+06	
10	1.2E-08	4.3E+07	
5	5.5E-09	9.1E+07	
1	1.6E-09	3.2E+08	
minimum dose	1.1E-10	4.4E+09	
>99.9	5.0E-03	100	

Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.

Table 5-9. Probabilistic Short-Term MOE Distributions and Risk Levels for Children Exposed to Chromium (VI) in Cold Climate (Soil Ingestion Only)			
Play set Only			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	1.5E-06	3.3E+05	
95	3.5E-07	1.4E+06	
90	1.6E-07	3.0E+06	
50	8.2E-09	6.1E+07	
10	1.5E-10	3.4E+09	
5	0.0E+00	N/A	
1	0.0E+00	N/A	
minimum dose	0.0E+00	N/A	
>99.9	5.0E-03	100	
Note: Percentiles include cases where dose = 0			
Play set and Deck			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	1.3E-06	3.8E+05	
95	3.8E-07	1.3E+06	
90	1.9E-07	2.7E+06	
50	1.4E-08	3.5E+07	
10	8.1E-10	6.2E+08	
5	3.4E-10	1.5E+09	
1	0.0E+00	N/A	
minimum dose	0.0E+00	N/A	
>99.9	5.0E-03	100	
Note: Percentiles include cases where dose = 0			

Figure 5-5

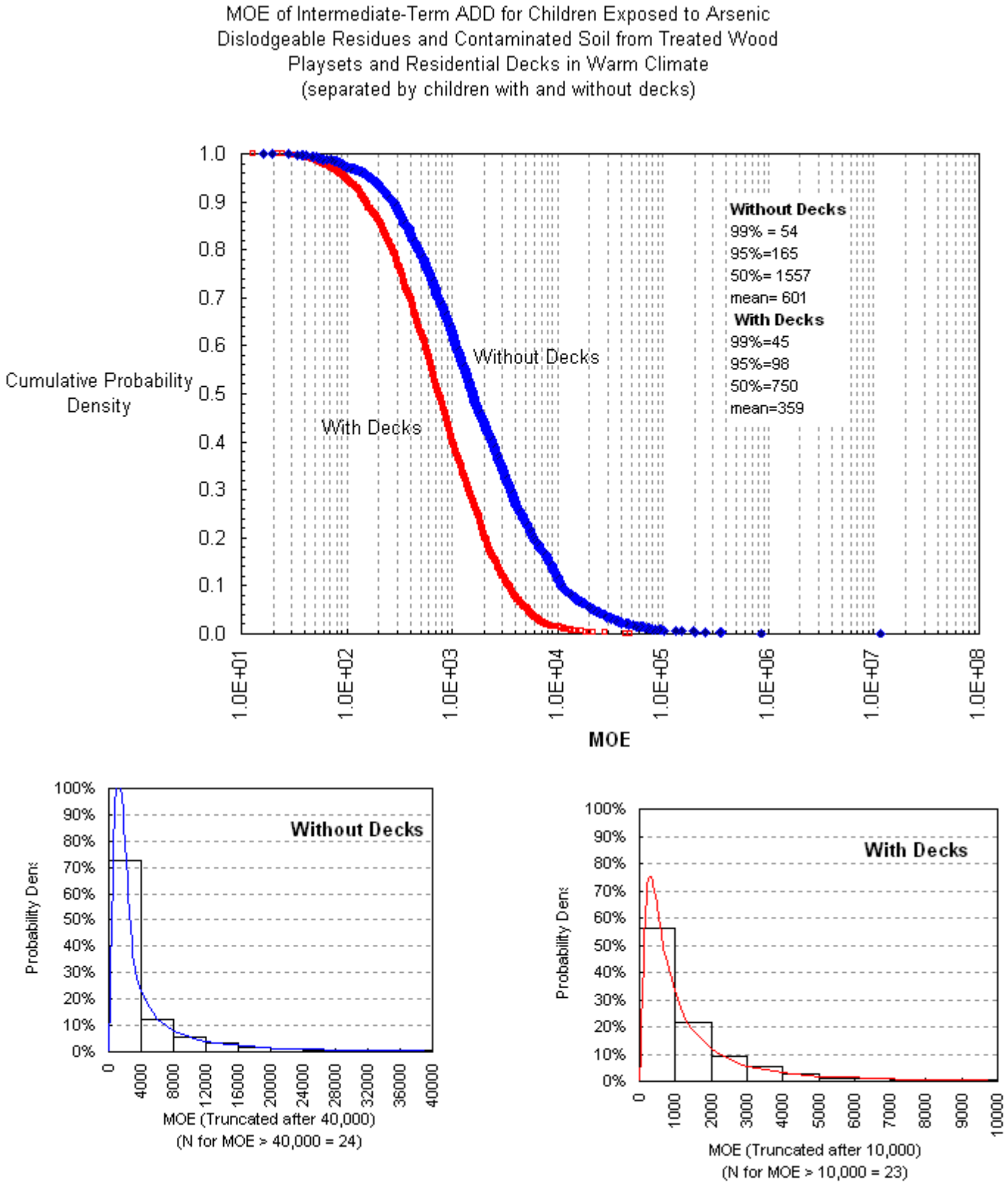

MOE of Intermediate-Term ADD for Children Exposed to Arsenic
Dislodgeable Residues and Contaminated Soil from Treated Wood
Playsets and Residential Decks in Warm Climate
(separated by children with and without decks)
Cumulative Probability Density
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Without Decks
With Decks
Without Decks
99% = 54
95%=165
50%= 1557
mean= 601
With Decks
99%=45
95%=98
50%=750
mean=359
1.0E+01
1.0E+02
1.0E+03
1.0E+04
1.0E+05
1.0E+06
1.0E+07
1.0E+08
MOE
Probability Dens
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Without Decks
0
4000
8000
12000
16000
20000
24000
28000
32000
36000
40000
MOE (Truncated after 40,000)
(N for MOE > 40,000 = 24)
Probability Dens
With Decks
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
MOE (Truncated after 10,000)
(N for MOE > 10,000 = 23)

Figure 5-6

MOE of Intermediate-Term ADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks)

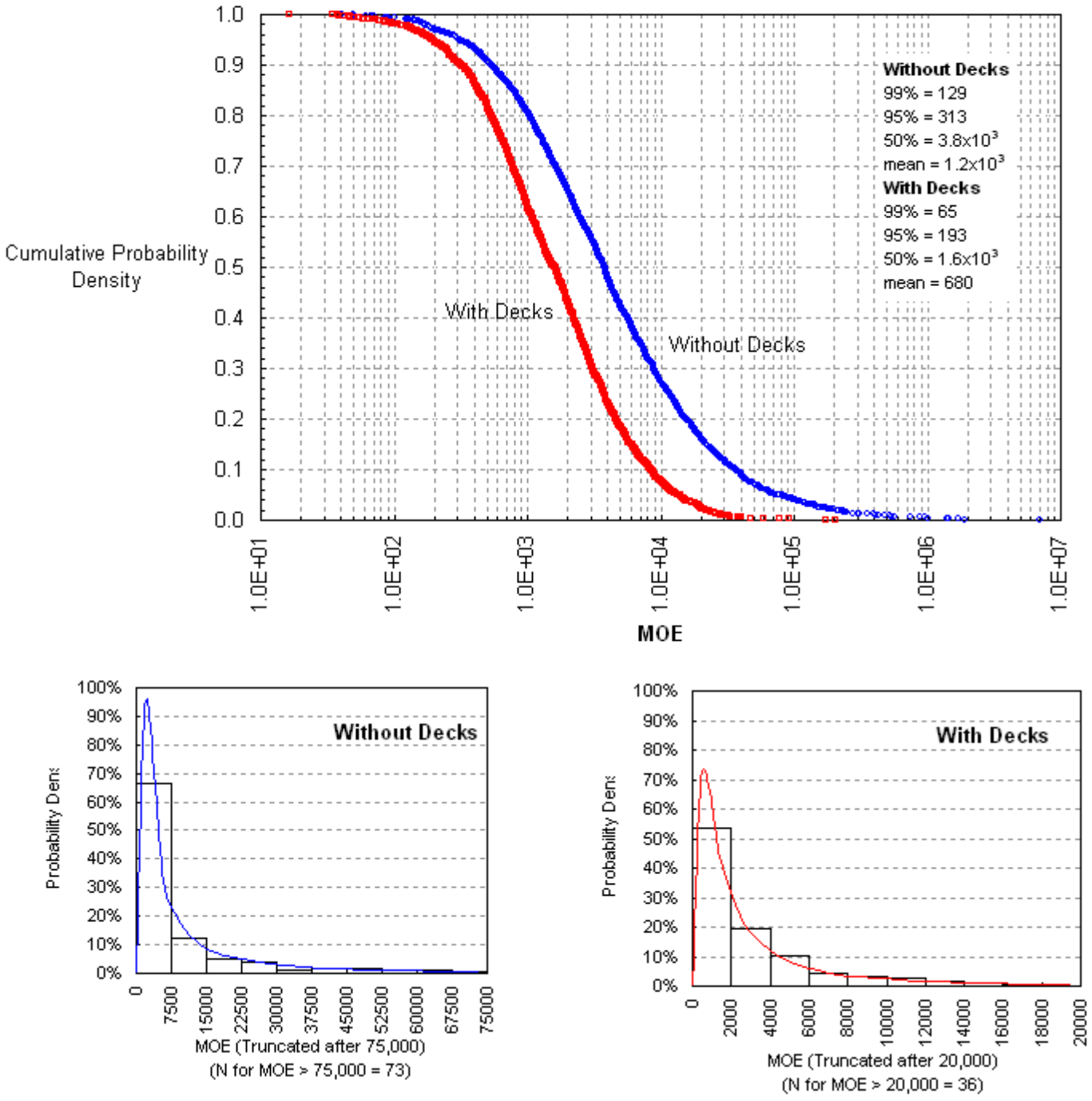


Table 5-10. Probabilistic Intermediate-Term MOE Distributions and Risk Levels for Children Exposed to Arsenic in Warm Climate (Based on the ADDs from SHEDS-WOOD)			
Play set Only			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 30**
99	9.3E-04	54	
95	3.0E-04	165	
90	1.8E-04	277	
50	3.2E-05	1.6E+03	
10	4.6E-06	1.1E+04	
5	2.3E-06	2.2E+04	
1	6.2E-07	8.0E+04	
minimum dose	4.3E-09	1.2E+07	
99.8	1.7E-03	30	
Play set and Deck			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 30**
99	1.1E-03	45	
95	5.1E-04	98	
90	3.3E-04	153	
50	6.7E-05	750	
10	1.5E-05	3.4E+03	
5	9.5E-06	5.3E+03	
1	4.4E-06	1.1E+04	
minimum dose	1.0E-06	4.9E+04	
99.7	1.7E-03	30	
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.			

Table 5-11. Probabilistic Intermediate-Term MOE Distributions and Risk Levels for Children Exposed to Arsenic in Cold Climate (Based on the ADDs from SHEDS-WOOD)			
Play set Only			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 30**
99	3.9E-04	129	
95	1.6E-04	313	
90	9.4E-05	535	
50	1.3E-05	3.8E+03	
10	1.3E-06	3.9E+04	
5	5.4E-07	9.2E+04	
1	5.0E-08	1.0E+06	
minimum dose	0.0E+00	N/A	
>99.9	1.7E-03	30	
Note: Percentiles include cases where dose = 0			
Play set and Deck			
Percentile of Exposure	Average Daily Dose (ADD) mg/kg/day	MOE	Risk Level **MOE = 30**
99	7.7E-04	65	
95	2.6E-04	193	
90	1.5E-04	323	
50	3.1E-05	1.6E+03	
10	5.9E-06	8.4E+03	
5	3.7E-06	1.3E+04	
1	1.7E-06	2.9E+04	
minimum dose	2.4E-07	2.1E+05	
99.9	1.7E-03	30	
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.			

Table 5-12. Probabilistic Intermediate-Term MOE Distributions and Risk Levels for Children Exposed to Chromium (VI) in Warm Climate (Soil Ingestion Only)			
Play set Only			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	5.8E-06	8.6E+04	
95	2.1E-06	2.4E+05	
90	9.9E-07	5.1E+05	
50	9.2E-08	5.4E+06	
10	8.2E-09	6.1E+07	
5	3.7E-09	1.3E+08	
1	6.3E-10	7.9E+08	
minimum dose	5.1E-13	9.7E+11	
>99.9	5.0E-03	100	
Play set and Deck			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	4.4E-06	1.1E+05	
95	1.6E-06	3.0E+05	
90	8.8E-07	5.7E+05	
50	1.1E-07	4.5E+06	
10	1.3E-08	3.9E+07	
5	6.8E-09	7.4E+07	
1	2.2E-09	2.3E+08	
minimum dose	2.9E-10	1.7E+09	
>99.9	5.0E-03	100	
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.			

Table 5-13. Probabilistic Intermediate-Term MOE Distributions and Risk Levels for Children Exposed to Chromium (VI) in Cold Climate (Soil Ingestion Only)			
Play set Only			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	1.3E-06	3.9E+05	
95	3.7E-07	1.4E+06	
90	1.5E-07	3.4E+06	
50	8.7E-09	5.8E+07	
10	3.9E-10	1.3E+09	
5	1.5E-10	3.3E+09	
1	1.3E-11	3.9E+10	
minimum dose	0.0E+00	N/A	
>99.9	5.0E-03	100	
Note: Percentiles include cases where dose = 0			
Play set and Deck			
Percentile of Exposure	Cr VI Average Daily Dose (ADD) mg/kg/day	Cr VI MOE	Risk Level **MOE = 100**
99	1.2E-06	4.1E+05	
95	3.5E-07	1.4E+06	
90	1.8E-07	2.8E+06	
50	1.6E-08	3.1E+07	
10	1.6E-09	3.1E+08	
5	8.1E-10	6.2E+08	
1	1.9E-10	2.6E+09	
minimum dose	8.4E-12	5.9E+10	
>99.9	5.0E-03	100	
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.			

5.3 Carcinogenic Effects

For carcinogens, risks were estimated as the probability of increased cancer incidence or excess lifetime cancer risk. A carcinogenic slope factor or Q_1* represents the 95 percent upper confidence limit (UCL) of the probability of response per unit intake of a chemical over a lifetime, and converts estimated intakes directly to incremental risk (U.S. EPA, 1990). Cancer risk was computed as follows:

$$\text{Risk} = \text{LADD} \times Q_1^*$$

Where:

LADD = Lifetime Average Daily Dose (mg/kg/day)
Q_1* = Carcinogenic slope factor [1/(mg/kg/day)]

The lifetime risk was based on a 6 year duration of exposure (ages 1-6 years) and averaged over a lifetime of 75 years.

Cancer risk results are presented from four different perspectives. First, risks are presented in the same manner as the non cancer effects; namely, the four different exposure points (i.e., mean, median, 95th percentile, and 99th percentile) are presented. Second, risks are shown in cumulative probability density and probability density plots. Third, percentiles from the cumulative distribution that correspond to the three levels of EPA's risk range (10^{-6}, 10^{-5}, and 10^{-4}) are presented. And fourth, total risk is shown for two broad sources of exposure: soils and residues.

The cumulative probability density and probability density plots for warm climates and cold climates for arsenic are presented in Figures 5-7 and 5-8, respectively. Risks due to both types of exposure (i.e., play sets only, and play sets and decks) are shown on the cumulative probability density plot. Figure 5-7 shows that risks for warm climate conditions are less than the EPA's target risk value of 10^{-6} only at extremely low cumulative probabilities (e.g., less than the 2nd percentile for both exposures to play sets alone as well as with deck exposure). For the cold climate conditions (Figure 5-8), the same pattern is evident. However, the cumulative probability curve shifted to the left slightly, as risks were lower due to lower levels of exposure.

Table 5-14 summarizes the arsenic cancer risks for children who contact CCA-treated play sets and decks in warm and cold climates at the three exposure points of interest. Warm climate exposures were greater than cold climate exposures. Thus cancer risks were correspondingly greater. Exposure at the mean and median were in the range 10^{-6} to10^{-5}. This range was exceeded with exposure to decks and play sets in warm climates at approximately the 95th percentile (1.3×10^{-4}). At the 99th percentile, the 10^{-4} risk level was exceeded for play sets and decks exposure for cold climate conditions.

Table 5-15 summarizes the chromium (VI) cancer risks for children who contact CCA-treated play sets and decks in warm and cold climates at the three exposure points of interest. Exposure at the mean and median were in generally in the range 10^{-10} to10^{-7}. The exception where

this range was exceeded occurred only with exposure to play sets in warm climates at the maximum value which corresponds to ~99.9^{th} percentile (1.4×10^{-6}). Risk was not exceeded at the warm climate for play sets and decks or for any of the other scenarios involved in cold climate conditions.

Figure 5-7

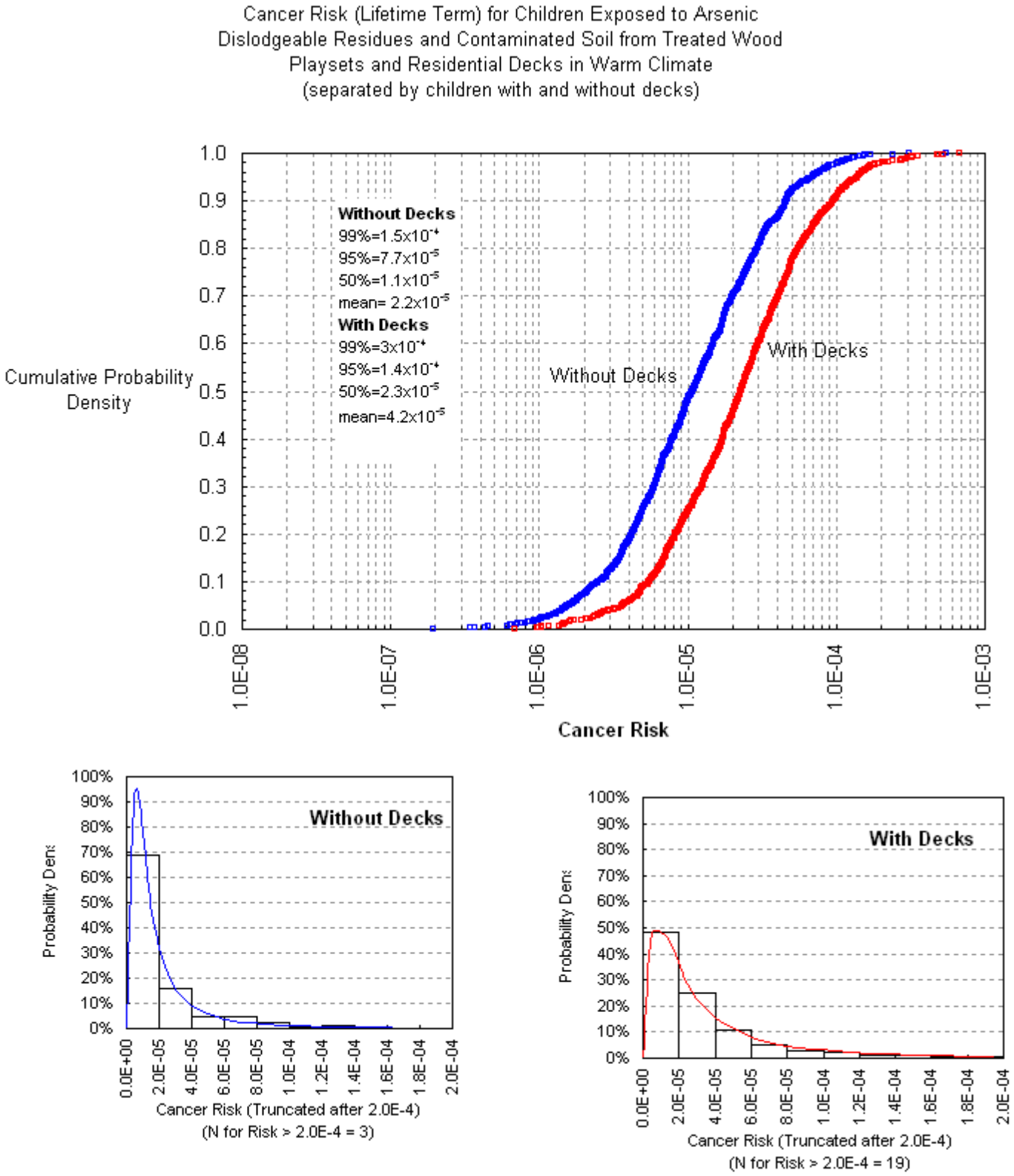

Cancer Risk (Lifetime Term) for Children Exposed to Arsenic
Dislodgeable Residues and Contaminated Soil from Treated Wood
Playsets and Residential Decks in Warm Climate
(separated by children with and without decks)
Cumulative Probability Density
Without Decks
99%=1.5x10-4
95%=7.7x10-5
50%=1.1x10-5
mean= 2.2x10-5
With Decks
99%=3x10-4
95%=1.4x10-4
50%=2.3x10-5
mean=4.2x10-5
Without Decks
With Decks
Cancer Risk
Without Decks
Probability Dens
Cancer Risk (Truncated after 2.0E-4)
(N for Risk > 2.0E-4 = 3)
With Decks
Probability Dens
Cancer Risk (Truncated after 2.0E-4)
(N for Risk > 2.0E-4 = 19)

Figure 5-8

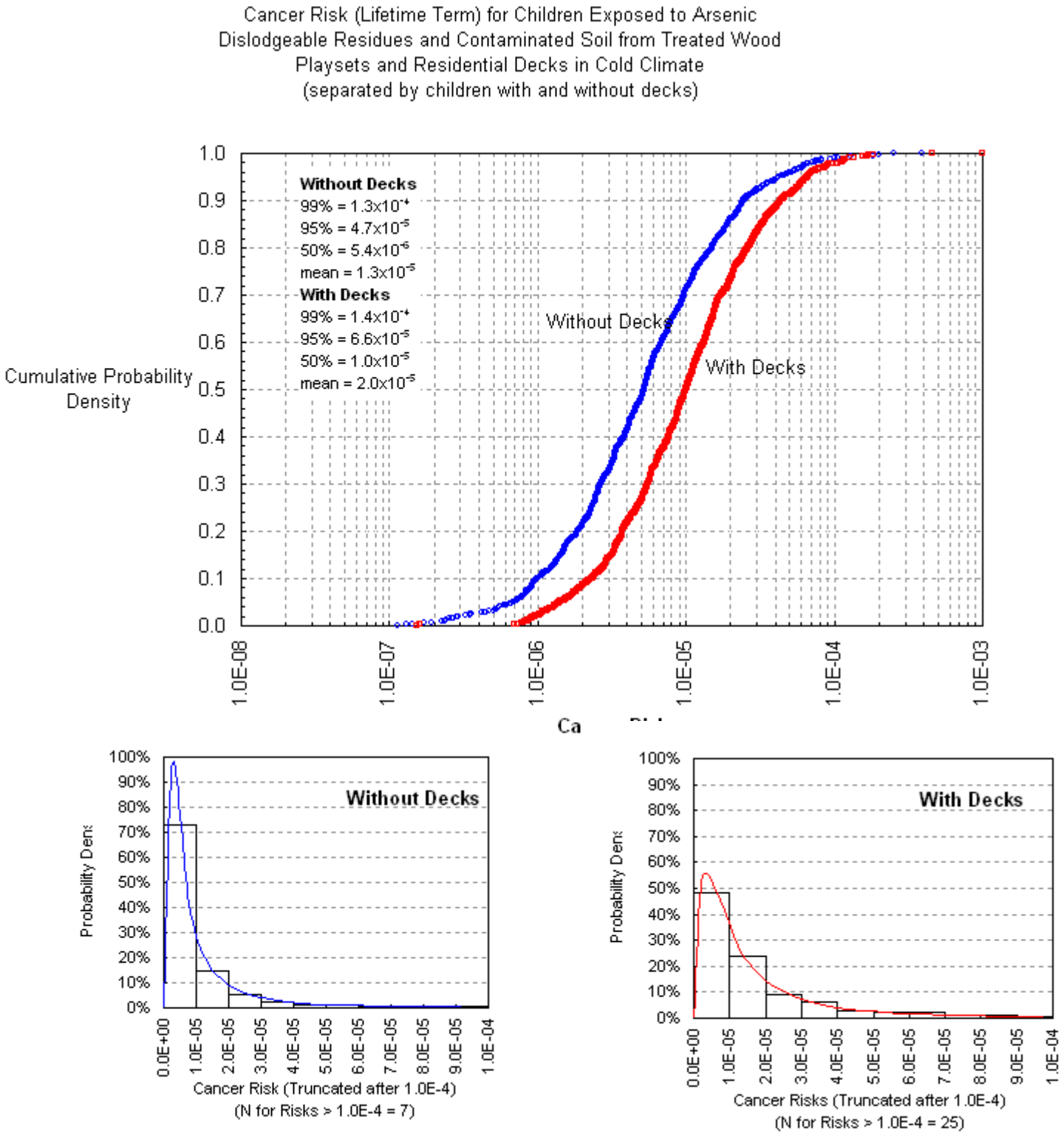

Cancer Risk (Lifetime Term) for Children Exposed to Arsenic
Dislodgeable Residues and Contaminated Soil from Treated Wood
Playsets and Residential Decks in Cold Climate
(separated by children with and without decks)
Cumulative Probability Density
Without Decks
99% = 1.3x10-4
95% = 4.7x10-5
50% = 5.4x10-6
mean = 1.3x10-5
With Decks
99% = 1.4x10-4
95% = 6.6x10-5
50% = 1.0x10-5
mean = 2.0x10-5
Without Decks
With Decks
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
Without Decks
Probability Dens
Cancer Risk (Truncated after 1.0E-4)
(N for Risks > 1.0E-4 = 7)
With Decks
Probability Dens
Cancer Risks (Truncated after 1.0E-4)
(N for Risks > 1.0E-4 = 25)

Table 5-14. Arsenic Cancer Risks								
Scenario	**Arsenic (Q1* =3.67 (mg/kg/day)$^{-1}$)**							
	Mean		**Median**		**95%ile**		**99%ile**	
	Warm	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**
Play set and Deck	4.2E-05	2.0E-05	2.3E-05	1.0E-05	1.4E-04	6.6E-05	3.0E-04	1.4E-04
Play set Only	2.2E-05	1.3E-05	1.1E-05	5.4E-06	7.7E-05	4.7E-05	1.5E-04	1.3E-04

Table 5-15. Chromium (VI) Cancer Risks								
Scenario	**Chromium(VI) (Q1* =0.79 (mg/kg/day)$^{-1}$)**							
	Mean		**Median**		**95%ile**		**99%ile**	
	Warm	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**	**Warm**	**Cold**
Play set and Deck	2.3E-08	6.7E-09	8.8E-09	1.5E-09	9.6E-08	3.1E-08	1.8E-07	6.2E-08
Play set Only	2.8E-08	4.6E-09	2.5E-06	8.3E-10	1.1E-07	1.9E-08	2.6E-07	7.0E-08

Tables 5-16 and 5-17 provide cumulative percentiles at the three specified risk levels for arsenic for warm and cold climates, play sets and decks and play sets only. For the warm climate, risks are less than 10^{-6} at the 2nd percentile for exposure to play sets only and less than the 1st percentile for exposure to decks and play sets. In cold climates, these percentiles are the 9th and 2nd, respectively. The upper end of EPA's target risk range (10^{-4}) is exceeded at cumulative percentiles that range from the 91st percentile for exposure to play sets and decks in a warm climate to the 98th percentile for play sets only in a cold climate.

Tables 5-18 and 5-19 provide cumulative percentiles at three specified risk levels for chromium (VI). For the warm climate, risks to play sets are primarily less than 10^{-6} for all exposures to play sets only except for one occurrence (1.4E-06) at the maximum condition (~99.9th percentile). For all other scenarios, risks are less than 10^{-6}.

Table 5-16. Probabilistic Cancer Risk Distributions and Risk Levels for children Exposed to Arsenic in Warm Climate (Based on LADDs from SHEDS-WOOD)

Play set Only

Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	4.2E-05	1.5E-04			
95	2.1E-05	7.7E-05			
90	1.3E-05	4.9E-05			
50	3.1E-06	1.1E-05			
10	7.5E-07	2.7E-06			
5	4.6E-07	1.7E-06			
1	2.0E-07	7.2E-07			
Minimum	5.3E-08	2.0E-07			
96.7	2.7E-05	1.0E-04			
46.1	2.7E-06	1.0E-05			
1.7	2.7E-07	1.0E-06			

Play set and Deck

Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	8.2E-05	3.0E-04			
95	3.7E-05	1.4E-04			
90	2.6E-05	9.5E-05			
50	6.3E-06	2.3E-05			
10	1.5E-06	5.7E-06			
5	1.0E-06	3.7E-06			
1	4.0E-07	1.5E-06			
Minimum	1.9E-07	6.9E-07			
91.0	2.7E-05	1.0E-04			
23.4	2.7E-06	1.0E-05			
0.2	2.7E-07	1.0E-06			

Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.

Table 5-17. Probabilistic Cancer Risk Distributions and Risk Levels for Children Exposed to Arsenic in Cold Climate (Based on LADDs from SHEDS-WOOD)					
Play set Only					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	3.6E-05	1.3E-04			
95	1.3E-05	4.7E-05			
90	7.3E-06	2.7E-05			
50	1.5E-06	5.4E-06			
10	2.9E-07	1.1E-06			
5	2.0E-07	7.2E-07			
1	6.4E-08	2.4E-07			
Minimum	3.1E-08	1.1E-07			
98.7	2.7E-05	1.0E-04			
69.4	2.7E-06	1.0E-05			
9.1	2.7E-07	1.0E-06			
Play set and Deck					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	3.7E-05	1.4E-04			
95	1.8E-05	6.6E-05			
90	1.2E-05	4.5E-05			
50	2.8E-06	1.0E-05			
10	6.5E-07	2.4E-06			
5	3.9E-07	1.4E-06			
1	2.3E-07	8.5E-07			
Minimum	4.2E-08	1.5E-07			
97.7	2.7E-05	1.0E-04			
48.8	2.7E-06	1.0E-05			
1.9	2.7E-07	1.0E-06			
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.					

Table 5-18. Probabilistic Cancer Risk Distributions and Risk Levels for Children Exposed to Chromium (VI) in Warm Climate (Based on LADDs from SHEDS-WOOD)					
Play set Only					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	3.3E-07	2.6E-07			
95	1.4E-07	1.1E-07			
90	8.2E-08	6.5E-08			
50	1.2E-08	9.3E-09			
10	1.5E-09	1.2E-09			
5	8.5E-10	6.8E-10			
1	2.1E-10	1.6E-10			
Minimum	3.3E-11	2.6E-11			
None	1.3E-04	1.0E-04			
None	1.3E-05	1.0E-05			
99.9	1.3E-06	1.0E-06			
Play set and Deck					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	2.3E-07	1.8E-07			
95	1.2E-07	9.6E-08			
90	7.5E-08	5.9E-08			
50	1.1E-08	8.8E-09			
10	1.4E-09	1.1E-09			
5	7.1E-10	5.6E-10			
1	2.1E-10	1.7E-10			
Minimum	2.9E-11	2.3E-11			
None	1.3E-04	1.0E-04			
None	1.3E-05	1.0E-05			
None	1.3E-06	1.0E-06			
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.					

Table 5-19. Probabilistic Cancer Risk Distributions and Risk Levels for Children Exposed to Chromium(VI) in Cold Climate (Based on LADDs from SHEDS-WOOD)					
Play set Only					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	8.8E-08	7.0E-08			
95	2.4E-08	1.9E-08			
90	1.4E-08	1.1E-08			
50	1.0E-09	8.3E-10			
10	2.9E-07	2.3E-07			
5	4.3E-11	3.4E-11			
1	7.8E-12	6.1E-12			
minimum	2.1E-12	1.7E-12			
none	1.3E-04	1.0E-04			
none	1.3E-05	1.0E-05			
none	1.3E-06	1.0E-06			
Play set and Deck					
Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
99	7.9E-08	6.2E-08			
95	3.9E-08	3.1E-08			
90	2.0E-08	1.6E-08			
50	1.9E-09	1.5E-09			
10	1.8E-10	1.4E-10			
5	1.1E-10	8.6E-11			
1	4.8E-11	3.8E-11			
minimum	5.9E-12	4.6E-12			
99.9	1.3E-04	1.0E-04			
none	1.3E-05	1.0E-05			
none	1.3E-06	1.0E-06			
Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.					

Figure 5-9 presents an approximate cumulative probability density plot for risks from soil and residue exposure. The lines in this plot are not true cumulative probabilities because risks were only calculated at the quartiles, as shown by the large dots; the lines merely connect the dots. Two observations are clearly shown in this plot. First, residue exposures have greater risk than soil exposure; and second, the difference between play set only versus play set and deck residue risk is less than the difference between residue and soil risk. At the 50th percentile, residue risk for play set and deck exposure is slightly greater than 10^{-5} and approximately 10^{-4} at the 95th percentile. The 10^{-4} risk level is exceeded for play set only exposure approaching the 99th percentile. Figure 5-10 is a bar chart of the risks from three different levels of exposure: 50th, 95th and 99th percentiles. At each level, there are four bars: soil and residue exposure for play sets alone and soil and residue exposure for both decks and play sets. Residue risk for play set only exposure exceeds the soil risk by a factor of approximately 6-7 at the 50$_{th}$ percentile and 95th percentiles, and by a factor of approximately 10 at the 99th percentile. For play set and deck exposure, residue risk is approximately 10 times greater that the soil risk at all three cumulative percentiles. Soil exposure risk exceeds 10^{-5} at the 95th percentile for both categories of exposure.

Residue risk for play sets only is slightly less than 10^{-4} and slightly greater than 10^{-4} for play sets and decks at the 95th percentile.

5.4 Summary

The potentially exposed population for this assessment was assumed to be children (ages 1-6 years) in the United States who contact CCA-treated wood and/or CCA-containing soil from public play sets (e.g., at a playground, a school, a daycare center). A subset of these children was also assumed to contact CCA-treated wood residues and/or CCA-containing soil from residential play sets (i.e., at the child's own home or at another home) and/or residential decks (i.e., at the child's own home or another home). This population was selected because of the particular focus by CPSC and other groups on playground play sets in conjunction with EPA's focus on estimating the risk to children from various primary sources of CCA-treated wood (Zartarian et al., 2003, 2005). Non cancer and cancer risks to children exposed to CCA-treated playsets and decks were calculated from doses generated using the SHEDS-Wood model. Non cancer risks were evaluated against OPP's guidance MOE values for arsenic and Cr (VI) for short- (1 day to 1 month) and intermediate-term (1 to 6 months) exposure duration. Lifetime (6 years of exposure averaged over 75 years) cancer risk from arsenic exposure was compared to risks ranging from 10^{-6} to 10^{-4}. Non cancer risk for arsenic was above the guidance MOE of 30 for all exposure scenarios, up to the 99$_{th}$ percentile. Cr (VI) risks were above the guidance MOE of 100 for all doses. Cancer risk exceeded the upper bound of the risk range, 10^{-4}, at cumulative percentiles ranging from the 91st for exposure to decks and playsets in warm climate conditions to the 99$_{th}$ for exposure to play sets only in cold conditions. Across all exposure scenarios, cancer risks were less than 10^{-6} at cumulative percentiles of the 9th and lower. Conversely, approximately 91% of the simulated exposures had risks exceeding 10^{-6}.

A screening level analysis comparing the risks from soil exposure versus residue exposure was conducted. Residue risk was greater than soil risk for both categories of exposure. For play set and deck exposure, residue risks were approximately an order of magnitude greater than that for soil; and slightly lesser differences were seen for play set only exposure. At the 95$_{th}$ percentile, soil risks exceeded 10^{-5} for both categories of exposure and residue risks were slightly greater than 10^{-4} for

playset and deck exposure.

Figure 5-9 Comparison of Total Arsenic Risks from Play sets and Decks for Warm Climate Baseline

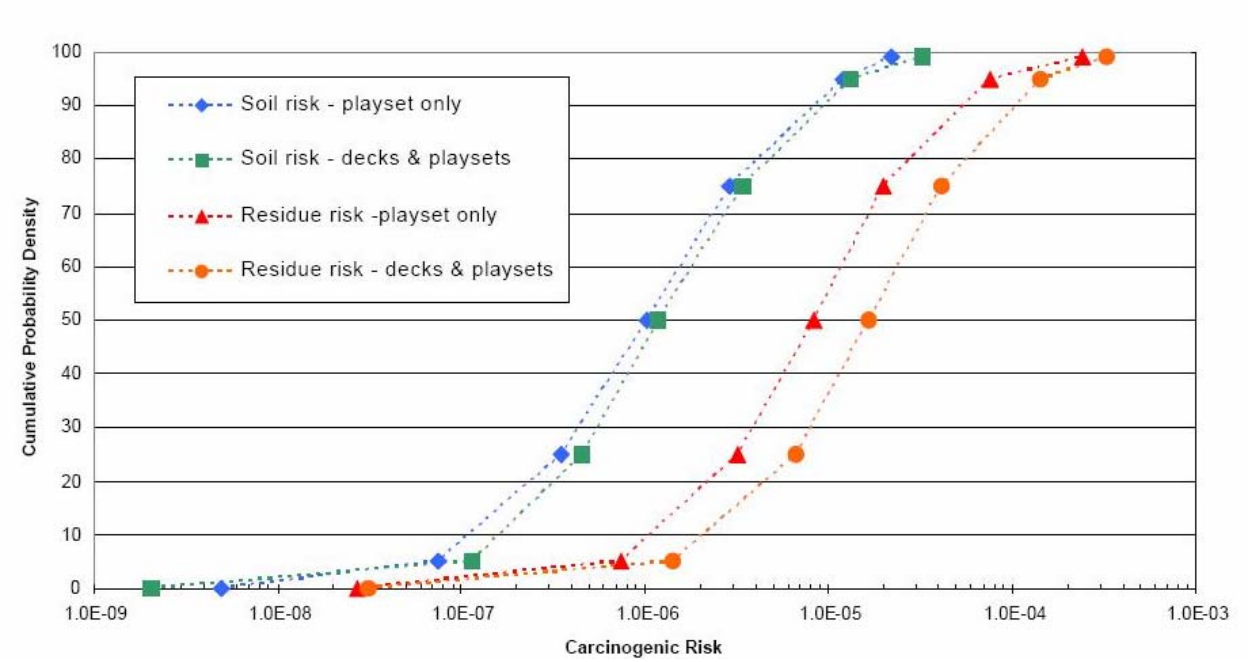
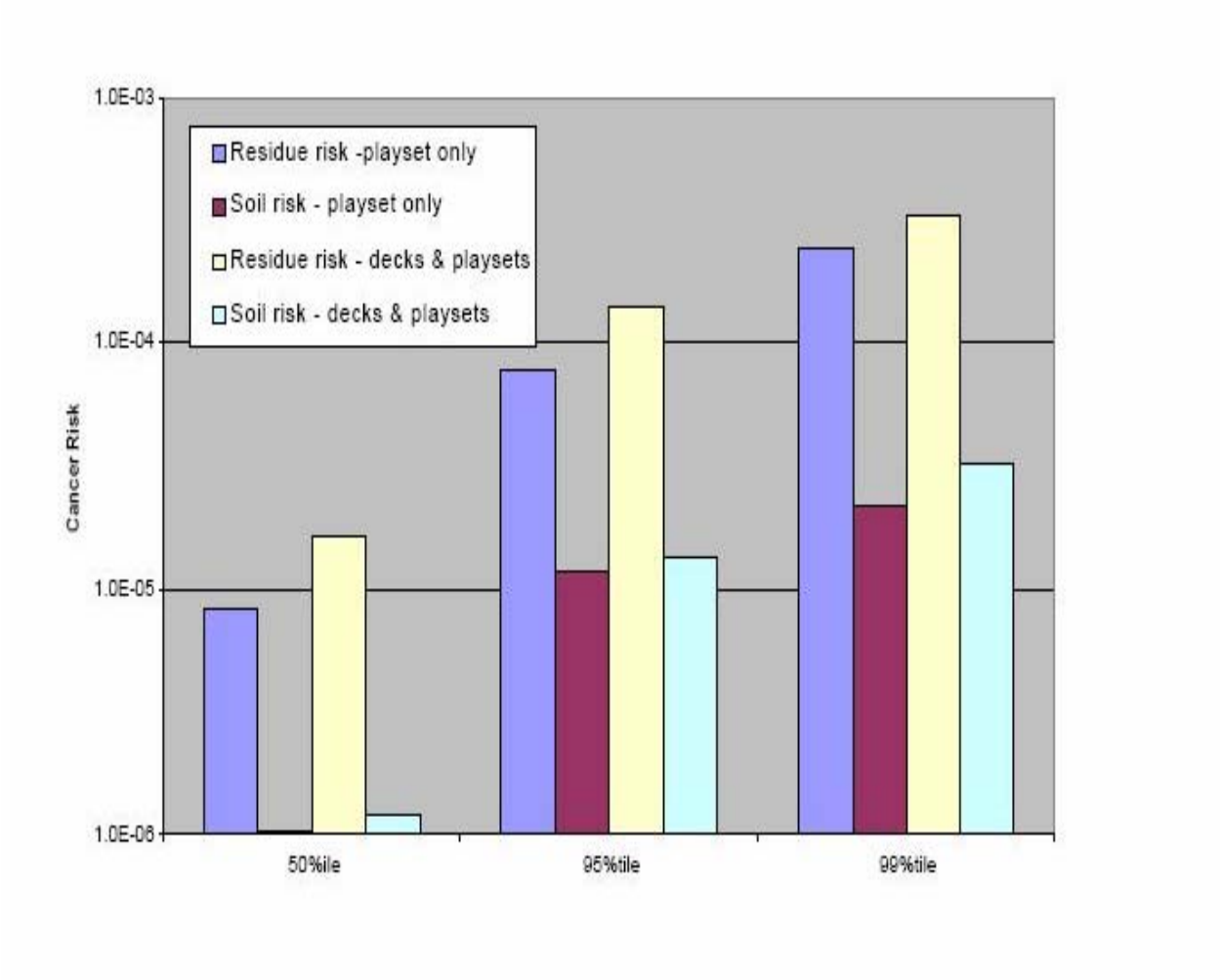


Figure 5-10 Comparison of Residue and Soil Total Arsenic Risks for Warm Climate Baseline



6.0 UNCERTAINTY ANALYSIS

In risk assessment, uncertainty refers to a lack of knowledge in the underlying science, while variability considers that some individuals in a population have more or less risk than others because of differences in exposure, dose-response relationship or both. Uncertainties are inherent in the risk assessment process. In order to appreciate the limitation and significance of the risk estimates, it is important to have an understanding of the sources and magnitudes of these uncertainties. Sources of uncertainty in this risk assessment include:

- Environmental media sampling and analysis;
- Chemical fate;
- Toxicity data;
- Exposure assessment modeling; and
- Risk characterization.

Over the course of EPA's evaluation of risks from exposure to CCA, the FIFRA SAP has made recommendations regarding input data and default assumptions used in risk assessment. These recommendations included criteria to evaluate the quality of data included in the modeling effort and appropriate decisions to be made in the absence of adequate data. The SAP provided the Agency with clear criteria to judge data quality in 1999 and 2003. Under conditions of moderate or high uncertainty (absence of sufficient data to fully capture the variability in exposure from these sources), the SAP suggested that the Agency should develop clear default assumptions to be employed until sufficient data are secured. They also recommended that these assumptions should err on the side of overestimation of exposure, or factors that contribute to exposure (U.S. EPA, 2001c).

The uncertainty in a risk assessment reflects the combined uncertainty of all the input variables that are used to estimate an exposure dose combined with the uncertainty of the toxicological parameters. Zartarian et al. (2005) conducted a thorough uncertainty analysis, evaluating model sensitivity and uncertainty through hundreds of iterations of the SHEDS-Wood model. Toxicological parameters have only been evaluated in a qualitative manner due to constraints of time and resources. Therefore, this uncertainty analysis is considered semi-quantitative.

6.1 Environmental Media Sampling and Analysis

Analytical data for chromium and arsenic residues on CCA-treated surfaces, as used in the SHEDS-Wood model, were taken from several literature sources, as described in Zartarian et al. (2005). The results of three data collection studies are used in CCA SHEDs-Wood model including:

1. Environmental Working Group (EWG) Study (2001, 2002);
2. Consumer Product Safety Commission (CPSC) study (2003); and
3. American Chemistry Council (ACC) study.

Table 7 of Zartarian et al. (2005) compares these three data collection studies. In the SHEDS-Wood model (Zartarian et al. 2005), Table 6 summarizes how SHEDS-Wood used CPSC, ACC, and EWG data in the CCA Assessment; the summary of distributions data for As and Cr residues on wood surfaces and in soil around playsets is shown in Table 5; the As and Cr residue data from ACC study is summarized in Table 8; and the As and Cr residue data from CPSC is summarized in table 9. Uncertainty in the exposure point concentration arises from how accurately these various data sets characterize the soil and dislodgeable residue concentrations in the underlying population of treated playsets and decks.

There are many significant variables that can affect the measurement of dislodgeable arsenic and chromium in CCA-treated wood surfaces and in the soil surrounding the treated wood products. Some of these variables include the following:

- The fraction of arsenic and chromium retained in the wood (retentions of CCA type C in wood can range anywhere from 0.25-2.50 pounds per cubic foot (pcf) depending on the different AWPA standards;

- The type of CCA formulation used to treat the wood (CCA treatment solutions are typically classified as either type A, B, or C since they vary in the proportion of arsenic to chromium compounds; however, CCA type C is most commonly used to treat dimensional lumber for above-ground residential applications). Data from type C was most often used in the study data used in this assessment;
- The type of pressure-treated wood (e.g., Douglas fir, southern pine, western cedar, red oak, etc.) can affect leaching and/or transfer of residues;
- The end use of wood (e.g., wood decks, construction or utility poles, marine timbers, fence posts, wood foundation lumber, plywood, and wood for playground structures or decks) determines the amount of CCA used for treatment;
- The degree that the wood has been sanded can affect residue levels;
- Variables in the pressure treatment process can influence the retention of CCA in wood (e.g., temperature and pH, too short of air seasoning time, rapid removal of water, rapid oven drying, etc.);
- The moisture content of the wood can affect CCA content and leaching; and
- The age of the CCA-treated wood can affect residue levels and leaching of CCA to surrounding soil.
- It was assumed that samples collected were representative of the area which the exposed population (children) may be exposed. However, the collected samples may not be completely representative, due to biases in sampling and to random variability of samples. For example, it has been suggested that arsenic concentrations on vertical surfaces were significantly higher than on horizontal surfaces (Ursitti et al 2004);

To the extent that the data sets used in SHEDS-Wood represent these variables, then these sources of variability are accounted for. However, it is not known how these factors are distributed across the underlying population of decks and playsets and if they are represented in the input data sets.

There is considerable uncertainty regarding the representativeness of the assumed exposure reduction based on the use of sealants such as oil stain, varnish, paint or sealant (e.g., polyurethane, acrylic or spar varnish) applied to pressure-treated wood may decrease the amounts of dislodgeable residues in CCA pressure-treated wood surfaces. For more information on the 2006 SAP review of the uncertainties and limitations of the surface coating studies please refer to the 2006 FIFRA SAP final meeting minutes report which is currently available on the following website link. http://www.epa.gov/scipoly/sap/meetings/2006/november/november2006finalmeetingminutes.pdf

6.2 Chemical Fate

In the environmental media (e.g. soil), chemicals are not homogeneously distributed. Conservative assumptions were made regarding the fate of arsenic and chromium in the environment. For arsenic, it was assumed that concentrations are relatively persistent and immobile. Thus, individuals were assumed to be exposed to the same concentration for the entire duration of exposure (i.e., 6 years). For chromium, all studies used to develop the probability density functions for exposure point concentrations reported total chromium, Cr (III) and Cr (VI). There was concern that assessing chromium (total) doses would overestimate the exposure. Therefore, an attempt was

made to determine the speciation of chromium in soil. One study (RTI International, 2003) analyzed Cr (VI) concentrations for a limited subset of samples. All of these samples were below the detection limit of the method. Due to the lack of data on Cr (VI), the Agency has decided to make a conservative assumption about speciation in soil. OPP adjusted the ADDs by multiplying by 0.10 (10%) to approximate Cr (VI) speciation. This conservative assumption most likely overestimates exposure to Cr (VI). This overestimation means that uncertainties around the Cr (VI) values are asymmetrical; the probability that concentrations are lower is much greater than the probability that concentrations are higher.

Migration, dispersion, dilution, retardation, degradation, and other attenuation or transformation processes may occur over time that could change the chemical concentrations in residues or soil. It has been conservatively assumed that the concentrations of arsenic are relatively persistent and immobile in both media. With reference to soil, this is an important factor to consider when evaluating the mitigation measures presented in Chapter 6.0. In calculating the exposure doses for these mitigation conditions, SHEDS-Wood used the same soil input distributions as were used for the baseline condition; only exposure to residue concentrations were reduced. Conceptually, a sealant would limit the migration of CCA to surrounding soils, however, there are no data available describing the effects of sealants on soil concentrations. Thus, the approach to estimating overall risk to surrounding soils may be conservative (i.e., risks are overestimated).

6.3 Toxicity Data

In general, the available scientific information is insufficient to provide a thorough understanding of all the potential toxic properties of chemicals to which humans are potential exposed. Consequently, varying degrees of uncertainty surround the assessment of adverse health effects in the exposed populations.

6.3.1 Uncertainties Associated with Arsenic Critical Toxicity Values

Varying degrees of uncertainty surround the assessment of adverse health effects in potentially exposed populations to arsenic. Some sources of uncertainty for toxic effects in humans may include:

- Extrapolating from a LOAEL to a NOAEL;
- Extrapolation of data due to intraspecies variation; and
- Extrapolation of epidemiological data from adult populations to children.

In general, cancer risk is a conservative estimate of the risk because the cancer slope factor is characterized as an upper-bound estimate. Therefore, the true risks to humans, while not identifiable, are unlikely to exceed the upper-bound estimates and in fact may be lower.

For inorganic arsenic, in this assessment, the slope factor used was 3.67 $(mg/kg/day)^{-1}$. This is the mean slope factor derived from a epidemiological study data from southwestern Taiwan and use linear model extrapolated to lower concentration for both lung and bladder cancers. This slope factor was used by the EPA's Office of Water when it established the MCL for arsenic in drinking

water (US EPA, 2001e). In 2001, NRC published an update to the 1999 NRC report and made some specific recommendations with respect to the EPA's Office of Water cancer risk estimate.

In 2005, the Agency submitted the draft IRIS Toxicological Review on Cancer Assessment for inorganic arsenics to Science Advisory Board (SAB) for review. In 2007, SAB released its final report. In general, SAB believes the SW Taiwan dataset still remains the most appropriate dataset for cancer risk. SAB agreed that inorganic arsenic has the potential for a highly complex mode of action for causing the health concerned effects. Although indirect genotoxicity suggests a threshold, studies do not show where the threshold might be or the shape of the dose-response curve at low dose levels. SAB still suggests using linear model until more is learned about pharmacokinetics/pharmacodynamics of the inorganic arsenics. The Agency is currently considering SAB's recommendations and their potential impact on the cancer potency estimate.

For non cancer effects, OPP assessed exposure using the MOE approach. This approach shows how many times the NOAEL or LOAEL exceed the predicted exposure. The MOE is a ratio of the LOAEL or NOAEL to the predicted exposure, thus, the uncertainties derive from the toxicity value and the manner in which exposure is estimated. Several conservative assumptions are considered in setting the acceptable amount by which the predicted exposure should exceed the LOAEL or NOAEL. Given the conservative assumptions used to generate the LOAEL and NOAEL, it is likely that the total uncertainty of the MOE is assymetrical. There is a greater probability that the true MOE is higher, and a lesser probability that the true MOE is lower.

In the current risk assessment, because the cancer slope factor used in this cancer risk assessment is derived from the epidemiology study using the Southwestern Taiwan data, it is generally believed that the sensitive population exposed to inorganic arsenic through drinking water during the most sensitive period of time is already included in the exposed population. No adjustment factor is applied for the children associated cancer risk. It is been questioned that the response of an early life exposure to a cancer causing agent may be different from the effects shown in populations exposed as adults. Although similar tumor response when compared to long-term exposures in adults, it has been noticed that short-term exposures in early life are likely to yield a greater tumor response than short-term exposures in adults (Ginsberg, 2003; Ginsberg et al, 2004; Ginsberg et al, 2007).

6.3.2 Uncertainty Associated with Arsenic Dermal Absorption Values

In 2001 SAP meeting, the Panel cited the research of Wester et al. (1993) as a source for the dermal absorption of soluble arsenic in water and soil. With radio-labeled arsenic mass-balance study, the results from this study were that mean dermal absorption rates for soluble arsenic were in the range of 2.0–6.4 percent of the applied dose for rhesus monkeys. Based on Wester et al. (1993), the Panel recommended using 2-3 % of dermal absorption rate for arsenic residue on the surface of wood.

Recently, instead of using radio-labeled mass balance approach, by using chemical analysis approach, Wester et al. (2004) and Lowney et al (2007) measured the dermal absorption of CCA-treated wood residues and arsenic-containing soil in the rhesus monkey, and found out the arsenic dermal absorption from both CCA-treated wood surface residue and arsenic containing soil were

much lower (approximately 0.01% for CCA-treated wood residues and 0.5% or less for arsenic containing soil) compared to the results published by Wester et al. (1993) for arsenic in water. The issue about the appropriateness of using the lower dermal absorption factor (0.01%) was discussed in the 2003 SAP.

The Panel found three areas of concern with respect to the 2004 Wester et al. study. These were:

a) Generic experimental issues such as sample size (n=3) and the absence of a mass balance, the former limiting statistical power and the latter being a significant shortcoming considering the use of an in vivo primate protocol.

b) The ACCR-skin contact scenario - the intimacy of contact between ACCR and skin was less certain than that for arsenic in aqueous solution (5 µL/cm2). Also compounds with negligible vapor pressures can only be transferred by direct contact or liquid phase diffusion and even a very thin gap between the external medium and skin could represent an absolute barrier to transport of non-volatiles (such as inorganic arsenic). Hence the vertical configuration employed by Wester et al. was not recommended. The Panel also stated that the authors overestimated the mass of ACCR required to calculate monolayer covering.

c) Pharmacokinetics of absorbed arsenic – Wester et al. (1993 and 2004) adjusted their results using urinary recovery of arsenic following i.v injection of soluble arsenic. However, it is unknown whether this adjustment is appropriate following dermal application since binding of arsenic by keratin in skin may delay excretion or following dermal absorption the fate of complexed arsenic may be different than that of inorganic arsenic.

Given the uncertainties discussed above, the Panel decided that "no quantitative estimate of dermal availability from ACCR could be derived from the 2003 Wester et al. experiments. The Wester et al. (2003) study was thus insufficient grounds to alter the dermal bioavailability assumption used SHEDS-Wood."

SAP concluded that "although this remains an area of uncertainty, research in this laboratory, using radiolabeled arsenic (Wester et al., 1993), suggests that this is a reasonable assumption for assessing the urinary excretion fraction of any absorbed dose of arsenic."

Although there are limitations in both Wester et al. (2004) and Lowney et al (2007) studies, the results indicate that the urinary arsenic levels following topical administration of arsenic in CCA residues are not distinguishable from background, the non-zero values for background urinary arsenic excretion, and the variability of the measured background values, impose some limits regarding the sensitivity of the model to detect an absorbed dose. The results also point out that percutaneous absorption of arsenic from CCA-treated wood surface residue and/or environmental media can be significantly different from soluble arsenic or even soluble arsenic mixed with environmental media. In order to address the potential uncertainty associated with the arsenic dermal absorption factor the arsenic cancer risk calculated with dermal absorption factor of 3% vs. 0.01 % is presented in Table 6-1.

Table 6-1 Comparison of Arsenic Risks Between Baseline and 0.01% Dermal Absorption				
Dermal Absorption Assumption	**Cancer Risk**			
	Playset and Deck		**Playset Only**	
	Median	**95%ile**	**Median**	**95%ile**
3% (Baseline)	2.3E-05	1.4E-04	1.1E-05	7.7E-05
0.01%	1.3E-05	1.1E-04	7.7E-06	6.6E-05

6.3.3 Uncertainty Associated with Early-Life Exposures

As discussed in Section 4.4, the Agency released the *Final Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). This document mentions the need to address early-life exposures from carcinogens. In addition, ORD has also published the *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b). U.S. EPA (2005b) presents an approach for assessing cancer susceptibility from early-life exposure to carcinogens.

For Arsenic, because the cancer slope factor used in this cancer risk assessment is derived from the epidemiology study using the Southwestern Taiwan data, it is generally believed that the sensitive population exposed to inorganic arsenic through drinking water during the most sensitive period of time is already included in the exposed population. In addition, Science Advisory Board (SAB) concluded "based on available data, it is still not clear whether children differ from adults with regard to their sensitivity to the carcinogenic effects of arsenics." (SAB, 2007). Therefore, an adjustment factor is not applied in the cancer risk assessment associated with arsenic exposure.

For chromium, because Cr (VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos and there is concern that older children are at risk because of the ability of Cr (VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations, based on the *EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (March, 2005b), it is concluded that the age dependent adjustments factors (ADAFs) should be applied for cancer risk assessments associated with children exposure to hexavalent chromium (Kidwell, 2008). The guideline proposed ADAFs are:

- Risk during the first 2 years of life (where the ADAF = 10);
- Risk for ages 2 through < 16 (ADAF = 3); and
- Risk for ages 16 until 70 years (ADAF = 1).

However, because it is difficult to differentiate the exposure pattern for children form age 1 to 6 for children playing around playground equipment, for conservatism, the ADAF of 10 is applied to all children exposure evaluated in this assessment (Age 1 to 6). Therefore current risk assessment is more conservative than what guideline suggested for children from age 2-6 exposure to chromium.

6.4 Exposure Assessment Modeling

6.4.1 Uncertainty Associated with Exposure Assessment

Exposure assessment is perhaps the most critical step in achieving a reliable estimate of health risks to humans. Little direct data exist to measure arsenic and chromium exposure in children. The exposure estimates used in this assessment were based on absorbed doses calculated by the SHEDS-Wood model (see Zartarian et al., 2005). This model predicted exposure and dose to arsenic and chromium using age and gender time-location-activity diaries for children 1-6 years old. All the data from SHEDS-Wood have been either recommended from the SAP or from the survey of studies in the EPA's Exposure Factor's Handbook (US EPA, 1997b). This information is used by several Agencies to estimate children's exposure durations at outdoor playsets and decks.

The SHEDS-Wood results showed that the significant exposure routes, in order of descending importance, were: residue ingestion via hand-to-mouth contact, dermal residue contact, soil ingestion, and dermal soil contact. The variability and uncertainty in the ADDs and LADDs from SHEDS-Wood were evaluated. Sensitivity of the model to the various input parameters was also evaluated. The following discussion summarizes these results; the full text can be found in Zartarian et al. (2005) (see Section 5).

Variability: Generally, there were several orders of magnitude difference in absorbed dose between the low end and high end percentiles for the various population estimates. This was due to differences in activity patterns, soil and residue concentrations, and exposure factors.

Uncertainty: Uncertainty was modeled using a non-parametric bootstrap approach for ADDs. The estimated uncertainty was indicated by a factor of 3 at the median and 4 at the 95th percentile.

Sensitivity: The most critical input variables to the model results were: wood surface residue-to-skin transfer efficiency, deck wood surface residue concentration, fraction of hand surface area mouthed, and hand washing events per day.

The estimated uncertainty of a factor of 3 to 4 appeared to be approximately symmetrical around the predicted absorbed dose.

In order to address the potential uncertainty associated with the exposure assessments, 2001 SAP recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks. It should designed with well-accepted epidemiological principles (including adequate sample size).

6.4.2 Uncertainty Associated with Pica behavior

Pica is an behavior pattern of appetite for some things that may be considered foods, such as soil. In order for these actions to be considered pica, they must persist for more than one month, at an age where eating such objects is considered developmentally inappropriate. In the risk

assessment, Pica behavior was excluded. Although it can make the risk results be more representative to the real situation, it may not be conservative enough for children having pica behavior.

6.4.3 Model Validation

In the 2001 SAP meeting, the Panel recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks, with the objectives of obtaining measurements of actual exposures, which could be used in risk assessment and to test the exposure model. Issue 11 addresses this issue. To quote: "The Panel recommended that the study should be designed according to well-accepted epidemiological principles, including adequate sample size, to resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. In 2003 SAP, a proposed biomonitoring study is been discussed and panel identified many deficiency in the proposal. Refer to the 2003 SAP final report for detailed discussion of the proposal and the identified major limitations.

Since then, there are two sets of studies involving children playing around playground equipments been published: (1) Kwon et al. (2004) and Wang et al. (2005); and Shalat et al (2006). The significance and limitations of these studies are discussed in following sections:

6.4.3.1 Shalat et al (2006) Study:

The Shalat et al study is a pilot Florida pilot study monitoring level of arsenic on a child's hand after individual contact with in-service CCA treated wood playsets. The mean and maximum hand loads from that study are 0.005 and 0.01 µg/cm2 respectively. Limitations in the Shibata data set may result in underestimates of hand loading potential include:

1. hand wash efficiency is unknown;
2. playtime in Shibata study was lower (maximum of 45 minutes);
3. appears that only soluble As on hands was analyzed; and,
4. limited number of replicates (n=4 for playing on CCA- and n=2 for partially CCA-treated play structures).

Exponent admitted the data is too limited for quantitative purpose. Exponent is considering using the study results to confirm Kwon et al (2004)'s finding. Because the imitations of the Shalat data set, Agency's conclusion is the confidence in the ability of the Kwon data set to predict maximum hand loading is not increased.

6.4.3.2 Kwon et al (2004) and Wang et al. (2005) Study

The Kwon et al. study is a Canadian field study designed to quantify the total amount of soluble arsenic on children's hands following a play period around parks with playground structure. It was conducted for eight playgrounds with CCA-treated wood and a control group of eight playgrounds without CCA-treated wood. After the play period (which varied by child), the hands were washed with deionized water. The age of the child and the duration of play were recorded for each study member. The mean and standard deviation of their ages were 4.7 ± 2.4yrs and the mean

duration of play was 74.4 ± 45.7 minutes. Kwon et al. also reported arsenic concentrations in the sand/soil in the vicinity of the playground structure. The hand washing samples were filtered and the sand/soil analyzed separately from the filtrate. As the sand/soil concentrations in the playgrounds were low (3.3 ± 1.7 mg/kg), the contribution of sand/soil particles to total hand exposure was also low, being on the order of one-tenth of the dislodgeable residue exposure.

Several factors may result in this data underestimating hand loading potential:

1. No accounting for possible removal by hand-to- mouth activity while on playground;
2. No assessment of dislodgeable residue levels on the structure to determine representativeness of play structures examined in the study;
3. No specific examination of activity of children while on playground to determine duration, type, or level of contact with play structure and to correlate with hand load values; and
4. Uncertainty regarding the effectiveness of the hand-wash technique to ensure the removal efficiency was adequate.

In addition, the objective of the Kwon et al. (2004) study and Wang et al. (2005) was to determine the quantitative amount of arsenic on the hands of children in contact with CCA-treated wood structures and soil in playgrounds; the studies were not designed to measure maximum dermal loading and the reported data are likely to lead to underestimates of inputs for that variable. Furthermore, there are 66 data points in the Kwon et al. (2004) study; this is relatively small when compared with more than 700 data points used in the SHEDS-Wood model. The values used in the SHEDS-Wood CCA assessment for transfer efficiency and maximum dermal loading were measured under well-controlled experimental conditions designed to collect data for those variables.

In order to address the Agency's concern, that Kwon et al (2004) did not measure the dislodgeable residue concentration of the playground structures in their study, three years after Kwon published their study results, the U.S. Wood Preservative Science Council sampled the wood surface of the playground equipment in the parks that Kwon et al (2004) studied. With same wipe method, the study results indicated the results from the playground equipments studied in Kwon et al's study is similar to the wood surface results used in SHEDS-Wood model. The skin transfer efficiency and wood surface arsenic residues are the two most important variables influencing the estimation of absorbed doses (Zartarian et al. (2005) and Xue et al., 2006).

In the SHED-Wood the residue transfer efficiency were derived by comparing hand wipe results to wood block residue results.

$TE_{surf\text{-}skin}$ = hand wipe results / wood block residue results.

Both hand wipe result and wood block result are derived in experimental conditions and were conducted on adults with specific pressure in estimating the hand and wipe loading of dislodgeable arsenic from CCA-treated wood. Baraj et al (2007 a, b) questioned that the approach may not represent the actual activity [children playing around the CCA-treated wood structures (playground equipments and/or deck)]. The Agency understands that it may be conservative to use the adult studies to derive the max loading concentration. For residue transfer efficiency $TE_{surf\text{-}skin}$, the Agency still considers that it is appropriate. Since the same experimental condition were applied in

generating both hand-wipe data and wood residue data, In Table 6-2, it appears cancer risks associated with arsenic calculated with Kwon data is about 10 times lower than the SHED-Wood results.

Table 6-2. Comparison of the Arsenic Cancer Risks – SHEDS-Wood vs. Kwon et al (2004)

Scenario	Arsenic (Q1* =3.67 (mg/kg/day)$^{-1}$)					
	Mean		Median		95%ile	
	Warm	Cold	Warm	Cold	Warm	Cold
SHED-Woods	2.2E-05	1.3E-05	1.1E-05	5.4E-06	7.7E-05	4.7E-05
Kwon Playset Only	NA	1.3E-06	NA	8.4E-07	NA	4.0E-06

The key important information on children's hand loadings and on duration of children's play time in these studies are insufficient to directly inform the estimate of maximum dermal hand loading or related SHEDS model inputs; time spent on playgrounds is not equivalent to hand contact with wood. Without knowing actual dermal contact time with the CCA-treated wood, one cannot know whether the maximum dermal loading was reached. Because of this and the other limitations listed above, we do not believe that the data from these studies would necessarily improve the accuracy of the SHEDS-Wood CCA exposure assessment presented in Zartarian et al. (2006) and Xue et al. (2006). As indicated in the article, the means of the SHEDS-Wood distributions are very similar to the values used in most of the other models, and the distributions capture the other values in many cases. The comparison presented in the paper indicates that SHEDS-Wood estimates are consistent with, or in the range of, other CCA models. As stated in the SAP (2004) report: "The general consensus of the Panel was that the current SHEDS-Wood model implementation represented a good faith effort on the part of the Agency. Even though one can question specific choices of distributional assumptions, overall the work seemed a reasonable effort and a sound basis for risk assessment within the limitations of available information."

6.4.4 Modeling Hand Washing vs. Baseline

ORD simulated hand washing using the SHEDS-Wood Model (Zartarian et al., 2005, 2006). OPP used the exposures of SHEDS-Wood Model to evaluate the effect of hand washing on cancer risks. The way in which SHEDS-Wood handled hand washing was by only reducing residue exposure and not soil exposure. One supposes that hand washing could also provide some reduction in the soil-hand-mouth pathway, but this was not explicitly modeled in SHEDS-Wood. Arsenic residues can be transferred from surface of wood to the surface of hands and subsequently be ingested by children through hand-to-mouth activity. The effectiveness of increased hand washing at reducing exposure, and thus, risk was evaluated

Results for the hand washing vs baseline scenarios are summarized in Table 6-3 and 6-4. Hand washing was only evaluated for the warm climate because this condition had the highest levels of risk. For table 6-3, the table is shown in two parts: the top portion is for risk from exposure for hand washing and the lower portion is for risk at baseline. Carcinogenic risks from arsenic are compared to the three levels of risk 10^{-6}, 10^{-5}, and 10^{-4} in Table 6-4. Values reported in the table are

the cumulative probabilities above which the respective risk level is exceeded. Note that when exposure includes both playsets and decks (i.e., greater exposure), the cumulative percentile exceeding the risk level decreased at all levels except at 10^{-4}. The 10^{-4} risk level was at the extreme tail of the distributions under all mitigation conditions. It was slightly less extreme for hand washing only; for that mitigation scenario, the 10^{-4} risk level fell at the 95th percentile.

Table 6-3 presents the risks based on reduction by hand washing vs baseline at the mean, median, and 95th percentile. Hand washing risks for exposure to playsets and decks was approximately 2 times greater than risks to playsets alone. Baseline risks at the 95th percentile, for comparison, were 1.4×10^{-4} for exposure to playsets and decks and 7.7×10^{-5} for playsets alone. The pattern was similar at the other estimates of exposure. These baseline risks were only slightly greater than the risks when exposure was reduced by hand washing. The evaluation of risk remaining after the simulated hand washing was considered in reference to the baseline risk discussed in Chapter 5.

Table 6-3. Cancer Risks Remaining Following Simulated Reductions from Hand Washing vs Baseline (Warm Climate Only)

Scenario	Arsenic (Q1* =3.67 (mg/kg/day)$^{-1}$)		
	Mean	Median	95%ile
Handwashing			
Playset and Deck	2.8E-05	1.7E-05	9.2E-05
Playset Only	1.9E-05	8.2E-06	6.8E-05
Baseline			
Playset and Deck	4.2E-05	2.3E-05	1.4E-04
Playset Only	2.2E-05	1.1E-05	7.7E-05

Carcinogenic risks from arsenic are compared to the three levels of risk 10^{-6}, 10^{-5}, and 10^{-4} in Table 6-4. For reference, the baseline percentiles at the 10^{-6} level (see Table 5-1) for warm climate conditions were the 3rd for playset only exposure and less than the 1st for exposure to playsets and decks. For hand washing the 10^{-6} risk level occurred at the 5th percentile for playsets alone and less than the 1st percentile for decks and playset exposure.

Table 6-4. Summary of Arsenic Risks Assuming for Hand Washing for Warm Climate Conditions

Scenario	Cumulative Percentiles at Specified Risk Levels		
	Risk Level of 10^{-6}	Risk Level of 10^{-5}	Risk Level of 10^{-4}
Playset Only			
1. Hand washing	3rd	56th	98th
2. Baseline	2nd	46th	97th
Playset and Deck			
1. Hand washing	<1st	31st	96th
2. Baseline	<1st	23rd	91st

6.5 Risk Characterization

There are various sources of uncertainty in each step of the risk assessment process. In the final estimate of risk, the uncertainty in the toxicity value is combined with the uncertainty in the absorbed dose estimate. This combined uncertainty is greater than the uncertainty in the exposure estimate, however, the question is - how much greater? This is not a simple question to answer. It is beyond the scope of this risk assessment to address that question in a quantitative manner. Thus, it is addressed in conceptual manner. Further limitations of this discussion are that it applies to the carcinogenic risk from exposure to arsenic, as that is the most critical and it is more appropriate to the baseline risk results (Chapter 5.0) and less so the mitigation risks (Chapter 6.0). (This is due to the lack of any information on the uncertainty of the assumed effectiveness of the mitigation measures.)

Uncertainty can be considered a cloud surrounding a value. If risks are presented as a CDF, then there is a cloud surrounding the entire curve. The shape of this cloud is determined by the uncertainty of the input variables and how these uncertainties are combined mathematically. There are standard approaches for estimating the combined uncertainty for the simple case of two input variables where the uncertainty of each has been quantified and it is symmetrical around the a central value of the variable. More sophisticated approaches are required when either of the uncertainties are asymmetrical.

In this risk assessment, only the uncertainty in the absorbed dose was characterized; the uncertainties in the toxicity values were not characterized. To generate an uncertainty estimate for the risk characterization, similar to the absorbed dose uncertainty estimate, would require: (1) knowledge of the uncertainty in the slope factor and NOAEL/LOAEL, and (2) running a Monte Carlo simulation to calculate risk that included a distribution function for the slope factor. Thus, the uncertainty of the risk characterization step can not be quantified.

What is known about the uncertainty around the input variables is very different. The slope factor in this assessment is not a mean value. It is at the high end of the distribution, based on the various conservative factors that are included in the formulation of the final value (e.g., low dose extrapolation and extrapolation from adults to children). Therefore, the “uncertainty cloud” around the slope factor is asymmetrical. How asymmetrical is not known; however, it is likely that the vast majority of the cloud is below the slope factor value and very little is above it. By contrast, uncertainty in the absorbed dose estimate appears to be symmetrical based on the analysis presented in the SHEDS-Wood report (Zartarian et al., 2005).

The uncertainty in the risk estimate is a combination of the symmetrical uncertainty in the absorbed dose and the asymmetrical uncertainty in the slope factor. It is beyond the scope of this assessment to mathematically combine those uncertainties. However, a relative estimate of the shape and location of the uncertainty cloud is possible. The first order estimate is based on the absorbed dose uncertainty. Combining the slope factor uncertainty would increase the size (dispersion) of the cloud and shift it so that it was asymmetrical around the risk estimate (i.e., more of the cloud is below the risk estimate than above it).

Therefore, it is concluded that the arsenic carcinogenic risk, (especially under the assumed mitigation measures) are conservative estimates of risk. The Cr (VI) non cancer MOEs are also considered to be conservative (i.e., MOEs are most likely higher) due to the assumption that 10% of total chromium was assumed to be present as Cr (VI). The non cancer arsenic MOEs are also considered to be conservative estimates, given the assumptions for the LOAEL.

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Appendix A: Hazard Identification and Toxicology Endpoint Selection for Inorganic Arsenic and Inorganic Chromium

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Hazard Identification and Toxicology Endpoint Selection for Inorganic Arsenic and Inorganic Chromium**

PC Code: 025002

FROM: Jonathan Chen, Ph.D. Toxicologist
Risk Assessment and Science Support Branch (RASSB)
Antimicrobial Division (7510C)

And

Timothy F. McMahon, Ph.D. Toxicologist
Immediate Office
Antimicrobial Division (7510C)

THROUGH: Norm Cook
Chief
RASSB
Antimicrobial Division (7510C)

TO: Lance Wormell,
Chemical Review Manager
AD

Attached are the Hazard Identification and Toxicology Endpoint Selection for Inorganic Arsenic and Inorganic Chromium.

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

March 12, 2008

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

TABLE OF CONTENTS

0.0 INTRODUCTION

The Agency recognizes that inorganic arsenic and inorganic chromium are the compounds of toxicological concern with respect to exposure to CCA-treated wood. In any risk assessment, the toxicity of the primary chemicals of concern must 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. 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 (ATSDR). 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). The Agency has not identified any endpoints of concern for Cr(III). For exposure to Cr(VI), the Agency has identified toxicological endpoints of concern and has used these endpoints in conjunction with exposure to Cr(VI) for evaluating risks associated with Cr (VI).

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.

1.0 HAZARD CHARACTERIZATION

1.1 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-treatment 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.

1.1.1 Acute Toxicity

The acute toxicity summary of inorganic arsenic (arsenic acid 7.5%) is summarized in **Table 1**. Humans are very sensitive to arsenic toxicity when compared with other experimental animals. Inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and nervous system functions, and eventually death. The effects seen after short-term arsenic exposure (appearance of edema, gastrointestinal or upper respiratory symptoms) differ from those after longer exposure (symptoms of skin and neuropathy). Some of the effects after short-term exposure tended to subside gradually from the 5th day of the illness, despite continuous intakes of the poison. In contrast, symptoms of peripheral neuropathy appeared in some individuals even after the cessation of arsenical intakes

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 LD50 in the range of 15-175 mg/kg (ATSDR , 2000a, 2007). Although there are incidents been reported fatalities following skin exposure to isopropyl alcohol solution containing 30% arsenic (Cheraghali et al., 2007), there are no studies reporting death in humans after dermal exposure to inorganic arsenic aqueous solution. No mortality at dermal doses up to 1000 mg/kg in animal studies. 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).

1.1.2 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, 2007; 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 µg/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. A prospective cohort study was conducted in these two cities during the period when drinking water arsenic levels in Antofagasta is 40µg/L and in Valparaiso is less than 1µg/L. By comparing the pregnancy and birth

Table 1. Acute Toxicity Summary of Arsenic Acid (75%)

Guideline Reference No.	Study Type	MRID/ Data Accession No.	Results	Toxicity Category
81-1 (OPPTS 870.1100)	Acute Oral	404090-01	Mouse LD_{50} = _ 141 mg/kg = _ 160 mg/kg M+F = 150 mg/kg	II
		26356	Rat LD_{50} = _ 76 mg/kg = _ 37 mg/kg M+F = 52 mg/kg	I
81-2 (OPPTS 870.1200)	Acute Dermal	26356	Rabbit LD_{50} = _ 1750 mg/kg = _ 2300 mg/kg	II
81-3 (OPPTS 870.1300)	Acute Inhalation	404639-02	Mouse LC_{50} = _ 1.153 mg/L = _ 0.79 mg/L M+F = 1.040 mg/L	II
81-4 (OPPTS 870.2400)	Primary Eye Irritation	26356	Rabbit 3/6 animals died by day 7. The 3 surviving animals were sacrificed on day 9 because of severe ocular irritation and corrosion.	I
81-5 (OPPTS 870.2500)	Primary Skin Irritation	26356	Rabbit At 30 minutes, all animals showed moderate to severe erythema and slight to severe edema. All animals died prior to the 24 hour observation.	I
81-6 (OPPTS 870.2600)	Dermal Sensitization	406462-01	Guinea Pig Not a Sensitizer	

information form these two cities, the results suggests that moderate arsenic exposure (<50µg/L) during pregnancy may associated with reduction in birth weight (Hopenhayn et al., 2003).

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 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.

In a transplacental carcinoginicity study (Waalkes et al., 2003), pregnant C3H mice were given drinking water containing sodium arsenite at 0, 42,5 and 85 ppm ad libitum from day 8 to 18 of gestation. These dosages were well tolerated and did not decrease the body weight of the dams during gestation and the birth weight of the offspring after birth. However, after weaning at 4 weeks, the offsprings were put into separate gender-base groups according to maternal exposure level. The offspring received no additional arsenic treatment. The study lasted 74 weeks in males and 90 weeks in females. A complete necropsy was performed on all mice tissues were examined. In male, there was a dose-related increase in the incidences of heptatocellular carcinoma, and adrenal tumor. In females offspring, dose-related increases in ovarian tumors and lung carcinoma incidences were observed. (Waalkes et al., 2003)

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 (2007a), 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 or information concerning possible dose-response relationships. "

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." Since the publication of these NRC Reports, numerous studies on arsenic research continue to become available; and in September 2005 EPA scientists presented the information and ask Scientific Advisory Board (SAB) to comments on the adequacy of the information on the impact of childhood exposure to inorganic arsenics. . SAB concluded, based on available data, it is still not clear whether children differ from adults with regard to their sensitivity to the carcinogenic effects of arsenics.".

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).

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.

There are numerous epidemiologic investigations that have examined the association between arsenic exposure and non-cancerous and cancer health effects. These epidemiologic investigations include many different designs including prevalence studies, cross-sectional

studies, case-control, cohort, nested case-control, and ecological studies. Each of these types of investigations has certain specific inherent limitations, but the majority of the investigations found some level of association between arsenic and non-cancerous health effects, and arsenic and cancer.

In humans, arsenic is known to cause cancer of the skin and cancer of the lung, bladder, liver, kidney, and prostate. Prevalence studies of skin cancer in Taiwan indicate some degree of dose-response activity between amount of As exposure and skin cancer and other manifestations including keratosis and hyperpigmentation. They found that ascending rates for skin cancer, keratosis and hyperpigmentation corresponded with As content of well water and identified a dose-response relationship between As concentration and blackfoot disease.

The Taiwanese population has been extensively studied due to the switch from surface water wells to artesian (ground water) wells for drinking water more than 80 years ago in an attempt to improve the sanitation and salt content of their drinking water. However, in certain areas of Taiwan these artesian wells have been discovered to be contaminated with naturally occurring arsenic resulting in widespread exposure to extensive populations in Taiwan. There have also been a number of investigations performed on populations in other regions of the world including Bangladesh, Japen, India, South America, and North America where associations between arsenic and cancer have been investigated. A significant dose-related increase in mortality for both males and females was identified in Cordoba, Argentina for low-, medium-, and high-exposure groups.

1.1.3 Metabolism

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, 2007a), but the relative proportions of these products vary greatly. There is also variation between species and among human populations in the rate and extent of methylation of inorganic arsenic. New study finds there are genetic variations in genes associated with arsenic metabolism: MMA reductase gene (identified as glutathione s-transferase omega 1-1 gene) and purine nucleoside phosphorylase gene (polymorphism)

1.2 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), nicotinic 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).

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 acerbate 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). The Agency has not identified any endpoints of concern for Cr (III). For exposure to Cr(VI), the Agency has identified toxicological endpoints of concern and has used these endpoints in conjunction with exposure to Cr(VI) for evaluating risks associated with Cr(VI).

1.2.1 Acute Toxicity

The acute toxicity summary of the Chromium (VI) is summarized in **Table 2**. 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, and 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 dismally 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).

Table 2: Acute Toxicity Summary of the Chromium (VI)

Guideline	**Study Type** [Substance]	**MRID/Literature**	**Results**	**Toxicity Category**
81-1 (OPPTS 870.1100)	Acute Oral/Rat [Chromic Acid, 100% a.i.]	434294-01	LD_{50} = _ 56 mg/kg = _ 48 mg/kg M+F = 52 mg/kg	I
81-2 (OPPTS 870.1200)	Acute Dermal/Rabbit [Chromic Acid, 100% a.i.]	434294-02	LD_{50} = _ >48 mg/kg = _ 48 mg/kg M+F = 57 mg/kg	I
81-3 (OPPTS 870.1300)	Acute Inhalation/Rat [Chromic Acid, 100% a.i.]	434294-03	LC_{50} = _ 0.263 mg/L = _ 0.167 mg/L M+F = 0.217 mg/L	I
81-4 (OPPTS 870.2400)	Primary Eye Irritation [Various Cr(VI) compounds]	Literature	Waiver Corrosive	I
81-5 (OPPTS 870.2500)	Primary Dermal Irritation [Various Cr(VI) compounds]	Literature	Waiver Corrosive	I
81-6 (OPPTS 870.2600)	Dermal Sensitization /Guinea Pig [Various Cr(VI) compounds]	Literature	Strong sensitizer	

1.2.2 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 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 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 educed 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 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). In male bonnet monkeys exposed to potassium dichromate in drinking water at level of 100, 200, and 400 ppm hexavalent chromium can bring toxic effects on the testis and epididymis, including spermatotoxicity (Aruldhas et al., 2004, 2005, and 2006).

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).

IARC (1990) concluded that there is sufficient evidence of respiratory carcinogenicity in humans occupationally exposed during chromate production. Human exposure to hexavalent chromium by the inhalation route has been linked to increased rates of cancer in several occupational studies. A number of retrospective studies have associated significant increases in respiratory cancer to hexavalent chromium exposure in workers engaged in chromate production and chromate pigment production. Increased incidence of lung cancer has also been observed in workers employed in the chromium plating industries.

In human population, through oral exposure, only one study was identified in which cancer risk was investigated in a population exposed to hexavalent chromium in drinking water. Zhang and Li (1987) studied a population of 155 subjects outside Jinzhou, China who were exposed to drinking water at a concentration of approximately 20 mg/L. The source of the contamination was a chromium ore smelting facility located in a rural area near the city of Jinzhou in Liaoning Province in northeastern China. Cr(VI) contamination was detected in area wells in 1965. Subjects were observed to have sores in the mouth, diarrhea, stomachache, indigestion, vomiting, elevated white blood cell counts with respect to the controls, and higher per capita rates of cancers, including lung cancer and stomach cancer. Beaumont et al. (2008) reevaluated the available information and confirmed that there is a substantial association between stomach cancer mortality and exposure to Cr(VI) contaminated drinking water compared with nearby uncontaminated area and with Liaoning Province. Lung cancer mortality was also increased, but only in the comparison with Liaoning Province. Sedman et al. (2006) reviewed and summarized the findings of this study as well as additional reports by the investigators. The limitations of the study are that the precise exposure conditions, exposure durations, and confounding factors can not be established (Reynolds, 2007).

In 2007, the National Toxicology Program (NTP) released the study results for 3-month toxicity studies in F344/N rats and B6C3F1, BALB/c, and am3-C57BL/6 mice and the two year cancer studies of male and female F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate (greater than 99.7% pure) in drinking water (NTP, 2007a and 2007b).

In a 90-day subchronic study by the National Toxicology Program (2007b), sodium dichromate dihydrate (>99.7% a.i., Lot no. 062001) was administered to 10 F344/N rats/sex/dose and 10 B6C3F1 mice/sex/dose (core study animals) via drinking water at dose levels of 0, 62.5, 125, 250, 500, or 1,000 mg sodium dichromate dihydrate/L for 3 months (14 weeks) (equivalent to approximately 0, 1.7, 3.5, 5.9, 11.2, and 20.9 mg hexavalent chromium/kg body weight per day for rats and 0, 3.1, 5.2, 9.1, 15.7, and 27.9 mg/kg per day for mice). The mean body weight gains of the 1,000 mg/L F 344/N rats at the end of the study were significantly lower than those of the controls for males and females (89% and 94%, respectively, of the control. Additionally, the mean body weight gain for the 500 mg/L male rats was significantly different from the control group (95% of the control). Final mean body weights and overall body weight gain of the male and female B6C3F1 mice exposed to 125 mg/L of sodium dichromate dihydrate and higher were significantly less than those of the control animals, as well as the overall body weight gain in the 62.5 mg/L male mice. Water consumption by both male and female rats exposed to at least 250 mg/L and mice exposed to 125 mg/L or higher sodium dichromate dihydrate was generally less than that of the controls. Decreases in urine volume and increases in urine specific gravity in the clinical pathology rats were also observed and attributed to the reduced water consumption.

Signs of microcytic hypochromic anemia were observed at all dose levels and represented by lower automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts. These results were considered to be treatment-related in both rats and mice, with lower severity in mice. Additionally, increased neutrophil lymphocyte, leukocyte, and monocyte counts, mostly observed at the higher dose levels, were attributed to inflammatory response related to the inflammatory lesions observed during the histopathological examination (e.g., gastric lesions). For the clinical chemistry analyses, serum cholesterol and triglyceride concentrations were decreased and considered to be related to muscle injury. Increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations may have resulted from altered hepatic function. However, the only liver lesions reported in rats were chronic focal inflammation in females, and this lesion was also observed in the controls.

Only nonneoplastic lesions were found in the animals, with the incidences of histiocytic cellular infiltration generally significantly increased in the duodenum of rats and mice, the liver of female rats, and the mesenteric lymph node of mice exposed to levels about 125 mg/L. In male and female rats exposed to 1,000 mg/L of sodium dichromate dihydrate, there was increased focal ulceration, regenerative epithelial hyperplasia, and squamous epithelia metaplasia in the glandular stomach. Incidences of epithelia hyperplasia was also significantly increased in the duodenum of all exposed groups of mice.

The effect of sodium dichromate dihydrate was also examined in three strains of mice: B6C3F$_1$, BALB/c, and *am3*-C57BL/6 mice. *Am3*-C57BL/6 mice at levels of Cr(VI) of 0, 8, 15, and 26 mg/kg/day, respectively, for B6C3F$_1$ mice; 0, 9, 14, and 24 mg/kg/day, respectively for BALB/c mice; and 0, 8, 15, and 25 mg/kg/day, respectively for *am3*-C57BL/6 mice (NTP, 2007b) . All strains showed the following treatment-related effects: decreased body weight and body weight gains; decreased water consumption; increased erythrocytic microcytosis; increased incidence of histiocytic infiltration of the small intestines; and increased incidence of pancreatic secretory depletion. An increased incidence of glycogen depletion in the liver was observed in B6C3F$_1$ and *am3*-C57BL/6 mice but not in the BALB/c mice and is attributed to decreased food consumption. BALB/c and *am3*-C57BL/6 mice displayed increased serum alanine aminotransferase levels. Based on these results, this study did not confirm the hepatotoxic effects (with the exception of the minor alanine aminotransferase response) earlier observed in BALB/c mice. Based on the findings, treatment-related effects were observed 8 mg/kg/day Cr(VI) for B6C3F$_1$ and *am3*-C57BL/6 mice and 9 mg/kg/day Cr(VI) for BALB/c mice.

In the two year rat study (NTP, 2007a), groups of 50 male and 50 female rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 5, 20, 60, or 180 mg/L chromium) for 2 years (equivalent to average daily doses of 0, 0.21, 0.77, 2.10, or 5.95 mg Cr(VI)/kg body weight for males and 0, 0.26, 0.95, 2.45 or 7 mg Cr(VI)/kg body weight for females). The incidences of squamous cell papillomas or squamous cell carcinomas in the oral mucosa or tongue of the 516 mg/L male and female rats were significantly greater than those in the controls (significant trend and pair-wise comparisons, both at $p<0.01$). The incidence in 172 mg/L females and the 516 mg/L males and females exceeded the historical control ranges for drinking water studies and for all routes of administration. Concentration-related non-neoplastic liver lesions were observed in males and females exposed to 57.3 mg/L or greater. These included histiocytic cellular infiltration, chronic inflammation, fatty change (females), and clear cell focus (females). As summarized in Table 4, increased incidences of histiocytic infiltration also occurred in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females exposed to 57.3 mg/L or greater.

In this B6C3F1 mouse oncogenicity study (NTP, 2007a), groups of 50 male mice were exposed to drinking water containing 0,14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0, 0.45, 0.9, 2.4, or 5.7 mg Cr(VI) /kg body weight for males). Groups of 50 female mice were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0, 0.3, 1.2, 3.2 or 8.8 mg Cr(VI)/kg body weight for females). the incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum combined) were increased in exposed groups of male and female mice. The incidences of adenomas in 257.4 mg/L males and 172 and 516 mg/L females were significantly greater than those in the controls. The incidences of carcinomas were significantly increased in the 257.4 mg/L males and 516 mg/L females. The incidences of combined adenomas or carcinomas combined in the 85.7 and 257.4 mg/L males and 172 and 516 mg/L females were significantly increased compared to that in the controls.. The incidences in the ≥85.7 mg/L males and ≥57.3

mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration. In the small intestine, the incidences of diffuse epithelial hyperplasia were significantly increased in the duodenum of all exposed groups of male and female mice. The incidences of cellular histiocytic infiltration were significantly increased in the duodenum of 85.7 and 257.4 mg/L males and in 172 and 516 mg/L females. In the jejunum, the incidences of diffuse epithelial hyperplasia and histiocytic cellular infiltration were significantly increased in 516 mg/L females. The incidences of histiocytic cellular infiltration of the liver in all exposed groups of females, of the mesenteric lymph node in all exposed groups of males and females, and of the pancreatic lymph node of 85.7 and 257.4 mg/L males and 172 and 516 mg/L females were significantly increased.

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.

There is clear evidence that Cr(VI) is a mutagen, including positive results from *in vitro* mutagenicity studies and from *in vivo* animal studies. 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). Evidence indicated Cr(VI) can be absorbed by animal and further pass the placental barrier to the embryo. Kirpnick-Sobol et al. (2006) reported that exposure of pregnant mice (C57BL/6J pun/pun) to either potassium dichromate (Cr VI; 62.5 or 125.0 mg/L) or chromium (III) chloride (1,875 or 3,750 mg/L) in drinking water during gestational days 10 to 20 resulted in significant increases in the frequencies of large-scale DNA deletions in their pups examined at 20 days of age. Kirpnick- Sobol et al. (2006) reported that in comparing the embryo chromium concentrations to DNA deletion frequency revealed that Cr(III) exposure lead to induction of DNA deletions at an ~3-fold lower embryo chromium concentration than dose exposure to Cr(VI).

1.2.3 Metabolism

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 approximately 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 thionyl 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.

2.0 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:

2.1 Inorganic Arsenic-Endpoint Selection

On August 21, 2001, the OPP's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Inorganic Arsenic** and established the toxicological endpoints for occupational exposure risk assessments. On October, 23-25 2001, the FIFRA Scientific Advisory Panel (SAP) met and discussed some issues about the end points proposed by the HIARC. The inorganic arsenic toxicological end-points selected for CCA occupational risk assessment are summarized in **Table 3**.

2.1.1 <u>Acute Reference Dose (aRfD)</u>

In the Office of Pesticide Program (OPP) in EPA, the acute reference dose (aRfD) was used in the risk assessment associated with oral exposure to food related chemicals. 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 use.

2.1.2 Chronic Reference Dose (cRfD)

The U.S. EPA has published a chronic RfD value for inorganic arsenic (USEPA IRIS, 1998). However, as with the acute RfD, in OPP, the chronic RfD in OPP was considered for evaluating risks associated with food and/or drinking water related chemical uses. Because there are no exposure scenarios relevant to the currently registered uses of inorganic arsenic, and specifically the registered uses in CCA-treated lumber, no chronic RfD value is needed for the current inorganic arsenic use in CCA-treated wood use.

2.1.3 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 patients with age information were ranging from 15 – 69 years). 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, and 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.

USEPA Region 8 has also 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 (USEPA Region 8, 2001). 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 (1998) can be used for acute and subchronic 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 Adverse 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 (1998) 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. The Region 8 report was part of the background documents presented to the 2001 SAP.

For the risk assessment, based on the recommendations of the SAP, the Agency decided to use a Margin of Exposure (MOE) of 30. This value of 30 was recommended on the basis that the severity of symptoms near or moderately above the LOAEL (0.05mg/kg/day) warranted a full uncertainty factor of 10 and an uncertainty factor of 3 for protection of children.

2.1.4 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.

For children playing around playground equipment, however, it is assumed the dermal exposure would be arsenic in wood surface residue and/or arsenic in soil, a dermal absorption value of 3% will be used (SAP, 2001).

Because the handlers and workers are exposed to the arsenic residue from the aqueous solution during mixing, loading, and handling or are exposed to newly treated, or "wet' wood which has arsenic residues on the surface of the wood, in the occupational assessment, a dermal absorption factor of 6.4 percent is used. 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.

2.1.5 Short (1-30 days) and Intermediate (30-180 days) Dermal Exposure

Since there are no appropriate dermal studies, same as studies selected for short- and intermediate-term incidental oral exposure, the 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) were selected for short (1-30 days) and intermediate (30-180 days) term dermal exposure scenarios. 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. An Margin of Exposure (MOE) of 30 should be applied to the LOAEL. This value consists of a 10x factor for intraspecies variation and an additional intraspecies uncertainty factor of 3 to provide for protection of children.

2.1.6 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.

2.1.7 Short-, Intermediate-, and Long-term Inhalation Exposure

Short-, intermediate-, and long-term endpoints were not identified in the HIARC report for inhalation exposures to arsenic. Since no inhalation studies are available, committee selected the same studies as for the dermal risk assessments. As discussed in endpoints selected for dermal exposure scenarios (Sections 2.1.5 and 2.1.6), acceptable Margin of Exposure (MOE) of 30 should be applied to the short- and intermediate inhalation scenarios. For long-term inhalation exposure scenarios, an acceptable margin of exposure of 3 should be applied.

2.1.8 Carcinogenicity

There is sufficient evidence from human data indicating arsenic exposure can cause cancer. In 1975, the U.S. Environmental Protection Agency (EPA) adopted a drinking water regulation for arsenic based on a U.S. Public Health Service standard set in 1942. The drinking water standard of 50 micrograms per liter (µg/L), which is equivalent to 50 parts per billion (ppb), remains in effect until 2006. EPA conducted risk assessments for arsenic-induced skin cancer in 1980, 1988, and 1992. The Agency's Integrated Risk Information System (IRIS) carcinogenic risk from oral exposure to arsenic is based on southwestern Taiwanese skin cancer studies published in 1977 and 1968. The slope factor published by EPA's Integrated Risk Information System (IRIS) is 1.5 $(mg/kg/day)^{-1}$.

In 1996, EPA charged the National Academy of Sciences (NAS) to review the Agency's characterization of potential health risks from ingestion of arsenic; the available data on carcinogenic and non-carcinogenic effects of arsenic in drinking water; the data on metabolism, kinetics, and mode(s) of action of arsenic; and research priorities. An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and increased incidences of skin cancer were observed in populations consuming drinking water high in inorganic arsenic. In order to evaluate the cancer risk associated with arsenic exposure in drinking water, in 1997, at EPA's request, the National Academy of Sciences' (NAS) Subcommittee on Arsenic of the Committee on Toxicology of the National Research Council (NRC) met. The NAS/NRC Subcommittee finished their work in March 1999. In general, the NRC report confirms and extends concerns about human carcinogenicity of drinking water containing arsenic and offers perspective on dose-response issues and needed research. The NRC recommended that EPA analyze risks of internal cancers both separately and combined. NRC used data from Wu et al. 1989 and Chen et al. 1992 to address several risk assessment issues.

EPA applied many of the recommendations from the 1999 NRC report in the risk haracterization used to support the January 2001 revised arsenic drinking water regulation. The Agency based its new 10 ppb arsenic standard on the risk of bladder and lung cancers from the Taiwanese data used by NRC and estimated 1-6 x 10^{-4} risk to the 90th percentile of the U.S. population.

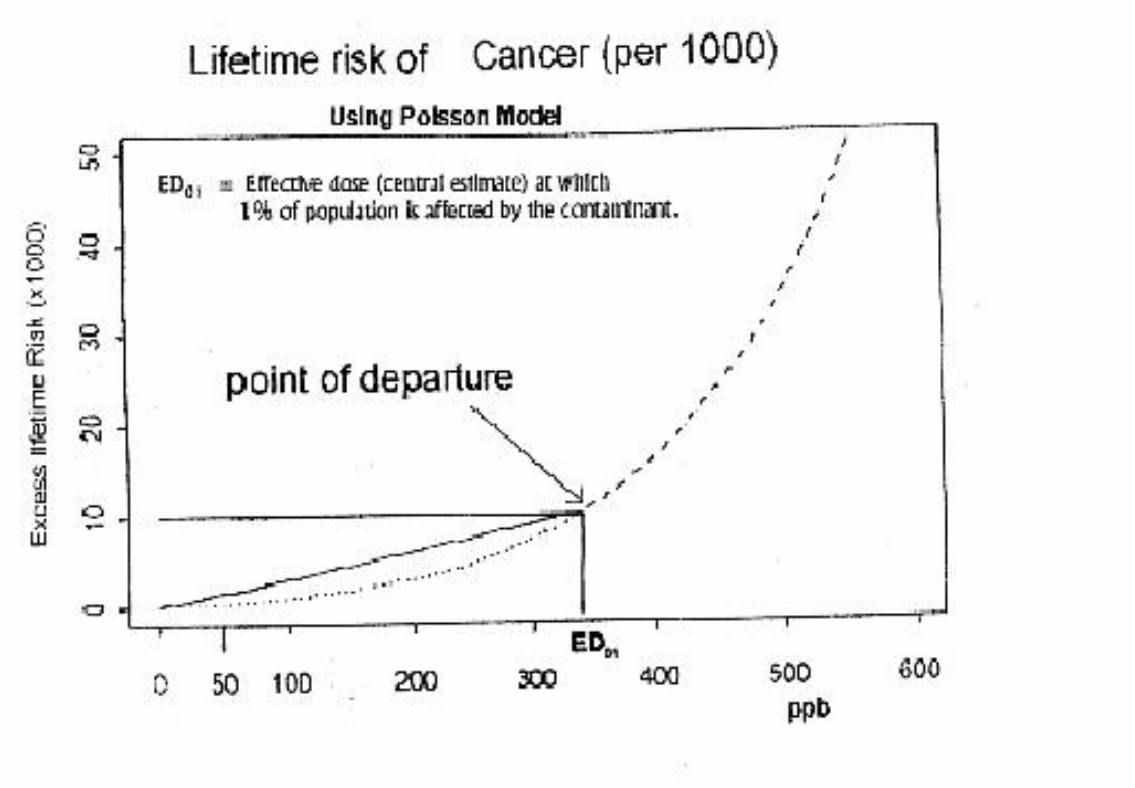
In the 2001 revised arsenic drinking water risk assessment, EPA used risk estimates taken from Morales et al. (2000). Morales et al. fit a variety of dose-response models to lung and bladder cancer data from an arseniasis-endemic region of southwestern Taiwan. Risk was assumed to increase linearly with dose, from zero to the effective dose (central estimate) at which 1% of population is affected by the chemical (ED01). The slope of the line extrapolated from ED01 to the origin was calculated and used as the cancer slope factor for cancer risk assessment (see **Plot 1** as an example). In the risk assessment associated with inorganic arsenic in drinking water in 2000 (EPA, 2001), EPA presented two sets of risk estimates, higher and lower:

For the higher set of risks: For the higher set of risks: EPA used the theoretical risk estimates taken directly from Morales et al. (2000). Assumed drinking water consumption in Taiwanese population is 3.5 L/day for male and 2.0 L/day for female. A drinking water consumption rate of 1.2 L/day is assumed for both male and female in U.S. population.

- **For the lower set of risks:** For the lower set of risks: EPA adjusted the theoretical risks to take into account possible higher arsenic consumption in Taiwan. For these estimates, EPA assumed that people in Taiwan consumed an additional 1 L/d of water in cooking, due to dehydration of rice and sweet potatoes, and a further 50 μg/d of arsenic directly from their food. A drinking water consumption rate of 1.0 L/day is assumed for both male and female in

U.S. population.

Following the risk assessment associated with inorganic arsenic in drinking water are presented in 2000, EPA asked the National Research Council (NRC) to meet again to: (1) review EPA's characterization of potential human health risks from ingestion of inorganic arsenic in drinking water;(2) review the available data on the carcinogenic and non-carcinogenic effects of inorganic arsenic; (3) review the data on the metabolism, kinetics and mechanism(s)/mode(s) of action of inorganic arsenic; and (4) identify research needs to fill data gaps.



PLOT 1: Example of how the cancer risk estimations are derived

In April 2001, EPA charged the NRC to review the risk analysis used to support the revised arsenic drinking water regulation in light of studies published since the 1999 NRC report. NRC released its update report in September 2001. NRC update report concluded that (1) arsenic--induced bladder and lung cancers still should be the focus of an arsenic-related cancer risk

assessment; (2) the southwestern Taiwan data are still the most appropriate for arsenic-related cancer risk assessments; and (3) present modes of action data are not sufficient to depart from the default assumption of linearity. The 2001 NRC update also made specific recommendations with respect to the overall cancer risk estimate.

The Agency incorporated the NRC's recommendations, and in September 2005 EPA scientists presented the proposed approach in the dose response assessment of cancer effects for inorganic arsenic to the Science Advisory Board (SAB). Linear dose response was selected for inorganic arsenic-induced bladder and lung cancer. The SAB released its final report in 2007 and concluded southwestern Taiwan data are still remains the most appropriate dataset for assessing the cancer risk. Inorganic arsenic has the potential for a highly complex mode of action in causing different forms of cancer. Although indirect studies suggest a threshold level, SAB concluded that studies do not show where the threshold might be or the shape of the dose-response curve at low dose levels. Therefore, SAB (2007) suggested still using of linear model until more is learned about the pharmacokinetics and pharmacodynamics in causing different forms of cancer in human population.

For this risk assessment, an oral cancer slope factor of 3.67 $(mg/kg/day)^{-1}$ was used. This is the mean slope factor derived from the higher risk approach for both lung and bladder cancers. This slope factor was used by the EPA's Office of Water when it established the MCL for arsenic in drinking water (U.S. EPA, 2001) and also by the Consumer Product Safety Commission when it performed its deterministic assessment for children's risks from CCA-treated playsets in March 2003 (CPSC, 2003). Attachment 1 presents how the slope factor was derived.

The slope factor published by EPA's Integrated Risk Information System (IRIS), 1.5 $(mg/kg/day)^{-1}$, is also under revision due to the recommendation by the NRC in 2001 and SBB (2007). If the Agency had used the current IRIS cancer slope factor (1.5 $(mg/kg/day)^{-1}$) instead of the slope factor used in the Office of Water's arsenic MCL document (3.67 $mg/kg/day)^{-1}$) (U.S. EPA, 2001), the cancer risk would be approximately 41% of the current cancer risk estimates in this document . For example, a reported cancer risk of 5.0E-4 using the cancer slope factor of 3.67$(mg/kg/day)^{-1}$ would be equivalent to 2.0E-4 using the IRIS cancer slope factor of 1.5 $(mg/kg/day)^{-1}$.

The inhalation unit risk (IUR) for a continuous 24-hour exposure is 4.3 x 10^{-3} $(\mu g/m^3)^{-1}$ which is equivalent to a cancer slope factor of 15.1 $(mg/kg/day)^{-1}$ for the general population. To assess inhalation cancer risks from an 8-hour work day, the 24-hour derived CSF is adjusted to an 8-hour exposure representing a typical work day (i.e., 24-hour CSF x (8-hr/24-hr)) or a potency factor (CSF) is 5.0 $(mg/kg/day)^{-1}$.

Table 3. Toxicological Endpoints for Assessing Exposures/Risks to Inorganic Arsenic (V)

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary	This risk assessment is not required.		
Chronic Dietary	This risk assessment is not required.		
Incidental Short- and Intermediate- Term Oral	LOAEL[(a)] = 0.05 mg/kg/day MOE = 30	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al.(1989) and Mizuta et al. (1956)
Dermal Short- and Intermediate-Term [(a)(b)]	LOAEL[(a)]= 0.05 mg/kg/day MOE = 30	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al.(1989) and Mizuta et al. (1956)
Dermal Long-Term [(a)(b)]	NOAEL[(a)] = 0.0008 mg/kg/day MOE = 3	Based on hyperpigmentation, keratosis and possible vascular complications.	Tseng et al. (1968) and Tseng (1977)
Inhalation Short- and Intermediate-Term[(c)]	LOAEL[(a)]= 0.05 mg/kg/day MOE = 30	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al.(1989) and Mizuta et al. (1956)
Inhalation, Long-Term	NOAEL[(a)] = 0.0008 mg/kg/day MOE = 3	Based on hyperpigmentation, keratosis and possible vascular complications.	Tseng et al. (1968) and Tseng (1977)
Carcinogenicity - Inhalation (Inhalation Risk)	CSF= 15.1[(d)] $(mg/kg/day)^{-1}$ (For general Population) CSF= 5.0[(e)] $(mg/kg/day)^{-1}$ (For 8 hour working day)	Lung cancer	Chronic epidemiological inhalation study on humans
Carcinogenicity - Oral Ingestion (Oral and Dermal Risks)	CSF = 3.67 [(f)] $(mg/kg/day)^{-1}$	Internal organ cancer (liver, kidney, lung and bladder) and skin cancer	Chronic epidemiological oral study on humans

Note: [(a)] MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level.

[(b)] The dermal absorption factor = 6.4%. (Note: The FIFRA Scientific Advisory Panel recommended use of a lower value of 2-3%. The occupational assessment in the risk assessment uses 6.4 percent dermal absorption because the handlers and workers are exposed to the arsenic residue from the aqueous solution during mixing, loading, and handling or are exposed to newly treated, or "wet' wood which has arsenic residues on the surface of the wood).

[(c)] For inhalation exposure, a default absorption factor of 100% is used. Route-to-route extrapolation is used to estimate the exposed dose.

[(d)] Inhalation unit risk (IUR) is derived from a 24 hour exposure inhalation unit risk with a value of 4.3×10^{-3} $(\mu g/m^3)^{-1}$. To convert the IUR to a cancer slope factor in units of $(mg/kg/day)^{-1}$ for the general population = IUR $(\mu g/m^3)^{-1}$ x 1/70 kg x 20 m^3/day x 1 mg/1,000 µg (EPA, 1989).

[(e)] For workers working 8 hour per day, the inhalation cancer slope factor (CSF) derived from the 24 hour IUR for general population, is adjusted for an 8 hour work day. CSF for 8-hr work day = general population CSF of 15.1 $(mg/kg/day)^{-1}$ x (8hrs/24 hrs) = 5.0 $(mg/kg/day)^{-1}$.

[(f)] CSF is derived from the risk assessment associated with inorganic in drinking water are presented in 2000. The 2001 National Research Council (NRC) update made specific recommendation with respect to the overall cancer risk estimates. The Agency is currently considering these recommendations and their potential impact on the cancer potency estimate. Based on the Agency's considerations of these recommendations, the current proposed cancer potency number may change in the final version of this risk assessment.

2.2 Inorganic Chromium Endpoint Selection

On August 28, 2001, the OPP's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Cr(VI)** and established the toxicological endpoints for occupational exposure risk assessments. On October, 23-25 2001, the FIFRA Scientific Advisory Panel (SAP) met and discussed some issues about the end points proposed by the HIARC. The recommended toxicity endpoints related to inorganic chromium (VI) are summarized in **Table 4.**

2.2.1 Acute Reference Dose (aRfD)

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.

2.2.2 Chronic Reference Dose (cRfD)

There are no exposure scenarios relevant to the currently registered uses of inorganic chromium, and specifically the registered uses in CCA-treated lumber. Therefore a chronic reference dose is not required for the risk assessment.

2.2.3 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 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).

2.2.4 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 $\mu M/cm^2$/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.

2.2.5 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. Nonetheless, it is apparent that both forms of chromium cause hypersensitivity reactions in humans.

For direct exposure of hexavalent chromium on wood surface, in order to address the potential dermal sensitization potential of Cr(VI), the agency proposed a quantitative approach to assessment of dermal sensitization, the Office of Pesticide Programs presented a set of issues to the FIFRA Scientific Advisory Panel (SAP) on May 4-6, 2004. The SAP issued their final report in July of 2004. The Panel concluded that this estimate of a Concentration of Concern for Dermal Sensitization (CCDS) should be protective against elicitation (i.e. reactions in already sensitized persons) and therefore would also be protective against induction (i.e. reaction in non-sensitized persons). SAP suggests that for dermal sensitization, the end-point selected for risk assessment should not based on on a LOAEL but on the MET10. The MET is defined by a specific response level; in the present case, the 10% response level was determined by the FIFRA SAP to be adequate and sufficiently conservative. The Panel also stressed that the Agency "consider all data as part of a weight of evidence approach.

As part of the SAP report in 2004, the Panel suggested a Repeat Open Application Test (ROAT) study could be conducted to better represent real-life exposures to treated wood containing hexavalent chromium for refinement of this risk assessment. In July of 2006, a Repeat Open Application Test (ROAT) study was submitted to the Office of Pesticide Programs for the purpose of refining further the level of concern recommended by the FIFRA SAP. The citation and executive summary of this study is listed below:

Proctor, D.; Gujral, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012506. 324 p. (MRID 46884001)

Proctor, D.; Gujral, S.; Fowler, J. (2006) Supplemental Information to the Final Report Titled "Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI)." Unpublished document dated August 24, 2006. Project No. FPRL #012506. 347 p. (MRID 46922901)

Proctor, D.; Gujral, S.; Su, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as Potassium Dichromate: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012406. Includes Supplemental Information documenting ethical conduct of the research. 664 p. (MRID 46930701)

EXECUTIVE SUMMARY:

A Repeat Open Application Test (ROAT) was performed on 60 chrome-sensitive human subjects and 10 non-sensitive control subjects. Sensitization status of subjects was confirmed through occluded patch testing. The purpose of this study was to develop a 10% minimum elicitation threshold value ($MET_{10\%}$) for elicitation of allergic contact dermatitis for hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution). The study design involved the application of five concentrations of hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution) to the right forearm of the test subjects and application of five concentrations of potassium dichromate to the left forearm of the same subjects. Ten additional subjects not sensitive to hexavalent chromium served as controls using the highest concentration of copper contained within the wood treatment solution.

Test subjects received application of both CopperShield® treatment solution and potassium dichromate once per day for 10 days. After a 6-hour exposure the subjects washed their forearms using soap provided to them. Prior to the next application, participants were evaluated for occurrence of any skin responses, including erythema, papules, pruritis, scaling, and vesicles. Results were evaluated by Dr. Fowler, who interpreted them as either allergic or irritant in nature and graded each response. Seventy-two hours following the last testing day participants were evaluated by Dr. Fowler to determine if an allergic contact dermatitis response had occurred. Results from the ROAT phase of the study were modeled using Benchmark Dose Software (BMDS) to fit the dose-response data and calculate the 10% Minimum Elicitation

Threshold value. Results of closed-patch testing with potassium dichromate using 12mm Finn Chambers showed that all participants for the ROAT phase of the study were confirmed to have sensitivity to hexavalent chromium. According to the report, the proportion of participants in the ROAT phase of the study who exhibited a high grade of ACD response (+3) in this patch test was much higher than than the overall proportion graded at +3 in the North American Contact Dermatitis Group database from 1998-2002. Twenty-six percent (26%) of the ROAT study participants showed a +3 reaction to the initial patch test, while the NACDG database of 495 individuals shows a 7.7% response percentage for a +3 reaction. Thus, in an effort to make the dose-response observed in this study more representative of the overall hexavalent chromium-sensitized population in the United States, the authors reported both unadjusted results and results adjusted to the NACDG database by simulating the percent response expected in the ROAT study if the proportions of +1, +2, and +3 responders in the current study had been consistent with those in the NACDG database.

In addition to this adjustment of the dose-response data, two scenarios were modeled from the CopperShield® results. Scenario 1 included only responses graded as allergic in nature. Scenario 2 combined both irritant and allergic responses in calculation of a 10% response level.

For Scenarios 1 and 2, the report stated that of all the models run, the unconstrained log-probit model provided the best fit for the dose-response data. For CopperShield®, the 10% MET values for Scenarios 1 and 2 of the unadjusted dose-response data were 270 and 91.8 ng $Cr(VI)/cm^2$ respectively, while 10% MET values for the adjusted data were 349 and 166 ng $Cr(VI)/cm^2$ respectively. With the exception of the Scenario 2 unadjusted data, these 10% MET values are higher than the value by Nethercott et al. (1994) of 89 ng $Cr(VI)/cm^2$ from occluded patch testing.

This study is classified **acceptable/non-guideline** and fulfills the purpose for which it was conducted.

Because this study involved intentional exposure of human subjects and reported a toxic endpoint, EPA's rule for the protection of human subjects of research requires review of the study by the Human Studies Review Board (HSRB). The ROAT study was presented to the HSRB on October 18, 2006 for their advice on its scientific and ethical merits.

The HSRB considered the ROAT study to be scientifically sound and ethically acceptable. The HSRB recommended defining the level of concern (10% MET) based on Scenario 2 data, combining allergic and irritant responses, without adjustment to the NACDG database. The HSRB recommended use of Scenario 2 data because:

- The principal investigator, Dr. Fowler, was not blinded to the dose levels on the test subjects

- Only one person made the observations of ACD vs irritation when two would have been more appropriate

- The control group of non sensitized individuals that received the ACC solution did not exhibit irritation (nor ACD).

In addition, the HSRB recommended that the non-normalized data set be used on the basis that the dose level used in the patch test portion of the ROAT study compared to the dose level for the individuals in the NACDG data base is unknown, and that there is uncertainty in comparing the data in the older NACDG data base and the data from the ROAT study (e.g., potential changes in the population's chromium sensitivity over time and how ROAT study test subjects would fit into the NACDG database).

Agency accept the HSRB's suggestion and the **92 ng Cr(VI)/cm^2** as recommended by the HSRB is a level of dermal exposure at which elicitation of allergic contact dermatitis is not expected to occur from repeated dermal contact was selected as Concentration of Concern for Dermal Sensitization (CCDS). Agency concluded that an uncertainty factor does not necessarily need to be applied to the MET as it is traditionally done in the case of the use of a LOAEL (MOE = 1), as the MET is more analogous to a benchmark dose, to which uncertainty factors are not routinely applied.

2.2.6 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. Linberg, 1983 studied respiratory symptoms, lung function and changes in nasal septum in 104 workers (85 males, 19 females exposed in chrome plating plants. Workers were interviewed using a standard questionnaire for the assessment of nose, throat and chest symptoms. Nasal inspections and pulmonary function testing were performed as part of the study. The median exposure time for the entire group of exposed subjects (104) in the study was 4.5 years (0.1-36 years). A total of 43 subjects exposed almost exclusively to chromic acid experienced a mean exposure of 2.5 years (0.2-23.6 years). The subjects exposed almost exclusively to chromic acid were divided into a low exposure group (8-hr TWA below 0.002 mg/m^3, N=19) and a high-exposure group (8-hr TWA above 0.002 mg/m^3, N=24). Exposure measurements using personal air samplers were performed for 84 subjects in the study on 13 different days. Exposure for the remaining workers 20 workers was assumed to be similar to that measured for workers in the same area. Nineteen office employees were used as controls for nose and throat symptoms. A group of 119 auto mechanics whose lung function had been evaluated by similar techniques was selected as controls for lung function measurements. Smoking habits of workers were evaluated as part of the study.

At mean exposures below 0.002 mg/m^3, 4/19 workers from the low-exposure group experienced subjective nasal symptoms. Atrophied nasal mucosa were reported in 4/19 subjects from this

group and 11/19 had smeary and crusty and septal mucosa, which was statistically higher than the controls. No one exposed to levels below 0.001 mg/m^3 complained of subjective symptoms. At mean concentrations of 0.002 mg/m^3 or above, approximately 1/3 of the subjects had reddened, smeary or crusty nasal mucosa. Atrophy was seen in 8/24 workers, which was significantly different from controls. Eight subjects had ulcerations in the nasal mucosa and 5 had perforations of the nasal septum. Atrophied nasal mucosa was not observed in any of the 19 controls, but smeary and crusty septal mucosa occurred in 5/19 controls.

Short-term effects on pulmonary function were evaluated by comparing results of tests taken on Monday and Thursday among exposed groups and controls. No significant changes were seen in the low-exposure group or the control group. Non-smokers in the high-exposure group experienced significant differences in pulmonary function measurements from the controls, but the results were within normal limits.

The authors concluded that 8 hour exposure to chromic acid above 0.002 mg/m^3 may cause a transient decrease in lung function, and that short-term exposure to greater than 0.002 mg/m3 may cause ulceration and perforation. Based on the result of this study, a LOAEL of 0.002 mg/m^3 can be identified for incidence of nasal septum atrophy following exposure to chromic acid mists in chrome plating facilities. Therefore, the LOAEL of continuous exposure of 0.002 mg/m^3 was based on ulcerations, perforations of the nasal septum and pulmonary function changes. A MOE of 30 is selected (3x to extrapolate from LOAEL to NOAEL and 10X for intraspecies extrapolation).

2.2.7 Carcinogenicity

The cancer endpoint for inhalation exposure is classified as group A (known human carcinogen) with an inhalation unit risk of $1.16x10^{-2}$ $(g/m^3)^{-1}$ (Table 5). The 24 hours inhalation unit risk is 1.16×10^{-2} $(g/m^3)^{-1}$ which can also be expressed as 0.0116 m^3/ g. To convert the air concentration to a dose to yield units of kg-day/mg or $(mg/kg/day)^{-1}$ the unit risk is expressed mathematically as 0.0116 m^3/ g x day/20 m^3 x 1000 g/mg x 70 kg = 40.6 $(mg/kg/day)^{-1}$. For workers working 8 hour per day, the inhalation potency factor is derived from the 24 hour inhalation potency factor for general population. CSF = 40.6 $(mg/kg/day)^{-1}$ x (8hrs/24 hrs) = 13.5 $(mg/kg/day)^{-1}$.

For oral and/dermal exposure, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Program (OPP) classified hexavalent chromium, Cr(VI), as "Likely to be Carcinogenic to Humans" based on the presence of oral mucosa and tongue tumors in male and female rats and tumors of the small intestine in male and female mice at doses that were adequate, but not excessive, to assess carcinogenicity (Kidwell, 2008). There is clear evidence that Cr(VI) is mutagenic and convincing evidence supporting a mutagenic mode of action. The decision is also qualitatively supported by human epidemiological data which indicates an association between exposure and increased stomach tumor incidence. The Committee recommended using a linear low-dose extrapolation approach (Q1*) for estimating the human cancer risk based on the most potent tumor type. Based on the

NTP (2007) female mouse carcinogenic study data, a potency factor (CSF) of 0.79 $(mg/kg/day)^{-1}$ is derived (Brunsman, 2008).

Data exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus., based on the EPA's guidelines for carcinogen risk assessment - Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005), CARC (Kidwell, 2008) concluded the age dependent adjustments factors (ADAFs) should be applied for cancer risk assessments associated with children exposure to hexavalent chromium.

The guideline proposed ADAFs are:

- Risk during the first 2 years of life (where the ADAF = 10);
- Risk for ages 2 through < 16 (ADAF = 3); and
- Risk for ages 16 until 70 years (ADAF = 1).

The 10-fold and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life exposure to carcinogens that act through a mutagenic mode of action. It is important to emphasize that these adjustments are combined with corresponding age-specific estimates of exposure to assess cancer risk.

Table 4. Toxicological Endpoints for Assessing Exposures/Risks to Chromium (VI)

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary	This risk assessment is not required.		
Chronic Dietary	This risk assessment is not required.		
Incidental Short- and Intermediate- Term Oral	NOAEL[(a)] = 0.5 mg/kg/day of chromic acid [0.12 mg/kg/day of Cr(VI)] MOE = 100	based on the increased incidence of maternal mortality and decreased body weight gain at LOAEL of 2.0 [0.48 mg/kg/day of Cr (VI)]	Developmental/Rabbit Tyl, 1991
Dermal Exposure[(b)] Systemic Effects (All Durations)	Because dermal irritation and dermal sensitization are the primary concern through the dermal exposure route, no toxicological end-point is selected for use in assessing dermal exposure risks to chromium.		
Dermal Exposure Dermal Effects (All Durations)	CCDS[(a)] = 92 ng Cr(VI)/cm^2 MOE = 1	Based on the MET_{10} (10% response level) which was determined by the FIFRA SAP to be adequate and sufficiently conservative.	Proctor, D.; Gujral, S.; Fowler, J. 2006
Inhalation Exposure (All Durations)	LOAEL[(a)] = 0.002 mg/m^3; (or 2.3 x 10^{-4} mg/kg/day) MOE = 30	based on nose and throat symptoms observed at the 0.002 mg/m^3 level	Linberg and Hedenstierna, 1983.
Carcinogenicity - Inhalation (Inhalation Risk)	CSF = 40.6 [(c)](mg/kg/day)$^{-1}$ (For general Population) CSF = 13.5 [(d)](mg/kg/day)$^{-1}$ (For 8 hour working day)	Lung tumors	IRIS
Carcinogenicity - Oral Ingestion (Oral and Dermal Risks)	CSF = 0.79 [(e)] (mg/kg/day)$^{-1}$ With age dependent adjustments factors (ADAFs) applied.	Female Mice - Small Intestine (Duodenum, Jejunum or Ileum) adenomas and/or carcinomas combined	NTP (2007a)

Note:

(a). MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level. CCDS = Concentration of Concern for Dermal Sensitization.

(b). The dermal absorption factor for Cr(VI) = 1.3% for handler dermal contact with chromated arsenical pesticides.

(c) The 24 hours inhalation unit risk is 1.16 x 10^{-2} ($\mu g/m^3$)$^{-1}$ which can also be expressed as 0.0116 $m^3/\mu g$. To convert the air concentration to a dose to yield units of kg-day/mg or (mg/kg/day)$^{-1}$ the unit risk is expressed mathematically as 0.0116 $m^3/\mu g$ x day/20 m^3 x 1000 $\mu g/mg$ x 70 kg = 40.6 (mg/kg/day)$^{-1}$ (EPA, 1989).

(d) For workers working 8 hour per day, the inhalation cancer slope factor (CSF) derived from the 24 hour CSF for the general population, is adjusted for an 8 hour work day . CSF for 8-hr work day = general population CSF of 40.6 (mg/kg/day)$^{-1}$ x (8hrs/24 hrs) = 13.5 (mg/kg/day)$^{-1}$.

(e) CARC (2008) classified hexavalent chromium, Cr(VI), as "Likely to be Carcinogenic to Humans" based on the presence of oral and tongue tumors and/or carcinomas for rats in both sexes, and the presences of adenoma and carcinoma in both sexes of mice at doses that were adequate but not excessive to assess the carcinogenicity. There are clear evidence that Cr(VI) is mutagenic. The decision is also qualitatively supported by the human epidemiological study. The Committee recommended using a linear low-dose extrapolation approach (Q1*) for estimating the human cancer risk based on the most potent tumor type.

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Attachment 1

US EPA's Risk Assessment for Arsenic in Drinking Water

US EPA's Risk Estimates for Arsenic in Drinking Water
8 March 2002

This spreadsheet contains the U.S. Environmental Protection Agency's estimates of the average lifetime excess risk of death from lung and bladder cancers due to arsenic in drinking water. EPA developed these risk estimates to support its January 2001 National Primary Drinking Water Regulation for arsenic (US EPA, 2001).

The calculations in this spreadsheet describe the theoretical, population-averaged risks of death for a single person drinking a given concentration of arsenic for their entire lifetime. Changes in exposure over time, aggravating or mitigating factors, and ordinary variation between people mean that any one person's risk will be different from the risks computed here. However, the risks in this spreadsheet represent EPA's best estimate of the average risks to people exposed to given levels of arsenic in drinking water in the U.S.

The risk estimates computed here provide only one piece of EPA's arsenic risk assessment. For its risk assessment, EPA combined estimates of risk for a single "average" person with information about the distributions of arsenic occurrence, sex, body weight, and drinking water consumption in the U.S, in order to estimate the expected numbers of lives saved under different regulatory options. EPA also considered information about other, nonquantifiable risks. Only one of these factors, the theoretical average risk of lung and bladder cancers, is described in this spreadsheet. For more information about EPA's arsenic risk assessment, see US EPA (2000, 2001).

To estimate the risks due to arsenic in drinking water, EPA used risk estimates taken from Morales et al. (2000). Morales et al. fit a variety of dose-response models to lung and bladder cancer data from an arseniasis-endemic region of southwestern Taiwan. Of the models in Morales et al., EPA used estimates from Model 1, fit with no comparison population. Model 1 is a Poisson regression model in which the logarithm of the hazard (rate of death among those surviving to a given age) increases linearly with arsenic dose and quadratically with age. The risk estimates from Model 1 are contained in the yellow cells of the "Calculations" worksheet. The estimates are characterized there (as in Morales et al.) by ED01, the level at which a person's lifetime risk of death increases by 1% (for example, from 2% to 3%), and LED01, a 95% lower confidence bound for ED01.

EPA presented two sets of risk estimates, higher and lower, in its final arsenic rule. For the higher set of risks, EPA used the theoretical risk estimates taken directly from Morales et al. (2000). Risk was assumed to increase linearly with dose, from zero to the ED01. For the lower set of risks, EPA adjusted the theoretical risks to take into account possible higher arsenic consumption in Taiwan. For these estimates, EPA assumed that people in Taiwan consumed an additional 1 L/d of water in cooking, due to rehydration of rice and sweet potatoes , and a further 50 ug/d of arsenic directly from their food. These assumptions resulted in lower risk estimates for the U.S., since the same number of cancer deaths in Taiwan were assumed to have resulted from higher arsenic exposure there. EPA also assumed a lower mean drinking water consumption in the U.S. A summary of EPA's assumptions for its high and low risk estimates is as follows:

		Low risk	High risk
Drinking water consumption, U.S.	L/d	1	1.2
Cooking water consumption, Taiwan	L/d	1	0
Additional arsenic consumed in food, Taiwan	ug/d	50	0

The attached "Calculations" worksheet contains all of the necessary assumptions, intermediate calculations, and results to derive EPA's theoretical mean risk estimates.

Exposure assumptions								
	Arsenic concentration in drinking water	US ppb			50			
Risk assumptions								
			Taiwan		U.S.			
			M	F	M	F		
	Body weight	kg	55	50	70	65		
	Drinking water consumption	L/d	3.5	2.0	1.2	1.2		
	Cooking water consumption	L/d	0.0	0.0				
	Additional As consumed in food	ug/d	0	0				
Results: Lifetime excess risk of death, bladder and lung cancer								
			bladder cancer		lung cancer		bladder + lung	
			M	F	M	F	M	F
	Morales ED01	US ppb	395	252	364	258	189	127
	Morales LED01	US ppb	326	211	294	213	163	111
	Slope of risk function, for the given occurrence level	/(US ppb)	0.0000253	0.0000397	0.0000275	0.0000388	0.0000528	0.0000784
	Standard error	/(US ppb)	0.0000033	0.0000047	0.0000040	0.0000050	0.0000051	0.0000068
	Lifetime excess risk of death	1	0.0012658	0.0019841	0.0013736	0.0019380	0.0026394	0.0039221
	Standard error	1	0.0001629	0.0002344	0.0001988	0.0002489	0.0002570	0.0003419
	Note: the risk slopes and ED01s don't depend on the occurrence level unless the "Additional As consumed in food" in Taiwan is >0.							

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Converting from ppb and $(ppb)^{-1}$
to µg/kg/d and $(\mu g/kg/d)^{-1}$

Suppose a person consumes *A* ppb (µg/L) of arsenic in drinking water. They weigh *K* kg and drink *C* L/d of water. Then in µg/kg/d, their exposure is

Appendix B

Risk Spreadsheets

Table 1. Percentiles of Population LADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Warm Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	970	6.00E-06	9.13E-06	3.12E-06	5.34E-08	4.60E-07	1.43E-06	7.02E-06	2.09E-05	4.15E-05	1.51E-04
Playset Total Dose	0	970	6.00E-06	9.13E-06	3.12E-06	5.34E-08	4.60E-07	1.43E-06	7.02E-06	2.09E-05	4.15E-05	1.51E-04
Playset Surf Inges-HandToMouth Dose	0	970	3.47E-06	6.06E-06	1.51E-06	2.37E-09	1.34E-07	5.73E-07	3.95E-06	1.25E-05	2.92E-05	1.05E-04
Playset Soil Inges-Direct Dose	0	970	3.09E-07	6.49E-07	1.00E-07	5.64E-10	6.69E-09	3.10E-08	3.19E-07	1.26E-06	3.39E-06	1.10E-05
Playset Surf Derm Dose	0	970	2.06E-06	3.25E-06	9.82E-07	2.75E-09	9.47E-08	4.21E-07	2.48E-06	7.71E-06	1.37E-05	4.21E-05
Playset Soil Derm Dose	0	970	1.59E-07	1.79E-07	1.05E-07	6.43E-09	2.10E-08	5.55E-08	2.02E-07	4.81E-07	8.06E-07	2.30E-06
Total Dose	1	982	1.14E-05	1.96E-05	6.28E-06	1.88E-07	1.02E-06	2.93E-06	1.30E-05	3.74E-05	8.20E-05	3.86E-04
Playset Total Dose	1	982	6.27E-06	1.18E-05	2.99E-06	6.74E-08	4.01E-07	1.30E-06	6.64E-06	2.05E-05	5.66E-05	2.14E-04
Playset Surf Inges-HandToMouth Dose	1	982	3.80E-06	8.64E-06	1.55E-06	3.04E-09	1.10E-07	5.66E-07	3.93E-06	1.26E-05	4.08E-05	1.73E-04
Playset Soil Inges-Direct Dose	1	982	2.40E-07	4.64E-07	9.19E-08	3.70E-10	6.54E-09	3.50E-08	2.54E-07	9.38E-07	2.18E-06	7.70E-06
Playset Surf Derm Dose	1	982	2.11E-06	3.55E-06	9.73E-07	1.11E-09	7.47E-08	3.63E-07	2.20E-06	8.58E-06	1.66E-05	4.70E-05
Playset Soil Derm Dose	1	982	1.24E-07	1.42E-07	8.25E-08	2.41E-09	1.84E-08	3.98E-08	1.53E-07	3.77E-07	7.57E-07	1.45E-06
Deck Total Dose	1	982	5.17E-06	8.56E-06	2.88E-06	7.21E-08	4.66E-07	1.32E-06	6.22E-06	1.66E-05	3.59E-05	1.73E-04
Deck Surf Inges-HandToMouth Dose	1	982	3.10E-06	6.21E-06	1.54E-06	7.90E-09	2.02E-07	6.55E-07	3.57E-06	1.01E-05	2.31E-05	1.36E-04
Deck Soil Inges-Direct Dose	1	982	4.66E-08	1.12E-07	1.42E-08	2.32E-11	4.97E-10	3.85E-09	4.28E-08	1.87E-07	4.90E-07	2.24E-06
Deck Surf Derm Dose	1	982	2.01E-06	2.68E-06	1.16E-06	1.47E-08	1.68E-07	5.09E-07	2.47E-06	6.76E-06	1.28E-05	3.64E-05
Deck Soil Derm Dose	1	982	2.43E-08	5.43E-08	1.06E-08	1.81E-11	5.44E-10	3.78E-09	2.58E-08	8.80E-08	2.31E-07	1.20E-06

Table 2. Percentiles of Population LADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	894	3.42E-06	6.88E-06	1.47E-06	3.07E-08	1.97E-07	6.61E-07	3.38E-06	1.28E-05	3.57E-05	0.000107
Playset Total Dose	0	894	3.42E-06	6.88E-06	1.47E-06	3.07E-08	1.97E-07	6.61E-07	3.38E-06	1.28E-05	3.57E-05	0.000107
Playset Surf Inges-HandToMouth Dose	0	894	2.87E-06	5.93E-06	1.2E-06	3.51E-09	1.4E-07	5.01E-07	2.81E-06	1.08E-05	3.1E-05	8.94E-05
Playset Soil Inges-Direct Dose	0	894	1.43E-08	5E-08	2.98E-09	8.83E-12	1.04E-10	6.61E-10	1.05E-08	5.69E-08	2.37E-07	1.03E-06
Playset Surf Derm Dose	0	894	5.25E-07	1.03E-06	2.33E-07	1.46E-09	3.12E-08	1.04E-07	5.28E-07	2.03E-06	4.95E-06	1.69E-05
Playset Soil Derm Dose	0	894	3.25E-09	9.74E-09	9.71E-10	1.03E-11	8.03E-11	3.42E-10	2.65E-09	1.18E-08	4.04E-08	1.94E-07
Total Dose	1	1059	5.48E-06	1.12E-05	2.82E-06	4.16E-08	3.87E-07	1.31E-06	5.97E-06	1.81E-05	3.68E-05	0.000274
Playset Total Dose	1	1059	2.97E-06	7.76E-06	1.35E-06	1.35E-08	1.68E-07	5.58E-07	3.16E-06	1.01E-05	2.14E-05	0.000213
Playset Surf Inges-HandToMouth Dose	1	1059	2.51E-06	6.98E-06	1.12E-06	1.01E-08	1.15E-07	4.44E-07	2.69E-06	8.86E-06	1.87E-05	0.000193
Playset Soil Inges-Direct Dose	1	1059	9.35E-09	2.83E-08	1.85E-09	2.54E-12	7.74E-11	4.71E-10	6.45E-09	3.87E-08	1.15E-07	5.73E-07
Playset Surf Derm Dose	1	1059	4.46E-07	8.73E-07	2.08E-07	2.34E-09	2.38E-08	8.98E-08	4.96E-07	1.68E-06	3.49E-06	1.94E-05
Playset Soil Derm Dose	1	1059	1.86E-09	4.27E-09	6.6E-10	5.61E-12	5.43E-11	2.45E-10	1.75E-09	7.24E-09	1.81E-08	5.57E-08
Deck Total Dose	1	1059	2.51E-06	4.05E-06	1.38E-06	2.81E-08	2.09E-07	6.37E-07	2.93E-06	8.32E-06	1.61E-05	6.25E-05
Deck Surf Inges-HandToMouth Dose	1	1059	2.04E-06	3.56E-06	1.03E-06	6.65E-09	1.31E-07	4.62E-07	2.31E-06	6.76E-06	1.4E-05	5.76E-05
Deck Soil Inges-Direct Dose	1	1059	4.14E-08	8.78E-08	1.27E-08	5.57E-12	6.36E-10	4.08E-09	3.91E-08	1.82E-07	4.55E-07	1.07E-06
Deck Surf Derm Dose	1	1059	4.24E-07	6.08E-07	2.38E-07	4.04E-09	3.49E-08	1.1E-07	4.8E-07	1.42E-06	3.17E-06	6.37E-06
Deck Soil Derm Dose	1	1059	6.72E-09	9.47E-09	3.33E-09	2.21E-11	2.73E-10	1.41E-09	8.26E-09	2.34E-08	4.85E-08	9.59E-08

Table 3. Probabilistic Estimates of Intermediate-Term ADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Warm Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	1436	8.31E-05	0.000182	3.21E-05	4.34E-09	2.3E-06	1.11E-05	8.23E-05	0.000303	0.000926	0.003095
Playset Total Dose	0	1436	8.31E-05	0.000182	3.21E-05	4.34E-09	2.3E-06	1.11E-05	8.23E-05	0.000303	0.000926	0.003095
Playset Surf Inges-HandToMouth Dose	0	1436	4.91E-05	0.000112	1.56E-05	1.99E-09	6.9E-07	4.49E-06	4.77E-05	0.000175	0.000629	0.001515
Playset Soil Inges-Direct Dose	0	1436	4.09E-06	1.35E-05	8.54E-07	1.41E-10	3.48E-08	2.62E-07	3.22E-06	1.82E-05	4.47E-05	0.000332
Playset Surf Derm Dose	0	1436	2.79E-05	7.5E-05	9.22E-06	4.63E-10	5.27E-07	2.89E-06	2.53E-05	0.00011	0.000277	0.001544
Playset Soil Derm Dose	0	1436	2.03E-06	3.09E-06	1.02E-06	1.36E-10	8.13E-08	4.1E-07	2.3E-06	7.89E-06	1.43E-05	3.34E-05
Total Dose	1	1504	0.000139	0.000231	6.67E-05	1.02E-06	9.52E-06	2.85E-05	0.00015	0.000513	0.001119	0.003901
Playset Total Dose	1	1504	7.79E-05	0.000153	2.87E-05	7.25E-10	2.09E-06	1.01E-05	7.73E-05	0.000332	0.000702	0.001854
Playset Surf Inges-HandToMouth Dose	1	1504	4.69E-05	9.93E-05	1.54E-05	2.31E-10	7.37E-07	4.79E-06	4.49E-05	0.000201	0.000478	0.001121
Playset Soil Inges-Direct Dose	1	1504	2.94E-06	7.84E-06	6.4E-07	3E-11	2.69E-08	1.89E-07	2.18E-06	1.28E-05	3.63E-05	0.000105
Playset Surf Derm Dose	1	1504	2.66E-05	5.89E-05	8.7E-06	4.07E-11	4.25E-07	2.87E-06	2.51E-05	0.000111	0.00029	0.000823
Playset Soil Derm Dose	1	1504	1.47E-06	2.07E-06	7.72E-07	4.98E-11	5.98E-08	2.96E-07	1.81E-06	5.39E-06	1.02E-05	2.94E-05
Deck Total Dose	1	1504	6.12E-05	0.000116	2.72E-05	0	2.71E-06	1.11E-05	6.39E-05	0.000218	0.000518	0.002377
Deck Surf Inges-HandToMouth Dose	1	1504	3.6E-05	6.46E-05	1.48E-05	0	1.07E-06	5.39E-06	3.82E-05	0.00014	0.000313	0.000774
Deck Soil Inges-Direct Dose	1	1504	6.01E-07	1.73E-06	1.36E-07	0	2.3E-09	3.28E-08	4.49E-07	2.39E-06	7.69E-06	3.32E-05
Deck Surf Derm Dose	1	1504	2.43E-05	5.92E-05	1.03E-05	0	8.75E-07	3.96E-06	2.4E-05	8.72E-05	0.000222	0.001603
Deck Soil Derm Dose	1	1504	3.21E-07	7.34E-07	1.07E-07	0	4.08E-09	3.14E-08	3.2E-07	1.23E-06	2.99E-06	1.27E-05

Table 4. Probabilistic Estimates of Intermediate-Term ADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	1448	4.01E-05	9.36E-05	1.3E-05	0	5.42E-07	4.15E-06	3.79E-05	0.00016	0.000389	0.001429
Playset Total Dose	0	1448	4.01E-05	9.36E-05	1.3E-05	0	5.42E-07	4.15E-06	3.79E-05	0.00016	0.000389	0.001429
Playset Surf Inges-HandToMouth Dose	0	1448	3.48E-05	8.47E-05	1.09E-05	0	4.02E-07	3.32E-06	3.11E-05	0.00014	0.000322	0.001302
Playset Soil Inges-Direct Dose	0	1448	2.22E-07	1.23E-06	2.17E-08	0	3.69E-10	4.69E-09	8.07E-08	7.31E-07	3.74E-06	3E-05
Playset Surf Derm Dose	0	1448	5.13E-06	1.02E-05	1.71E-06	0	8.18E-08	6.06E-07	5.3E-06	2.17E-05	5.54E-05	0.000127
Playset Soil Derm Dose	0	1448	4.09E-08	1.84E-07	8.39E-09	0	2.78E-10	2.2E-09	2.8E-08	1.45E-07	4.86E-07	4.14E-06
Total Dose	1	1481	7.35E-05	0.000152	3.07E-05	2.44E-07	3.72E-06	1.33E-05	7.61E-05	0.00026	0.000767	0.003046
Playset Total Dose	1	1481	4.18E-05	0.000115	1.34E-05	0	6.77E-07	4.66E-06	3.96E-05	0.000152	0.000434	0.002773
Playset Surf Inges-HandToMouth Dose	1	1481	3.58E-05	0.000103	1.08E-05	0	4.93E-07	3.85E-06	3.39E-05	0.000127	0.000381	0.002545
Playset Soil Inges-Direct Dose	1	1481	9.33E-08	3.76E-07	1.21E-08	0	2.39E-10	2.87E-09	5.13E-08	3.9E-07	1.28E-06	9.18E-06
Playset Surf Derm Dose	1	1481	5.84E-06	1.47E-05	1.87E-06	0	8.97E-08	6.35E-07	4.93E-06	2.32E-05	6.41E-05	0.000227
Playset Soil Derm Dose	1	1481	1.89E-08	5.34E-08	4.67E-09	0	2.06E-10	1.26E-09	1.59E-08	7.45E-08	1.99E-07	9.73E-07
Deck Total Dose	1	1481	3.17E-05	6.25E-05	1.31E-05	0	1.2E-06	5.13E-06	3.24E-05	0.000118	0.000318	0.000775
Deck Surf Inges-HandToMouth Dose	1	1481	2.59E-05	5.23E-05	1.02E-05	0	6.57E-07	3.66E-06	2.66E-05	9.95E-05	0.000256	0.000709
Deck Soil Inges-Direct Dose	1	1481	4.78E-07	1.2E-06	1.11E-07	0	2.75E-09	3.14E-08	4.02E-07	2.14E-06	5.55E-06	2.01E-05
Deck Surf Derm Dose	1	1481	5.25E-06	1.46E-05	1.99E-06	0	1.89E-07	7.69E-07	4.98E-06	1.85E-05	5.5E-05	0.000418
Deck Soil Derm Dose	1	1481	7.56E-08	1.43E-07	2.99E-08	0	1.17E-09	9.92E-09	8.14E-08	2.86E-07	6.83E-07	2.26E-06

Table 5. Probabilistic Estimates of Short-Term ADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Warm Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2451	0.000101	0.000253	3.87E-05	0	2.87E-06	1.38E-05	9.31E-05	0.000357	0.001126	0.004896
Playset Total Dose	0	2451	0.000101	0.000253	3.87E-05	0	2.87E-06	1.38E-05	9.31E-05	0.000357	0.001126	0.004896
Playset Surf Inges-HandToMouth Dose	0	2451	6.16E-05	0.00018	1.93E-05	0	9.44E-07	6.02E-06	5.54E-05	0.000226	0.000711	0.004166
Playset Soil Inges-Direct Dose	0	2451	4.28E-06	1.17E-05	1.03E-06	0	4.24E-08	2.94E-07	3.29E-06	1.76E-05	5.69E-05	0.000197
Playset Surf Derm Dose	0	2451	3.27E-05	8.41E-05	1.01E-05	0	5.38E-07	3.37E-06	2.74E-05	0.000126	0.00039	0.001592
Playset Soil Derm Dose	0	2451	2.09E-06	2.88E-06	1.08E-06	0	8.2E-08	4.09E-07	2.63E-06	7.5E-06	1.47E-05	2.81E-05
Total Dose	1	2450	0.000136	0.000232	6.29E-05	2.18E-08	7.4E-06	2.72E-05	0.000148	0.000513	0.001121	0.003115
Playset Total Dose	1	2450	8.79E-05	0.000179	3.34E-05	0	2.71E-06	1.25E-05	8.66E-05	0.000364	0.00084	0.002873
Playset Surf Inges-HandToMouth Dose	1	2450	5.44E-05	0.000124	1.8E-05	0	8.74E-07	5.9E-06	4.96E-05	0.000235	0.000568	0.002124
Playset Soil Inges-Direct Dose	1	2450	3.82E-06	1.13E-05	8.36E-07	0	3.68E-08	2.48E-07	2.86E-06	1.46E-05	5.32E-05	0.000209
Playset Surf Derm Dose	1	2450	2.79E-05	6.21E-05	9.25E-06	0	4.76E-07	2.94E-06	2.62E-05	0.000116	0.000268	0.000983
Playset Soil Derm Dose	1	2450	1.74E-06	2.62E-06	8.37E-07	0	7.34E-08	3.34E-07	2.05E-06	6.46E-06	1.29E-05	3.23E-05
Deck Total Dose	1	2450	4.85E-05	9.92E-05	1.88E-05	0	0	5.24E-06	5.1E-05	0.000184	0.000442	0.001238
Deck Surf Inges-HandToMouth Dose	1	2450	2.95E-05	6.77E-05	1.04E-05	0	0	2.54E-06	2.91E-05	0.000116	0.000269	0.001044
Deck Soil Inges-Direct Dose	1	2450	4.9E-07	1.7E-06	8.14E-08	0	0	1.29E-08	3.49E-07	2.19E-06	5.78E-06	3.49E-05
Deck Surf Derm Dose	1	2450	1.82E-05	3.82E-05	6.47E-06	0	0	1.74E-06	1.83E-05	7.37E-05	0.000185	0.00058
Deck Soil Derm Dose	1	2450	2.04E-07	4.78E-07	5.6E-08	0	0	1.1E-08	1.91E-07	9.24E-07	2.38E-06	6.91E-06

Table 6. Probabilistic Estimates of Short-Term ADD for Children Exposed to Arsenic Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2442	5.06E-05	0.000163	1.33E-05	0	0	3.52E-06	4.43E-05	0.000202	0.000591	0.005335
Playset Total Dose	0	2442	5.06E-05	0.000163	1.33E-05	0	0	3.52E-06	4.43E-05	0.000202	0.000591	0.005335
Playset Surf Inges-HandToMouth Dose	0	2442	4.39E-05	0.000144	1.09E-05	0	0	2.89E-06	3.81E-05	0.000179	0.000519	0.004791
Playset Soil Inges-Direct Dose	0	2442	2.21E-07	1.2E-06	1.95E-08	0	0	3.69E-09	9.51E-08	7.87E-07	3.22E-06	4.03E-05
Playset Surf Derm Dose	0	2442	6.48E-06	2.06E-05	1.69E-06	0	0	4.33E-07	5.58E-06	2.51E-05	6.59E-05	0.000543
Playset Soil Derm Dose	0	2442	3.52E-08	1.23E-07	7.04E-09	0	0	1.63E-09	2.31E-08	1.51E-07	4.49E-07	3.59E-06
Total Dose	1	2441	6.72E-05	0.00012	2.83E-05	0	2.15E-06	1.01E-05	7.47E-05	0.000251	0.000548	0.001937
Playset Total Dose	1	2441	4.19E-05	8.8E-05	1.37E-05	0	0	3.78E-06	4.14E-05	0.000182	0.000387	0.001591
Playset Surf Inges-HandToMouth Dose	1	2441	3.59E-05	7.71E-05	1.16E-05	0	0	3.09E-06	3.55E-05	0.000156	0.000347	0.001378
Playset Soil Inges-Direct Dose	1	2441	1.44E-07	7.8E-07	1.39E-08	0	0	2.31E-09	6.65E-08	5.98E-07	2.05E-06	3.03E-05
Playset Surf Derm Dose	1	2441	5.81E-06	1.35E-05	1.6E-06	0	0	4.8E-07	5.31E-06	2.3E-05	6.28E-05	0.000208
Playset Soil Derm Dose	1	2441	2.35E-08	6.93E-08	4.78E-09	0	0	1.01E-09	1.78E-08	1.03E-07	3.06E-07	1.47E-06
Deck Total Dose	1	2441	2.53E-05	5.71E-05	6.91E-06	0	0	5.7E-07	2.52E-05	0.000109	0.00025	0.001321
Deck Surf Inges-HandToMouth Dose	1	2441	2.11E-05	4.98E-05	5.34E-06	0	0	3.07E-07	2.04E-05	9.17E-05	0.000224	0.001124
Deck Soil Inges-Direct Dose	1	2441	3.75E-07	1.16E-06	5.46E-08	0	0	1.17E-09	2.75E-07	1.75E-06	5E-06	2.75E-05
Deck Surf Derm Dose	1	2441	3.75E-06	8.67E-06	1.08E-06	0	0	7.68E-08	3.86E-06	1.64E-05	3.91E-05	0.000197
Deck Soil Derm Dose	1	2441	5.93E-08	1.49E-07	1.26E-08	0	0	3.75E-10	5.54E-08	2.57E-07	6.86E-07	3.18E-06

Table 7. Probabilistic Estimates of Intermediate-Term ADD for Children Exposed to Chromium Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Warm Climate (separated by children with and without decks who contact treated playsets)

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2477	7.13E-05	0.000179	2.82E-05	6.4E-09	2.16E-06	1.04E-05	6.94E-05	0.000272	0.000583	0.005958
Playset Total Dose	0	2477	7.13E-05	0.000179	2.82E-05	6.4E-09	2.16E-06	1.04E-05	6.94E-05	0.000272	0.000583	0.005958
Playset Surf Inges-HandToMouth Dose	0	2477	4.2E-05	0.000131	1.32E-05	5.07E-09	6.76E-07	4.08E-06	3.82E-05	0.000164	0.000421	0.004735
Playset Soil Inges-Direct Dose	0	2477	4.71E-06	1.71E-05	9.2E-07	5.13E-12	3.75E-08	2.59E-07	3.34E-06	2.07E-05	5.82E-05	0.000453
Playset Surf Derm Dose	0	2477	2.24E-05	5.13E-05	7.81E-06	1.3E-09	3.88E-07	2.51E-06	2.16E-05	9.24E-05	0.00021	0.001183
Playset Soil Derm Dose	0	2477	2.25E-06	3.63E-06	1.13E-06	9.1E-12	7.65E-08	4.23E-07	2.67E-06	7.76E-06	1.58E-05	6.02E-05
Total Dose	1	2412	0.000117	0.000194	5.93E-05	1.35E-06	8.98E-06	2.68E-05	0.000132	0.000398	0.000893	0.003773
Playset Total Dose	1	2412	6.56E-05	0.000119	2.7E-05	5.37E-11	1.94E-06	1.03E-05	7.04E-05	0.000264	0.0006	0.001543
Playset Surf Inges-HandToMouth Dose	1	2412	3.88E-05	7.79E-05	1.35E-05	2.93E-11	6.73E-07	4.33E-06	3.87E-05	0.000165	0.000364	0.000987
Playset Soil Inges-Direct Dose	1	2412	3.65E-06	1.42E-05	7.82E-07	6.69E-13	3.25E-08	2.27E-07	2.61E-06	1.46E-05	4.09E-05	0.000396
Playset Surf Derm Dose	1	2412	2.14E-05	4.48E-05	8.03E-06	2.31E-11	4.06E-07	2.45E-06	2.18E-05	8.12E-05	0.000198	0.000649
Playset Soil Derm Dose	1	2412	1.66E-06	2.52E-06	8.33E-07	6.72E-13	6.9E-08	3.2E-07	1.95E-06	5.94E-06	1.22E-05	3.3E-05
Deck Total Dose	1	2412	5.09E-05	0.000108	2.47E-05	0	2.49E-06	1.05E-05	5.25E-05	0.000178	0.000369	0.002575
Deck Surf Inges-HandToMouth Dose	1	2412	3.11E-05	7.41E-05	1.32E-05	0	1.1E-06	5.08E-06	3.14E-05	0.00011	0.000263	0.001825
Deck Soil Inges-Direct Dose	1	2412	4.73E-07	1.34E-06	1.04E-07	0	3.97E-09	3.16E-08	3.93E-07	2.03E-06	5.09E-06	3.09E-05
Deck Surf Derm Dose	1	2412	1.91E-05	3.72E-05	8.97E-06	0	8.11E-07	3.84E-06	2.03E-05	6.69E-05	0.000149	0.000825
Deck Soil Derm Dose	1	2412	2.34E-07	5.11E-07	7.62E-08	0	5.1E-09	2.68E-08	2.37E-07	9.07E-07	2.27E-06	8.51E-06

Table 8. Probabilistic Estimates of Intermediate-Term ADD for Children Exposed to Chromium Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks who contact treate

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2424	3.39E-05	6.75E-05	1.41E-05	0	8.17E-07	5.06E-06	3.61E-05	0.000124	0.000286	0.001353
Playset Total Dose	0	2424	3.39E-05	6.75E-05	1.41E-05	0	8.17E-07	5.06E-06	3.61E-05	0.000124	0.000286	0.001353
Playset Surf Inges-HandToMouth Dose	0	2424	2.83E-05	5.95E-05	1.09E-05	0	5.72E-07	3.77E-06	2.97E-05	0.000103	0.00025	0.001129
Playset Soil Inges-Direct Dose	0	2424	8.14E-07	3.53E-06	8.67E-08	0	1.52E-09	1.86E-08	3.76E-07	3.68E-06	1.29E-05	0.000109
Playset Surf Derm Dose	0	2424	4.65E-06	8.97E-06	1.79E-06	0	1.01E-07	6.25E-07	4.94E-06	1.93E-05	3.83E-05	0.000221
Playset Soil Derm Dose	0	2424	1.44E-07	4.25E-07	3.19E-08	0	1.01E-09	8.56E-09	1.16E-07	6.18E-07	1.69E-06	1.06E-05
Total Dose	1	2482	6.16E-05	0.000108	3.07E-05	2.44E-07	4E-06	1.35E-05	6.92E-05	0.000211	0.000468	0.002819
Playset Total Dose	1	2482	3.41E-05	8.3E-05	1.32E-05	0	8.59E-07	4.66E-06	3.5E-05	0.000124	0.000321	0.002711
Playset Surf Inges-HandToMouth Dose	1	2482	2.87E-05	6.97E-05	1.05E-05	0	6.12E-07	3.56E-06	2.92E-05	0.000107	0.000293	0.002146
Playset Soil Inges-Direct Dose	1	2482	5.34E-07	2.21E-06	6.12E-08	0	1.22E-09	1.32E-08	2.59E-07	2.11E-06	8.89E-06	4.76E-05
Playset Surf Derm Dose	1	2482	4.85E-06	1.44E-05	1.79E-06	0	1.12E-07	6.32E-07	4.74E-06	1.84E-05	4.43E-05	0.000565
Playset Soil Derm Dose	1	2482	9.18E-08	2.62E-07	2.13E-08	0	7.82E-10	5.87E-09	7.08E-08	3.93E-07	1.06E-06	4.85E-06
Deck Total Dose	1	2482	2.74E-05	4.4E-05	1.27E-05	0	1.12E-06	5.2E-06	3.1E-05	0.0001	0.000214	0.000592
Deck Surf Inges-HandToMouth Dose	1	2482	2.27E-05	3.81E-05	9.94E-06	0	6.84E-07	3.89E-06	2.59E-05	8.3E-05	0.000191	0.000501
Deck Soil Inges-Direct Dose	1	2482	3.32E-07	1.43E-06	4.03E-08	0	8.62E-10	9.4E-09	1.52E-07	1.27E-06	6.43E-06	2.57E-05
Deck Surf Derm Dose	1	2482	4.41E-06	7.52E-06	2.07E-06	0	1.79E-07	8.2E-07	4.97E-06	1.61E-05	3.84E-05	0.000124
Deck Soil Derm Dose	1	2482	4.43E-08	1.19E-07	1.02E-08	0	3.39E-10	2.84E-09	3.64E-08	1.76E-07	6.51E-07	2.23E-06

Table 9. Probabilistic Estimates of Short-Term ADD for Children Exposed to Chromium Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Warm Climate (separated by children with and without decks who contact treate

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2438	7.84E-05	0.000139	3.14E-05	6.1E-09	2.93E-06	1.18E-05	8.06E-05	0.000313	0.000675	0.001635
Playset Total Dose	0	2438	7.84E-05	0.000139	3.14E-05	6.1E-09	2.93E-06	1.18E-05	8.06E-05	0.000313	0.000675	0.001635
Playset Surf Inges-HandToMouth Dose	0	2438	4.73E-05	9.4E-05	1.51E-05	3.11E-09	8.44E-07	4.96E-06	4.62E-05	0.000198	0.000491	0.001173
Playset Soil Inges-Direct Dose	0	2438	5.2E-06	1.56E-05	1.07E-06	2.63E-10	4.57E-08	3.07E-07	3.83E-06	2.12E-05	6.57E-05	0.000287
Playset Surf Derm Dose	0	2438	2.36E-05	4.79E-05	8.35E-06	7.17E-10	4.67E-07	2.58E-06	2.25E-05	0.000104	0.000224	0.000718
Playset Soil Derm Dose	0	2438	2.3E-06	3.59E-06	1.14E-06	1.34E-10	8.49E-08	4.21E-07	2.72E-06	8.04E-06	1.82E-05	4.27E-05
Total Dose	1	2444	0.000122	0.000242	6.1E-05	6.28E-07	7.41E-06	2.45E-05	0.000133	0.000402	0.001011	0.00507
Playset Total Dose	1	2444	7.99E-05	0.000178	2.94E-05	0	2.26E-06	1.11E-05	7.8E-05	0.000296	0.000846	0.003279
Playset Surf Inges-HandToMouth Dose	1	2444	4.93E-05	0.000124	1.53E-05	0	7.17E-07	4.91E-06	4.58E-05	0.000187	0.000593	0.002452
Playset Soil Inges-Direct Dose	1	2444	4.66E-06	1.46E-05	9.13E-07	0	2.66E-08	2.6E-07	3.26E-06	1.87E-05	6.91E-05	0.00028
Playset Surf Derm Dose	1	2444	2.4E-05	5.82E-05	7.82E-06	0	3.97E-07	2.57E-06	2.28E-05	9.82E-05	0.000224	0.001532
Playset Soil Derm Dose	1	2444	1.9E-06	3.34E-06	8.51E-07	0	5.89E-08	3.14E-07	2.17E-06	7.06E-06	1.49E-05	7.85E-05
Deck Total Dose	1	2444	4.26E-05	0.000118	1.69E-05	0	0	5.61E-06	4.67E-05	0.00015	0.000345	0.00417
Deck Surf Inges-HandToMouth Dose	1	2444	2.69E-05	9.02E-05	9.33E-06	0	0	2.68E-06	2.67E-05	9.42E-05	0.000244	0.003416
Deck Soil Inges-Direct Dose	1	2444	4.16E-07	1.36E-06	7.83E-08	0	0	1.54E-08	3.17E-07	1.74E-06	5.01E-06	2.62E-05
Deck Surf Derm Dose	1	2444	1.51E-05	3.27E-05	5.85E-06	0	0	1.81E-06	1.7E-05	5.6E-05	0.000137	0.000749
Deck Soil Derm Dose	1	2444	1.89E-07	4.39E-07	5.58E-08	0	0	1.39E-08	1.65E-07	8.54E-07	2.03E-06	6.02E-06

Table 10. Probabilistic Estimates of Short-Term ADD for Children Exposed to Chromium Dislodgeable Residues and Contaminated Soil from Treated Wood Playsets and Residential Decks in Cold Climate (separated by children with and without decks who contact treate

Pathway	Deck	n	mean	std	p50	min	p05	p25	p75	p95	p99	max
Total Dose	0	2448	3.75E-05	7.91E-05	1.32E-05	0	0	4.18E-06	3.97E-05	0.000155	0.000343	0.001866
Playset Total Dose	0	2448	3.75E-05	7.91E-05	1.32E-05	0	0	4.18E-06	3.97E-05	0.000155	0.000343	0.001866
Playset Surf Inges-HandToMouth Dose	0	2448	3.15E-05	6.81E-05	1.03E-05	0	0	3.15E-06	3.25E-05	0.000133	0.000286	0.001571
Playset Soil Inges-Direct Dose	0	2448	8.55E-07	3.38E-06	8.18E-08	0	0	1.53E-08	3.95E-07	3.46E-06	1.53E-05	6.3E-05
Playset Surf Derm Dose	0	2448	5.02E-06	1.23E-05	1.65E-06	0	0	5E-07	5.09E-06	1.89E-05	4.99E-05	0.000283
Playset Soil Derm Dose	0	2448	1.24E-07	3.32E-07	2.76E-08	0	0	6.37E-09	9.9E-08	5.26E-07	1.52E-06	6.27E-06
Total Dose	1	2443	6.4E-05	0.00011	2.78E-05	0	2.31E-06	1.11E-05	6.9E-05	0.000241	0.000599	0.001281
Playset Total Dose	1	2443	3.87E-05	7.79E-05	1.35E-05	0	0	3.86E-06	4.09E-05	0.000155	0.000397	0.001008
Playset Surf Inges-HandToMouth Dose	1	2443	3.29E-05	6.84E-05	1.08E-05	0	0	2.95E-06	3.47E-05	0.000137	0.000347	0.00089
Playset Soil Inges-Direct Dose	1	2443	6.64E-07	4.17E-06	5.6E-08	0	0	9.12E-09	2.94E-07	2.42E-06	9.01E-06	0.000145
Playset Surf Derm Dose	1	2443	5.07E-06	1.12E-05	1.68E-06	0	0	4.65E-07	4.77E-06	2.03E-05	5.74E-05	0.000159
Playset Soil Derm Dose	1	2443	9.04E-08	2.56E-07	1.85E-08	0	0	3.91E-09	6.86E-08	4.04E-07	1.18E-06	3.95E-06
Deck Total Dose	1	2443	2.53E-05	6.2E-05	7.98E-06	0	0	8.36E-07	2.59E-05	0.000101	0.000249	0.001281
Deck Surf Inges-HandToMouth Dose	1	2443	2.13E-05	5.52E-05	6.11E-06	0	0	5.44E-07	2.1E-05	8.57E-05	0.000226	0.00116
Deck Soil Inges-Direct Dose	1	2443	3.01E-07	1.4E-06	1.92E-08	0	0	5.6E-10	1.16E-07	1.15E-06	4.95E-06	3.5E-05
Deck Surf Derm Dose	1	2443	3.6E-06	7.74E-06	1.18E-06	0	0	1.16E-07	3.75E-06	1.52E-05	3.51E-05	0.00012
Deck Soil Derm Dose	1	2443	4.28E-08	1.95E-07	4.16E-09	0	0	2.01E-10	2.1E-08	1.64E-07	5.92E-07	4.7E-06

Table 11. Summary of mean Arsenic and Chromium population absorbed dose values by exposure pathway for the short-term, intermediate-term, and lifetime scenarios (for children exposed to home playsets, public playsets, and decks)

Pathway	As Warm Short-Term	As Cold Short-Term	Cr Warm Short-Term	Cr Cold Short-Term	As Warm Int.-Term	As Cold Int.-Term	Cr Warm Int.-Term	Cr Cold Int.-Term	As Warm LADD	As Cold LADD
Total Dose	1.18E-04	5.89E-05	1.00E-04	5.07E-05	1.12E-04	5.70E-05	9.36E-05	4.79E-05	8.74E-06	4.53E-06
Playset Total Dose	9.43E-05	4.63E-05	7.91E-05	3.81E-05	8.04E-05	4.10E-05	6.85E-05	3.40E-05	6.14E-06	3.17E-06
Playset Surf Inges-HandToMouth Dose	5.80E-05	3.99E-05	4.83E-05	3.22E-05	4.80E-05	3.53E-05	4.04E-05	2.85E-05	3.63E-06	2.68E-06
Playset Soil Inges-Direct Dose	4.05E-06	1.82E-07	4.93E-06	7.60E-07	3.50E-06	1.57E-07	4.19E-06	6.73E-07	2.74E-07	1.16E-08
Playset Surf Derm Dose	3.03E-05	6.15E-06	2.38E-05	5.05E-06	2.72E-05	5.49E-06	2.19E-05	4.75E-06	2.09E-06	4.82E-07
Playset Soil Derm Dose	1.91E-06	2.94E-08	2.10E-06	1.07E-07	1.75E-06	2.98E-08	1.96E-06	1.18E-07	1.42E-07	2.50E-09
Deck Total Dose	2.42E-05	1.26E-05	2.13E-05	1.26E-05	3.13E-05	1.60E-05	2.51E-05	1.39E-05	2.60E-06	1.36E-06
Deck Surf Inges-HandToMouth Dose	1.48E-05	1.05E-05	1.35E-05	1.07E-05	1.84E-05	1.31E-05	1.54E-05	1.15E-05	1.56E-06	1.10E-06
Deck Soil Inges-Direct Dose	2.45E-07	1.88E-07	2.08E-07	1.50E-07	3.08E-07	2.42E-07	2.33E-07	1.68E-07	2.35E-08	2.24E-08
Deck Surf Derm Dose	9.11E-06	1.88E-06	7.56E-06	1.80E-06	1.24E-05	2.65E-06	9.41E-06	2.23E-06	1.01E-06	2.30E-07
Deck Soil Derm Dose	1.02E-07	2.97E-08	9.44E-08	2.14E-08	1.64E-07	3.82E-08	1.16E-07	2.24E-08	1.22E-08	3.65E-09

Table 12. Summary of 95th Percentile Arsenic and Chromium population absorbed dose values by exposure pathway for the short-term, intermediate-term, and lifetime scenarios (for children exposed to home playsets, public playsets, and decks)

Pathway	As Warm Short-Term	As Cold Short-Term	Cr Warm Short-Term	Cr Cold Short-Term	As Warm Int.-Term	As Cold Int.-Term	Cr Warm Int.-Term	Cr Cold Int.-Term	As Warm LADD	As Cold LADD
Total Dose	4.47E-04	2.29E-04	3.63E-04	1.95E-04	4.21E-04	2.13E-04	3.44E-04	1.70E-04	3.02E-05	1.66E-05
Playset Total Dose	3.58E-04	1.90E-04	3.10E-04	1.55E-04	3.15E-04	1.58E-04	2.68E-04	1.24E-04	2.06E-05	1.12E-05
Playset Surf Inges-HandToMouth Dose	2.29E-04	1.65E-04	1.96E-04	1.36E-04	1.91E-04	1.34E-04	1.64E-04	1.04E-04	1.26E-05	9.27E-06
Playset Soil Inges-Direct Dose	1.61E-05	7.05E-07	2.00E-05	2.92E-06	1.53E-05	5.50E-07	1.75E-05	2.81E-06	1.07E-06	4.76E-08
Playset Surf Derm Dose	1.20E-04	2.39E-05	1.01E-04	2.01E-05	1.10E-04	2.24E-05	8.52E-05	1.87E-05	7.91E-06	1.78E-06
Playset Soil Derm Dose	7.14E-06	1.26E-07	7.59E-06	4.69E-07	6.31E-06	1.09E-07	7.08E-06	4.94E-07	4.21E-07	9.75E-09
Deck Total Dose	1.17E-04	6.56E-05	9.80E-05	6.31E-05	1.57E-04	7.67E-05	1.10E-04	6.71E-05	1.16E-05	5.91E-06
Deck Surf Inges-HandToMouth Dose	7.16E-05	5.47E-05	6.02E-05	5.21E-05	9.34E-05	6.19E-05	6.94E-05	5.62E-05	6.89E-06	4.86E-06
Deck Soil Inges-Direct Dose	1.12E-06	8.95E-07	8.99E-07	5.23E-07	1.40E-06	1.14E-06	1.08E-06	5.91E-07	1.19E-07	1.08E-07
Deck Surf Derm Dose	4.38E-05	9.58E-06	3.66E-05	9.15E-06	5.67E-05	1.13E-05	4.29E-05	1.00E-05	4.56E-06	9.56E-07
Deck Soil Derm Dose	4.99E-07	1.56E-07	4.58E-07	7.72E-08	8.03E-07	1.86E-07	5.58E-07	9.75E-08	5.58E-08	1.72E-08

Appendix C Risk Spreadsheets for Special Scenarios

Table C-1. Probabilistic Cancer Risk Distributions and Risk Levels for children Exposed to Arsenic in Warm Climate (Reducing Exposure by Washing Hands) (Based on LADDs from SHEDS-WOOD)

Playset Only

Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
maximum	2.3E-04	8.4E-04			
99	3.8E-05	1.4E-04			
95	1.9E-05	6.8E-05			
90	1.2E-05	4.4E-05			
50	2.2E-06	8.2E-06			
10	5.9E-07	2.2E-06			
5	3.6E-07	1.3E-06			
1	2.1E-07	7.6E-07			
minimum	1.1E-07	4.1E-07			
97.6	2.7E-05	1.0E-04			
56.0	2.7E-06	1.0E-05			
2.5	2.7E-07	1.0E-06			

Playset and Deck

Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
maximum	7.9E-05	2.9E-04			
99	4.7E-05	1.7E-04			
95	2.5E-05	9.2E-05			
90	1.6E-05	6.0E-05			
50	4.7E-06	1.7E-05			
10	1.1E-06	4.2E-06			
5	6.9E-07	2.5E-06			
1	4.6E-07	1.7E-06			
minimum	2.3E-07	8.5E-07			
95.9	2.7E-05	1.0E-04			
30.5	2.7E-06	1.0E-05			
0.1	2.7E-07	1.0E-06			

Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.

Table C-2. Probabilistic Cancer Risk Distributions and Risk Levels for children Exposed to Arsenic in Warm Climate ((Dermal Residue Absorption Rate = 0.01%) (Based on LADDs from SHEDS-WOOD)

Playset Only

Percentile of Exposure	Lifetime Average Daily Dose (LADD) mg/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
maximum	1.8E-04	6.6E-04			
99	4.3E-05	1.6E-04			
95	1.8E-05	6.6E-05			
90	1.0E-05	3.8E-05			
50	2.1E-06	7.7E-06			
10	4.4E-07	1.6E-06			
5	3.2E-07	1.2E-06			
1	1.9E-07	7.0E-07			
minimum	4.2E-08	1.5E-07			
97.7	2.7E-05	1.0E-04			
57.4	2.7E-06	1.0E-05			
3.6	2.7E-07	1.0E-06			

Playset and Deck

Percentile of Exposure	Lifetime Average Daily Dose (LADD) ug/kg/day	Cancer Risk	Risk Level		
			A = 1.0E-6	**B = 1.0E-5**	**C = 1.0E-4**
maximum	2.2E-04	8.1E-04			
99	7.6E-05	2.8E-04			
95	2.9E-05	1.1E-04			
90	1.9E-05	6.8E-05			
50	3.7E-06	1.3E-05			
10	7.8E-07	2.8E-06			
5	5.4E-07	2.0E-06			
1	2.5E-07	9.0E-07			
minimum	1.4E-07	5.3E-07			
97.7	2.7E-05	1.0E-04			
57.1	2.7E-06	1.0E-05			
3.5	2.7E-07	1.0E-06			

Note: Shaded area indicates all the percentiles of the population that meet the risk level set by the Agency.

Table C-3. SHEDs Wood Estimates for Kwon Arsenic Exposure Distributions for Cold Climate (Playsets Only)

Short-term Exposure Distributions		Intermediate-term Exposure Distributions		Lifetime Exposure Distributions	
	Playset Only		Playset Only		Playset Only
Average	4.2E-06	Average	4.0E-06	Average	3.6E-07
Stdev	8.6E-06	Stdev	6.3E-06	Stdev	4.8E-07
Max	1.3E-04	Max	6.8E-05	Max	8.7E-06
P99	4.5E-05	P99	3.3E-05	P99	2.4E-06
P95	1.5E-05	P95	1.5E-05	P95	1.1E-06
P90	9.7E-06	P90	9.6E-06	P90	7.2E-07
P75	4.1E-06	P75	4.6E-06	P75	4.0E-07
P50	1.7E-06	P50	1.9E-06	P50	2.3E-07
P10	1.8E-07	P10	2.8E-07	P10	7.9E-08
P05	0.0E+00	P05	1.6E-07	P05	6.1E-08
P01	0.0E+00	P01	4.0E-08	P01	3.7E-08
Min	0.0E+00	Min	0.0E+00	Min	1.2E-08

Appendix D Comparison of Residue and Soil Risk

Figure D-1 Comparison of Total Arsenic Risks from Playsets and Decks for Warm Climate Baseline

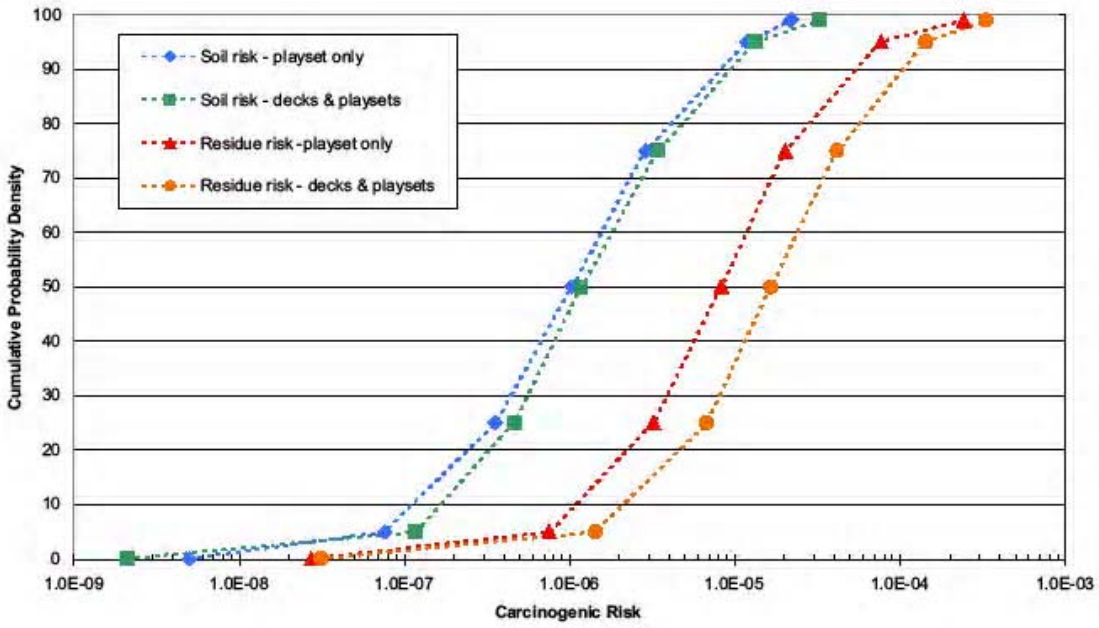


Figure D-2

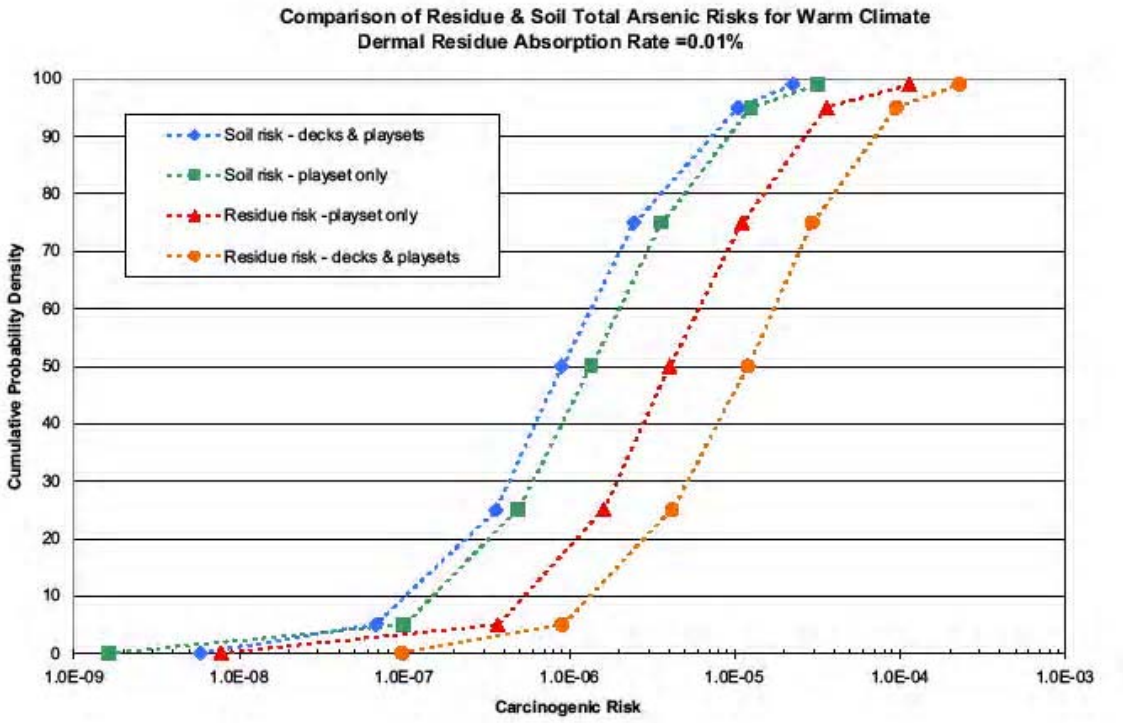
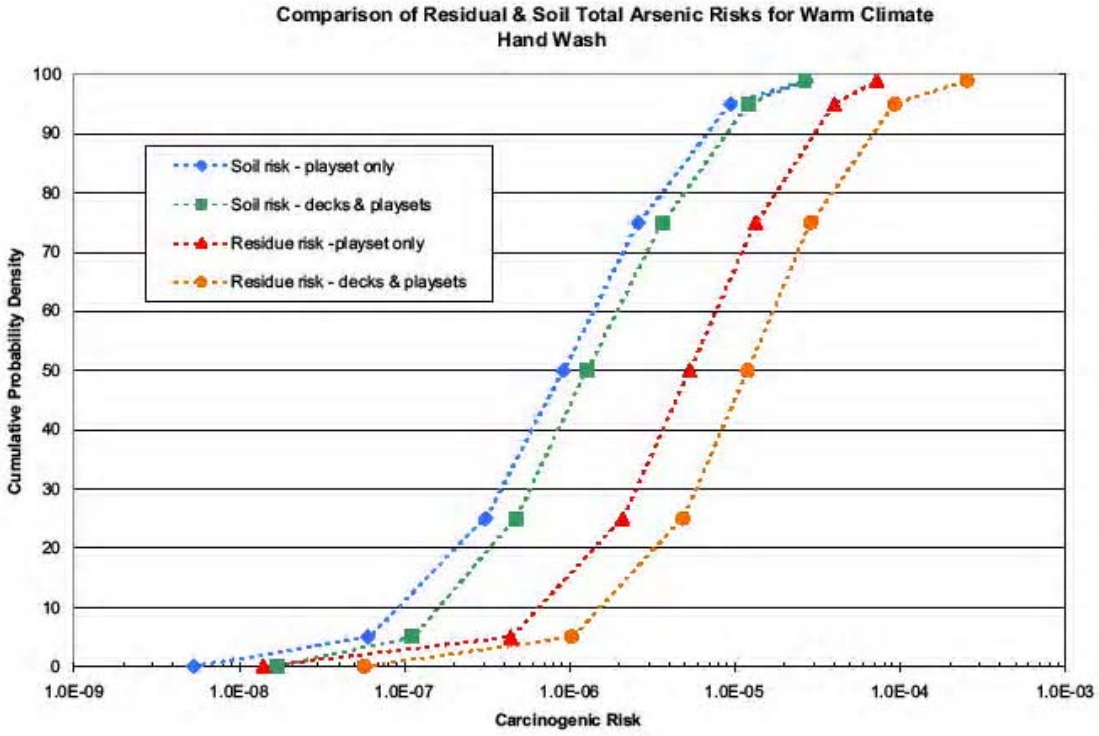

Comparison of Residue & Soil Total Arsenic Risks for Warm Climate
Dermal Residue Absorption Rate =0.01%
Soil risk - decks & playsets
Soil risk - playset only
Residue risk -playset only
Residue risk - decks & playsets
Cumulative Probability Density
100
90
80
70
60
50
40
30
20
10
0
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
Carcinogenic Risk

Figure D-3


Comparison of Residual & Soil Total Arsenic Risks for Warm Climate
Hand Wash
Soil risk - playset only
Soil risk - decks & playsets
Residue risk -playset only
Residue risk - decks & playsets
Cumulative Probability Density
100
90
80
70
60
50
40
30
20
10
0
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
Carcinogenic Risk

Appendix E

Summary of Relative Bioavailability Studies
Prepared by Jonathan Chen, Ph.D 9-15-2003

SUMMARY OF RELATIVE BIOAVAILABILITY STUDIES
Prepared by Jonathan Chen, Ph.D 9-15-2003

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 relative bioavailability through oral route for both arsenic in soil vs. arsenic in water and arsenic in dislodgeable wood residue vs arsenic in water are discussed.

I. ARSENIC IN SOIL

I -A STUDY SUMMARY

The arsenic relative bioavailability from soils were studied in different animal models . These studies are summarized below.

I- A-1 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).

I- A-2 Groen et al. 1993

Arsenic was administered as an intravenoussolution (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%.

I- A-3 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).

I- A-4 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%).

I- A-5 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).

I- A-6 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.

I- A-7 American Chemistry Council (ACC), 2003a.

The bioavailability of arsenic in soil affected by CCA-treated wood has been studied in juvenile swine (ACC, 2003a). The soil was collected near the base of utility poles treated with CCA Type C wood. The poles were installed on the site for around 5 years. The arsenic concentration in the utility pole soil was 320 µg/g. Groups of five swine were given oral doses of sodium arsenate or utility pole soil twice a day for 15 days. The amount of arsenic absorbed by each animal was evaluated by measuring the amount of arsenic excreted in the urine (as measured on days 8 to 9 and 10 to 11). The urinary excretion fraction (UEF) (the ratio of the amount excreted per 48 hours divided by the dose given per 48 hours) was calculated for sodium arsenate and the utility pole soil using linear regression analysis. By using sodium arsenate as a relative frame of reference, the mean RBA estimate for the soil affected by the CCA-treated wood is 49% (90th % CI = 41% - 58%).

The study design, the soil types and the results of these studies are summarized in **Table I-1.**

I-B DISCUSSION AND CONCLUSION

The issue has been discussed in the October 23- 25, 2001 FIFRA Scientific Advisory Panel Meeting. In the meeting, the Agency as the panel members to comment on the choice of the data set and value chosen for representation of the relative bioavailability of inorganic arsenic from ingestion of arsenic-contaminated soil. The panel considered that a research is needed to obtain data on the relative bioavailability of arsenic from soil contamination specifically resulting from CCA-treated wood applications. Based on this consideration, ACC (2003) conducted the study with soil contaminated directly from CCA-treated wood with the juvenile swine model. This is the only study using soil that is contaminated with CCA-treated soil. Although, only one soil type is involved in the study, after evaluating all available information, the Agency decide to use 49% as the relative bioavailabilty value in the risk assessment.

II. ARSENIC IN WOOD RESIDUE

In the October 23- 25, 2001 FIFRA Scientific Advisory Panel Meeting, the panel member also suggested the Agency to look into the relative bioavailability issue associated with the absorption of arsenic from non-soil substances (such as wood chips or other buffer material) that might be subject to incidental ingestion. For playground equipment, the dislodgeable arsenic from CCA-treated wood become the primary concern.

To address this issue, ACC sponsored a study (2003b). A study using juvenile

swine as test animals was performed to measure the gastrointestinal absorption of arsenic in dislodgeable material obtained from the surface of chromated copper arsenate (CCA)-treated wood. The CCA residue was collected from the surface of 1,456 CCA-treated boards of wood (Southern Yellow Pie or Ponderosa Pine) that had been weathered in the environment for 1 to 4 years. The arsenic concentration in the dislodgeable arsenic material was 3500 µg/g. Groups of five swine were given oral doses of sodium arsenate or dislodgeable arsenic twice a day for 12 days. The amount of arsenic absorbed by each animal was evaluated by measuring the amount of arsenic excreted in the urine (as measured on days 6 to 7, 8 to 9, and 10 to 11). The urinary excretion fraction (UEF) (the ratio of the amount excreted per 48 hours divided by the dose given per 48 hours) was calculated for sodium arsenate and the dislodgeable arsenic using linear regression analysis. Using sodium arsenate as a relative frame of reference, the RBA estimate for the test material is 29% (90th % CI = 26% - 32%).

The Agency consider this is a valid study and the result (29%) will be used as the relative bioavailability of dislodgeable srsenic from CCA-treated wood.

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Appendix F

Summary Table for the SHEDS-Wood December, 2003 SAP Meeting Minutes

Please refer to the following website for a complet discussion of the background information that was used to generage the questions presented to the SAP panel in 2003. http://www.epa.gov/scipoly/sap/meetings/2003/dec3/dec35meetingminutes.pdf

OPP Questions to SAP (12/2003)	SAP RECOMMENDATIONS TO OPP
Issue 1: Documentation, completeness, and clarity of the model source code and the exposure assessment report	
Question A: The Source Code Directory on the CD provided to the SAP includes annotated code for the exposure and dose algorithms used in the SHEDS-Wood model. Are these algorithms consistent with the descriptions in the SHEDS-Wood CCA exposure assessment report? Does the revised SHEDS-Wood version 2 code (i.e., the code submitted for the December 2003 SAP) accurately reflect changes to the version 1 methodology (i.e., the code and methodology presented to the August 2002 SAP) described in the report?	The Panel concluded that the algorithms used in the model align with those identified in the exposure assessment report. The model was correctly programmed and the advice from previous FIFRA SAPs has been accurately incorporated and well documented.
Question B: The SHEDS-Wood CCA exposure assessment report presents the model construct, selected model inputs, model results, and comparison to other CCA model estimates. Please comment on the clarity, completeness and usefulness of this document.	The exposure assessment documentation is clear. The tables of user-specified assumptions are extensive but the assumptions hard-coded in the scripts could be highlighted better.
Issue 2. Modifications to SHEDS-Wood model code and the exposure scenarios selected	
Question A: Considering the limitations of available information and state-of-the-art modeling methods required for the assessment of children's exposures from contacting CCA treated wood residues and CCA containing soil, are the revisions made to the SHEDS-Wood code or algorithms scientifically sound and acceptable ?	The general consensus of the Panel was that the current SHEDS-Wood model implementation represented a good faith effort on the part of the Agency. Even though one can question specific choices of distributional assumptions, overall the work seemed a reasonable effort and a sound basis for risk assessment within the limitations of available information. It is clear to the Panel that the SHEDS-Wood model code is flexible enough to implement any reasonable new scenarios, given that distributions and associated parameter estimates of the random variable components of the scenario model can be specified.
Question B: The SHEDS-Wood model has been modified using feedback from the August 2002 SAP. In particular, the recent assessment includes: assessment of exposures of children contacting only CCA treated public playsets; sensitivity of results to changing the age group of exposed children to 1-13 years, and; a separate analysis for children exhibiting pica soil ingestion behavior. The Panel is requested to comment on the appropriateness of the new exposure scenarios in the revised probabilistic	The Panel commented that anyone reviewing the current scenarios understands their limitations, including that the underlying population whose risk is being assessed is NOT children in general but is limited specifically to children contacting only CCA-treated public play sets. It was felt that this population limitation should be emphasized more in the documentation to avoid confusing the public. It is clear that this is not a population-based assessment for all children.

exposure and dose assessment.	
Issue 3. Key input variables and specification of associated variability distributions	
Sensitivity and uncertainty analyses of the SHEDS-Wood model results identified key input variables influencing the model results. **Question A.** Has the Agency used the best available information for developing input distributions for these variables? If not, are there any other data that EPA should be aware of? Considering the limitations and uncertainties with available information, are the choices made in developing distributions for each of these key variables using the available information reasonable and scientifically sound? **Question B.** In some of these instances (see Table 12, page 58), because of data limitations, the Agency has made simplifying assumptions to represent them as point estimates based on professional judgment. Are the simplifying assumptions presented in the draft exposure assessment for making these decisions adequately supported by relevant scientific data? Are the choices made to quantify these variables (i.e., selected distributions or point estimates) reasonable and sound? **Question C**. Are the methods used for fitting variability distributions that are assigned to model input variables for the CCA assessment appropriate? **Question D.** The Panel is requested to comment on whether any other model inputs are either key drivers of results or sources of large model uncertainty. Do these model input variables and the distributions assigned to them appropriately reflect available scientific data? Did EPA appropriately integrate the available data to derive the distributions for these input variables?	It was the consensus of the Panel that, by and large, the best information on input variables at this time has been used. The communication of this information by the Agency could be better, however, since the process by which professional judgment is incorporated into the selection of data sets and distributions is not always clear. The impact of this lack of clarity is that the model appears less reasonable and scientifically sound than it probably is. The Panel concluded that the set of variables related to human activity patterns (average number of days per year a child plays around CCA-treated playsets; frequency of hand washing; daily soils ingestion rate; average fraction of non-residential time a child plays on/around CCA-treated playsets) would benefit most from additional work by the Agency, and the impact of professional judgment more systematically addressed.
Issue 4: Methods and results for sensitivity and uncertainty analyses	
Question A: The Panel is requested to comment on the utility and suitability of the statistical diagnostic tools used by SHEDS for analyzing model results (e.g., variability analyses, sensitivity analyses, uncertainty analyses).	The Panel found in general that the methods and results of the SHEDS-Wood model sensitivity and uncertainty analyses were approached in a useful and suitable manner. The conclusions of the sensitivity and uncertainty analyses are robust with respect to choice of analytical method. Nevertheless, the results of the variability and uncertainty analyses may be limited by the application of parametric statistical

	methods to probability distributions of model inputs and outputs that are highly skewed.
Question B: Is the bootstrap approach that is used for fitting uncertainty distributions, which has been revised in response to prior SAP comments, implemented properly, or are there alternative approaches that are recommended?	The bootstrap approach used to construct probability distributions representing uncertainty appeared to be implemented appropriately. Although alternative approaches are available for fitting uncertainty distributions from available data, using such methods is unlikely to yield an appreciable difference in the uncertainty that can be extracted directly from a given data set.
Question C: Are the uncertainty distributions assigned to chemical and non-chemical specific model input parameters appropriate? **Question D**: The Panel is requested to comment on whether the modeling approach and documentation appropriately identify and address critical sources of uncertainty in the model and the resulting exposure estimates. Does EPA's documentation adequately describe the uncertainties inherent in the data used for modeling and the influence of these uncertainties on interpretation of the modeling results? **Question E.** Does the Panel recommend performing any additional uncertainty analyses to evaluate the impacts of using alternative input distributions on the modeling results (e.g., to address uncertainties in various factors determining the frequency of children's exposures to CCA-treated wood in playsets and decks)?	In cases where the available data are applicable (i.e., specific to the model use) and representative (e.g., an appropriate sample of U.S. children), the uncertainty distributions described in the SHEDS-Wood report are probably reasonable and in general appear appropriate. In cases where the available data are not specific to their use in the model or representative of the appropriate portion of the U.S. population, then the uncertainty distributions generated by the bootstrap method may not be appropriate. Generally, it is likely that overall uncertainties are substantially understated because (1) influential variables for which no variability estimates were made were also not subject to the bootstrap uncertainty analysis, and (2) any procedure that relies on internal fluctuations within a data set will tend to incorporate only random error and neglect sources of systematic error among studies, such as unrepresentativeness of the studied population for the target population of exposed children. Omitted from the uncertainty analysis is a lack of knowledge about the appropriate scenarios to include in the model and the algorithms (and corresponding data) used to simulate physical events. The Panel recommended that the Agency perform additional uncertainty analyses that include the parameters not treated as uncertain heretofore. In addition, the Agency should articulate the purpose of the uncertainty analysis is to aid in establishing a protocol for expressing uncertainty about the various model inputs.

Issue 5: Special Model Simulations	
A number of special simulations with the SHEDS-Wood model were conducted in order to examine the importance of specific exposure scenarios or the impact of certain input assumptions. **Question A.** The Panel is requested to comment on the appropriateness of the justifications made in characterizing the key factors or inputs for each of these special simulations. Did the Agency provide adequate technical rationale and justification for its choices for these alternative exposure scenarios or input distributions? Do the results from these special analyses reflect proper use of available information? **Question B**: Do any of the findings from these special analyses necessitate the Agency to consider revising certain scenarios or inputs to the baseline assessment?	The Panel was generally satisfied that the special simulations conducted by the Agency are well justified. The scenarios investigated are logical additions to the overall sensitivity analysis and are in some cases directly responsive to stakeholder concerns.
Issue 6: Evaluation of the SHEDS-Wood model results	
Question A: Has EPA provided adequate documentation of the overall plausibility of the exposure estimates generated by the SHEDS-Wood model for CCA? Are the comparisons with the results of other selected exposure assessments appropriate and appropriately presented? Are there any other types of benchmarking approaches or data to assess the reliability of the overall exposure model or specific model elements?	The Agency adequately documented six other exposure assessments in terms of the dose equations, input variables, and the levels of estimated exposure. In general, the exposures from these exposure assessments are in the same range as the output from the SHEDS-Wood model. In some cases, this may be due to overlap of the data available for the exposure assessments. The comparison revealed the limitations for comparison of these data sets due to their different approaches. The comparison neither validates nor invalidates the estimates from the SHEDS-Wood model.
Issue 7: Overall completeness and acceptability of the SHEDS-Wood probabilistic CCA exposure assessment	
Question A: In addition to the comments and suggestions already offered by the Panel members under the specific issues raised previously, considering the availability of data and information, does the Panel recognize any critical gaps in information or methodologies that still need to be addressed for the CCA exposure and dose assessment?	The Panel commended the Agency on an overall conscientious effort to respond to the various suggestions made by the previous FIFRA SAP. Overall the forms used by the Agency to describe the distributions are reasonable, and the Panel believed that other reasonable distributional forms are unlikely to appreciably alter the principal findings.

Issue 8. Formation of chemical complex after fixation	
Question A: The Panel is requested to comment on the Nico et. al. (2003) study and particularly on the arsenic and chromium chemical complex from CCA treated wood surface residue, and whether the Panel believes that the chemical complex is formed during the fixation process. What is the meaning of this complex cluster formation to the current risk assessment?	The Panel concluded that the Nico study, while important in the understanding of the nature of the Cr and As fixation in CCA wood and of the nature of the complex in wood particles, may not represent dislodgeable residues in general.
Issue 9. Relative Bioavailability (RBA) of dislodgeable wood residue	
Question A: Does the Panel agree that, in light of the Casteel study and the Nico study discussed in issue 8, the Agency should use 27% for the RBA to estimate the bioavailable dose.	The Panel concluded that: (a) inadequacies in the study design; (b) the likelihood that actual residues found on skin are more bioavailable than in CCA wood residue samples; and (c) the likelihood that ingested CCA wood residue samples are more bioavailable in pigs than in humans, leads to conflicting possible interpretations of the Casteel et al. study. Thus, due to these deficiencies, the Panel could not suggest a value for the RBA of CCA-wood residues dislodged by skin.
Issue 10. Dermal absorption of dislodgeable wood residue	
Question A: Taking into consideration the Nico et al. study mentioned in issue 8, the Panel is requested to comment on whether this new study conducted by Wester et al. provides a more appropriate estimate of dermal absorption from contact with CCA-treated wood surfaces than the earlier 1993 Wester et al. study.	No quantitative estimate of dermal availability from CCA wood residue samples can be derived from the 2003 Wester et al. experiments. That study therefore represents insufficient grounds for alteration of the dermal bioavailability assumption used in SHEDS-Wood. The Panel noted that the current default dermal availability used by the Agency (a Beta distribution with mean and median of about 3% per 24 hours) falls closer to the low end of the 2-8% range of availability of inorganic arsenic that would be derived from the 1993 and 2003 Wester et al. studies if correction by intravenous response is assumed appropriate for dermal application of inorganic arsenic; that it is similar to an adjusted LOD for the CCA wood residue sample experiments, and that the form of arsenic transferred to the skin of persons contacting decks and playsets is unknown.

Issue 11. Proposed biomonitoring pilot study	
In the 2001 SAP meeting, the Panel recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks. Recently, a proposed protocol for a pilot study was submitted to OPP for peer review and EPA has provided the Panel with a copy of the proposed protocol for the pilot study **Question A.** The Panel is requested to comment on the strengths and limitations of the approach to be employed in the proposed pilot study to help resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. In the statistical analysis, the sensitivity and accuracy of analytical method for quantification of arsenic in urine to detect changes, the determination of intraindividual variation and interindividual variation based on the current knowledge of exposure; and any other aspects of the proposed pilot study that might affect its utility. **Question B.** The Panel is asked to describe approaches for gathering additional data – e.g., data on the efficiency of transfer of surface residues to the skin surface (which has been identified as one of most critical model inputs based on the uncertainty analysis) – to improve the estimates of exposure and / or the level of confidence in such estimates, and with respect to these approaches, as well as the proposed pilot study, to comment on the cost of data generation, the amount of time to generate the data, and the degree to which the data will reduce uncertainty about the accuracy of the model estimates.	The Panel concluded that the proposed biomonitoring study by the Wood Preservative Science Council, as it stands, is not responsive to the 2001 SAP request. It is more appropriately a "Preliminary Study" in which data of some potential utility may be gathered, but which in no way assesses exposures or doses likely to be experienced by the target group: children coming into contact with CCA-treated wood products. The study proposal as presented is deficient in many ways, some of which may be matters of the level of detail presented. The Panel questioned whether the preliminary study could be carried out successfully to address the goals mentioned. It is the Panel's recommendation that a proposal for an appropriate pilot/preliminary study responsive to the recommendations of the 2001 SAP be discussed before implementation by all stakeholders– the public, EPA, and industry, and re-fashioned to be more responsive to all needs. After receiving input from these three groups, a new study design should, if appropriate, be amended so that it may be implemented in a way that provides information useful to allparties and reflective of the need to understand exposure through this specific pathway. The willingness of the regulated industry to entertain outside peer-review in this matter is encouraging as each stakeholder will be involved in various study components. With more thorough peer-review including involvement of EPA SHEDS-Wood personnel, a re-designed biomonitoring study could be an excellent source of information on actual levels of exposure and absorption, and be used to improve the SHEDS-Wood model.
Issue 12. Lifetime Average Daily Dose and Estimate of Risk	
Question A. The Panel is requested to comment on whether in this probabilistic approach of using the upper bound arsenic cancer slope factor combined with using high-end LADDs would result in a significant overestimation of the risk for the more highly exposed percentiles of the population? If this is an overestimate, what other values would the panel recommended using as replacements, or in addition to the values that were used that would minimize the overestimation of risk without substantially	The Panel concluded that it is not appropriate to characterize the quoted arsenic cancer slope factor as an "upper bound." The arsenic cancer slope factor cited by the Agency is derived from a central estimate ED01. In the spirit of the extensive sensitivity analysis performed by the Agency on the exposure estimates, the Panel believed it would be fair and appropriate for the Agency to at least disclose the magnitude and direction of change in the CCA risk estimates that would result from adoption of the revised NRC estimates and other technical considerations that are

underestimating the risk for such percentiles. In this assessment, the estimated risks are considered approximations because inaccuracies may occur when exposures are summed across routes at the quartile level especially in the upper percentile. This is due to the way the Monte Carlo simulations were conducted and the outputs summarized. **Question B.** The Panel is requested to comment on the range of percentiles, if any, at which there is a significant decrease in the reliability of the estimates of risk.	under current discussion within the Agency on arsenic and other cancer risks.

Appendix G: Inorganic Hexavalent Chromium (Cr(VI)): Report of the Cancer Assessment Review Comments

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

TXR No.: 0054811

MEMORANDUM

DATE: March 12, 2008

SUBJECT: Inorganic Hexavalent Chromium (Cr(VI)): Report of the Cancer Assessment Review Committee

PC Codes: 021101 (chromic acid), 068302 (potassium dichromate), 068304 (sodium dichromate), 068306 (disodium dichromate dihydrate)

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: **Jonathan Chen, Toxicologist, RASSB**
Antimicrobials Division (7510P)

The Cancer Assessment Review Committee met on November 28, 2007 to evaluate the carcinogenic potential of Inorganic Hexavalent Chromium (Cr(VI)). Attached please find the Final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

INORGANIC HEXAVALENT CHROMIUM
(Cr(VI))

[PC CODES: 021101 (chromic acid), 068302 (potassium dichromate), 068304 (sodium dichromate), 068306 (disodium dichromate dihydrate)]

March 12, 2008

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Jonathan Chen, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Karlyn Bailey

Lori Brunsman, Statistician

William Burnam, Chair — Retired

Marion Copley

Ray Kent

Mary Manibusan

Rob Mitkus

Nancy McCarroll

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist — See attached sheet

Other Attendees: Nancy Chiu (Office of Water), Santhini Ramasamy (Office of Water) Jenny Tao (OPP/AD)

DATA PRESENTATION: Jonathan Chen, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

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John Pletcher, Consulting Pathologist 

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

On November 28, 2007, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Program (OPP) met to evaluate the carcinogenic potential of inorganic hexavalent chromium (Cr(VI)). This was the first time this compound was assessed for carcinogenicity by the CARC.

In 2007, the National Toxicology Program (NTP) released the study results for 3-month toxicity studies in F344/N rats and B6C3F1, BALB/c, and am3-C57BL/6 mice (NTP, 2007b), and the two year cancer studies of male and female F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate (greater than 99.7% pure) in drinking water. Based on this newly released information and existing scientific evidence, the CARC met on November 28, 2007 to evaluate the carcinogenic potential of inorganic hexavalent chromium, Cr(VI) through the oral route of exposure. As stated in the EPA Integrated Risk Information System (IRIS) report (US EPA, 1998), hexavalent chromium, Cr(VI), is classified in Group A, known human carcinogen by the inhalation route of exposure. Under the EPA, 1986 guidelines, carcinogenicity of Cr(VI) by the oral route of exposure was not determined and was classified in Group D (US EPA, 1998).

Jonathan Chen of the Risk Assessment and Science Support Branch (RASSB) in the Antimicrobials Division (AD) presented the study results for the chronic toxicity/carcinogenicity studies in F344 rats and B6C3F1 mice. In the NTP 2-year rat chronic toxicology/carcinogenicity study, groups of 50 male and 50 female F344 rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 5, 20, 60, or 180 mg/L chromium) for 2 years (equivalent to average daily doses of 0, 0.21, 0.77, 2.10, or 5.95 mg Cr(VI)/kg body weight for males and 0, 0.26, 0.95, 2.45 or 7 mg Cr(VI) /kg body weight for females). In the NTP 2-year B6C3F1 mouse chronic toxicology/carcinogenicity study, groups of 50 male mice were exposed to drinking water containing 0, 14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0, 0.45, 0.9, 2.4, or 5.7 mg Cr(VI) /kg body weight for males). Groups of 50 female mice were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate for 2 years (equivalent to average daily doses of approximately 0, 0.3, 1.2, 3.2 or 8.8 mg Cr(VI) /kg body weight for females).

The CARC concluded the following:

Carcinogenicity

Rat

Oral Mucosa and Tongue Tumors:

- *Male rats:*

The incidences of oral mucosa and tongue tumors for average daily doses of 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 0.21, 0.77, 2.10, or 5.95 mg Cr(VI)/kg body weight/day, respectively) were as follows:

Squamous Cell Papilloma and Squamous Cell Carcinoma:

0/50 (0%), 1/50 (2%), 0/49 (0%), 0/50 (0%), 7/49 (12%)

Male rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 516 mg/L dose group with the controls, for combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, both at $p<0.01$. When compared to historical control data (1/300 (0.3%), with a range of 0-2% for drinking water), the incidence of squamous cell papillomas or carcinomas in the high dose (12%) exceeded the historical control group range (0–2%). **Therefore, the CARC considered the oral mucosa and tongue tumors seen in males at the high dose to be treatment-related. In addition, these tumors are considered to be rare.**

- *Female rats*:

The incidences of combined oral mucosa and tongue tumors for average daily doses of 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 0.26, 0.95, 2.45 or 7 mg Cr(VI) /kg body weight for females) were as follows:

Squamous Cell Papilloma and Squamous Cell Carcinoma:

1/50 (2%), 1/50 (2%), 0/50 (0%), 2/50 (4%), 11/50 (22%)

Female rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 516 mg/L dose group with the controls, for combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, at $p<0.01$. In the 172 mg/L dose group, the incidence of 2/50 (4%), while not statistically significant by a pair-wise comparison, was considered to be biologically significant. When compared to historical control data (3/250 (1.2%) for drinking water), the incidence of oral and tongue squamous cell papillomas or squamous cell carcinomas in the two high dose groups (4% and 22%) exceeded the historical control group range (0 – 2%). **Therefore, the CARC considered the oral mucosa and tongue tumors seen at**

both the 172 and 516 mg/L dose groups to be treatment-related. In addition, these tumors are considered to be rare.

• *Adequacy of Dosing*: The CARC considered dosing at the top dose of 516 mg/L sodium dichromate dihydrate to be adequate, but not excessive, in both sexes for the assessment of carcinogenicity of Cr(VI) in rats. This was based on non-neoplastic liver lesions (including histiocytic cellular infiltration, chronic inflammation, fatty change (females)) and histiocytic infiltration in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females. In addition, decreased body weight was seen in high dose males (↓6-9%) and females (↓4-10%) compared to the controls throughout the study and by the end of the study body weights were 88% and 89% of the respective controls. According to the NTP report, the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 172 and 516 mg/L rats was less than that by the controls throughout the study.

Mouse

Tumors of the small intestine (duodenum, jejunum, or ileum)

- *Male mice:*

The incidences of combined small intestine tumors (duodenum, jejunum, or ileum) for the control, 14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate groups (0, 0.45, 0.9, 2.4, or 5.7 mg Cr(VI) /kg body weight /day, respectively), were as follows:

Adenoma:	1/50 (2%),	1/50 (2%),	1/50 (2%),	5/50 (10%),	17/50 (34%)
Carcinoma:	0/50 (0%),	2/50 (4%),	1/50 (2%),	3/50 (6%),	5/50 (10%)
Combined:	1/50 (2%),	3/50 (6%),	2/50 (4%),	7/50 (14%),	20/50 (40%)

Male mice had a statistically significant trend, and statistically significant pair-wise comparisons of the 257.4 mg/L dose group with the controls, for combined small intestine, duodenum, jejunum and ileum adenomas, and combined adenomas and carcinomas, all at $p < 0.01$. There was also a statistically significant trend, and a statistically significant pair-wise comparison of the 257.4 mg/L dose group with the controls, for combined small intestine, duodenum, jejunum and ileum carcinomas, both at $p < 0.05$. There was a statistically significant pair-wise comparison of the 85.7 mg/L dose group with the controls for combined small intestine, duodenum, jejunum and ileum combined adenomas and carcinomas, at $p < 0.05$. At the top two doses, the incidences of all tumor types (adenomas (34%), carcinomas (10%), and combined (40%)) exceeded the historical controls ranges (0-6% for adenoma, 0-4% for carcinoma, and 0-10% for adenoma or carcinoma combined). **Therefore, the CARC concluded that the small intestine tumors seen in male mice at both the 85.7 and 257.4 m/L dose groups were treatment-related. These are considered to be rare tumors. This decision was supported by the presence of nonneoplastic hyperplasia in the small intestine in both the chronic and subchronic mouse studies.**

- *Female mice*:

The incidences of small intestine tumors (duodenum, jejunum, and ileum) for the control, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (0, 0.3, 1.2, 3.2 or 8.8 mg Cr(VI) /kg body weight /day) groups respectively, were as follows:

Adenoma:	0/50 (0%),	1/50 (2%),	2/50 (4%),	15/50 (30%),	16/50 (32%)
Carcinoma:	1/50 (2%),	0/50 (0%),	2/50 (4%),	3/50 (6%),	7/50 (14%)
Combined:	1/50 (2%),	1/50 (2%),	4/50 (8%),	17/50 (34%),	22/50 (44%)

Female mice had statistically significant trends, and statistically significant pair-wise comparisons of the 172 and 516 mg/L dose groups with the controls, for combined small intestine, duodenum, jejunum and ileum adenomas, and combined adenomas and carcinomas, all at $p < 0.01$. There was also a statistically significant trend at $p < 0.01$, and a statistically significant pair-wise comparison of the 516 mg/L dose group with the controls at $p < 0.05$, for combined small intestine, duodenum, jejunum and ileum carcinomas. In the 57.3 mg/L dose group, the incidences of adenomas (4%), carcinomas (4%) and combined (8%), while not statistically significant, were considered to be biologically significant. The tumor responses at the top three doses exceeded the spontaneous tumor incidence rates of historical control ranges (0-2% for adenoma, 0-2% for carcinoma, and 0-4% for adenoma/ carcinoma combined). **Therefore, the CARC concluded that the increased incidence of small intestine tumors at the top three doses in female mice were treatment related. These are considered to be rare tumors. This decision was supported by the presence of nonneoplastic hyperplasia in the small intestine in both the chronic and subchronic mouse studies.**

• *Adequacy of Dosing*: Dosing at the high dose (257.4/516 mg/L, males/females) was considered adequate, but not excessive, in male and female mice. This was based on the presence of diffuse epithelial hyperplasia and cellular histiocytic infiltration in the duodenum and jejunum of male and/or female mice. Histiocytic cellular infiltration was also seen in the liver and mesenteric and pancreatic lymph nodes. In addition, mean body weights of 257.4 mg/L males were less than controls for the first 4 months of the study, but by the end of the study, the mean body weight of 257.4 mg/L males was only slightly less than that of the control group. Mean body weights of 172 and 516 mg/L females were less than those of the controls for the first 8 months of the study. By the end of the study, the mean body weight of 172 mg/L females was 8% less than that of the controls, and the mean body weight of 516 mg/L females was 15% less than that of the control group. The NTP report stated that the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 85.7 and 257.4 mg/L males and 172 and 516 mg/L females was less than that by the controls throughout the study.

Structure-Activity Relationship

According to the Oncologic Cancer Expert System report, in general, virtually all Cr-containing compounds are of some carcinogenicity concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route. The carcinogenic potential of inorganic chromium compounds is affected by their oxidation state, crystallinity, and solubility, which affect the extent of compound uptake by cells. Hexavalent compounds are more easily taken up by cells than trivalent; and crystalline compounds are more easily taken up than amorphous compounds. Sparingly soluble and insoluble compounds are more likely than soluble compounds to be retained at the site of exposure, and thus have more of an opportunity to be taken up by the cells. Organic chromium compounds containing a Cr-C covalent bond are treated as inorganic compounds because the Cr-C covalent bond is expected to be easily hydrolyzed in aqueous solution. Since the substance is a(an) inorganic or organic compound, and the oxidation state of chromium is hexavalent, and exposure to this soluble substance is expected to be by the oral route, the level of carcinogenicity concern is MODERATE. The final level of concern for this Cr-containing inorganic or organic compound, when the anticipated exposure is via the oral route, is MODERATE.

Mutagenicity

There is clear evidence that Cr(VI) is a mutagen, including positive results from *in vitro* mutagenicity studies and from *in vivo* animal studies, as well as data showing lipid peroxidation in blood and micronuclei induction in the buccal epithelial cells of humans. For this reason, a mutagenic mode of action (MOA) analysis is under way. It is briefly described below and will be the subject of a later document.

Mutagenic Mode of Action

In response to the 2005 revised U.S Environmental Protection Agency (EPA) Cancer Guidelines, a strategy is in place to combine genetic toxicology data with other information to determine whether a carcinogen operates through a mutagenic mode of action (MOA) (USEPA, 2005a,b). This information is necessary for EPA to decide whether age-dependent adjustment factors (ADAFs) should be applied to the cancer risk assessment. A decision tree has been developed as part of this approach and outlines the critical steps for analyzing a compound for carcinogenicity through a mutagenic MOA (*e.g.,* data analysis, determination of mutagenicity in animals and in humans). Agents showing mutagenicity in animals and/or humans proceed through the Agency's framework analysis for MOAs. Chromium (VI) is carcinogenic in animals and humans via both the inhalation and oral routes. Following oral exposure, Cr(VI) induced oral cavity tumors in male and female rats and tumors of the small intestine in male and female mice. Cr(VI) is also mutagenic, producing consistent positive results for mutagenic activity in numerous *in vitro* assays, in animals (mice and rats) and in humans (lipid peroxidation in blood, micronuclei induction in buccal cells) occupationally exposed to Cr(VI). Accordingly,

Cr(VI) was processed through the framework analysis and key steps leading to tumor formation were identified and include: interaction of cellular components (DNA) with Cr(VI), mutagenesis, hyperplasia and tumor formation. Within the timeframe and tumorigenic dose range for early events, genetic changes in mice (single/double-stranded DNA breaks, Comet assay at 0.59 to 9.5 mg/kg) can commence within 24 hours of treatment. Supporting evidence is also found for cell proliferation, indicating that mutagenicity, associated with oxidative damage, DNA adduct formation and cytotoxicity, leads to a proliferative response, which occurs early (90 days) in the process of tumor induction. Overall, the weight of evidence evaluation supports Cr(VI) acting through a mutagenic MOA. In addition, no data were found that an alternative MOA might be operative. Therefore, the Cancer Guidelines recommend a linear extrapolation for the oral exposure risk assessment. Data also exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus, it is recommended that the ADAFs be applied. Details will be provided in the MOA document currently in preparation.

Human Epidemiological Studies

The carcinogenic activity of chromium has been known since the late 19th century when the first cases of nasal tumors were reported in Scottish chrome pigment workers (Costa and Klein 2006). Sedman et al. (2006) concluded from their review of several occupational studies that human exposure to Cr(VI) by inhalation has been linked to increased rates of cancer in several occupational studies. A number of retrospective analyses have associated significant increases in respiratory cancer to Cr(VI) worker exposure in the chromate and chromate pigment production industry. The Gibb et al. (2000) investigation of 2,357 chrome production workers is considered to be the most comprehensive and firmly established Cr(VI) as a human lung carcinogen (Costa and Klein 2006).

While several studies of human ingestion of chromium exist in the open literature, these investigations do not provide strong causal support for an association between Cr(VI) and cancer. However, one study was found in which oral ingestion has been implicate as an exposure route associated with Cr(VI)-induced cancer. In the study of Zhang and Li (1986), 155 subjects were exposed to $\approx$ 20 mg/L Cr(VI) through drinking water in the Liaoning Province of northeastern China. The source of contamination was a chromium ore smelting facility located in a rural area outside of Jinzhou; Cr(VI) was detected in 28% of the area wells in 1965. Contamination levels in 55% of these wells were >20 mg/L Cr(VI). Higher per capita rates of cancers, including lung and stomach cancers were found. In a retrospective analysis of the Zhang and Li study, Beaumont et al. (2008) confirmed that there was a substantial association between stomach cancer and mortality and Cr(VI) contaminated drinking water compared to a nearby uncontaminated area.

Classification and Quantification of Carcinogenicity

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified hexavalent chromium, Cr(VI), as **"Likely to be Carcinogenic to Humans"** based on the presence of oral mucosa and tongue tumors in male and female rats and tumors of the small intestine in male and female mice at doses that were adequate, but not excessive, to assess carcinogenicity. There is clear evidence that Cr(VI) is mutagenic and convincing evidence supporting a mutagenic mode of action. The decision is also qualitatively supported by human epidemiological data which indicates an association between exposure and increased stomach tumor incidence.

The Committee recommended using a linear low-dose extrapolation approach (Q_1*) for estimating the human cancer risk based on the most potent tumor type. Data also exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus, it is recommended that the ADAFs be applied.

I. INTRODUCTION

On November 28, 2007, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Program met to evaluate the carcinogenic potential of inorganic hexavalent chromium (Cr(VI)). This was the first time this compound was assessed for carcinogenicity by the CARC.

II. BACKGROUND INFORMATION

Chromium is found naturally in water, soil and food. Chromium in the ambient air occurs from industrial sources. In water, hexavalent chromium (Cr(VI)) contamination can be attributed to various industrial processes including electroplating operations, leather tanning, and textile manufacturing. Although chromium can occur in every one of the oxidation states from -2 to +6, only the ground states (0), +2, +3 and +6 are common. The hexavalent form of chromium is a strong oxidizing agent which can be easily reduced to Cr(III). The trivalent chromium is the most stable oxidation state. It can easily form coordination compounds, complexes, and chelaters. Therefore, chromium plays an important role in the fixation of Chromated Copper Arsenate (CCA) in treated wood.

All toxicity data have been generated on various inorganic Cr(VI) compounds: chromic acid, potassium dichromate, potassium chromate and sodium chromate. Although the physical properties of these substance are different (i.e., pH, solubility, etc.), these substances are all ionized in the body to Cr(VI) and, therefore, exert the same pharmacological/toxicological effects.

As stated in the EPA Integrated Risk Information System (IRIS) report (US EPA, 1998), hexavalent chromium, Cr(VI), is classified in Group A, known human carcinogen, by the inhalation route of exposure. Under the EPA, 1986 guidelines, carcinogenicity of Cr(VI) by the oral route of exposure was not determined and was classified in Group D (US EPA, 1998).

In 2007, the National Toxicology Program (NTP) released its study results of 3-month toxicity studies in F344/N rats and B6C3F1, BALB/c, and am3-C57BL/6 mice (NTP, 2007b), and the two year cancer studies of male and female F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate (greater than 99.7% pure) in drinking water (NTP, 2007a). The CARC was asked to evaluate the carcinogenic potential of inorganic hexavalent chromium (Cr(VI)) through the oral route based on the new information.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. 2-Year Chronic Toxicity and Carcinogenicity Study in Rats (NTP, 2007a)

Reference:
National Toxicology Program (NTP) (2007a) NTP Draft Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS No. 7789-12-0) in F344 Rats and B6C3F1 Mice (Drinking Water Studies). Southern Research Institute, Birmingham, AL. NTP TR 546 (NIH Publication No. 07-5887), 2007. Published by the National Institutes of Health, U.S. Department of Health and Human Services.

A. Experimental Design

Groups of 50 male and 50 female rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 5, 20, 60, or 180 mg/L chromium) for 2 years (equivalent to average daily doses of 0, 0.21, 0.77, 2.10, or 5.95 mg Cr(VI)/kg body weight for males and 0, 0.26, 0.95, 2.45 or 7 mg Cr(VI)/kg body weight for females).

B. Discussion of Tumor Data

Survival Analysis

As summarized in the Table 1, survival of the exposed groups was similar to that of the control groups.

Tumor Analysis

The tumor analysis data are summarized in Table 2. Exposure to sodium dichromate dihydrate resulted in the development of neoplasms of the squamous epithelium that lines the oral mucosa and tongue. Male rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 516 mg/L (5.95 mg/kg/day Cr (VI)) dose group with the controls, for combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, both at $p < 0.01$. There was also a statistically significant trend at $p < 0.01$, and a statistically significant pair-wise comparison of the 516 mg/L (5.95 mg/kg/day Cr (VI)) dose group with the controls at $p < 0.05$, for oral mucosa squamous cell carcinomas. Female rats had statistically significant trends, and statistically significant pair-wise comparisons of the 516 mg/L (7.0 mg/kg/day Cr (VI)) dose group with the controls, for oral mucosa squamous cell carcinomas, and combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, all at $p < 0.01$.

The incidence in 172 mg/L females and the 516 mg/L males and females for the oral cavity neoplasms exceeded the historical control ranges for drinking water studies and for all routes of administration.

Table 1. Survival of Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 41, Table 2 in NTP, 2007a)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Animals initially in study	50	50	50	50	50
Missing[a]	0	0	1	0	1
Moribund	16	15	16	9	16
Natural deaths	6	5	3	5	4
Animals surviving to study termination	28	30	30	36	29
Percent probability of survival at end of study[b]	56	60	61	72	59
Mean survival (days)[c]	695	670	672	692	694
Survival analysis[d]	P=0.904N	P=1.000N	P=1.000N	P=0.221N	P=1.000N
Female					
Animals initially in study	50	50	50	50	50
Moribund	12	15	9	10	18
Natural deaths	5	3	9	4	1
Animals surviving to study termination	33[e]	32	32	36	31
Percent probability of survival at end of study	66	64	64	72	62
Mean survival (days)	696	691	694	686	685
Survival analysis	P=0.748	P=0.959	P=0.965	P=0.806N	P=0.745

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposed group is indicated by N.
[e] Includes one animal that died during the last week of the study

Table 2. Incidences of Neoplasms of the Oral Cavity in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 53, NTP, 2007a, Table 6)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Number Necropsied	50	50	49	50	49
Oral Mucosa					
Squamous Cell Papilloma[a]	0	0	0	0	1
Squamous Cell Carcinoma[b]					
Overall Rate[c]	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	6/49 (12%)
Adjusted Rate[d]	0.0%	0.0%	0.0%	0.0%	13.6%
Terminal Rate[e]	0/28 (0%)	0/30 (0%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First Incidence (days)	---[g]	---	---	---	543
Poly-3 test[f]	P<0.001	---[h]	---	---	P=0.015
Tongue					
Squamous Cell Papilloma	0	0	0	0	1
Squamous Cell Carcinoma	0	1	0	0	0
Oral Mucosa or Tongue[i]					
Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall Rate	0/50 (0%)	1/50 (2%)	0/49 (0%)	0/50 (0%)	7/49 (12%)
Adjusted Rate	0.0%	2.4%	0.0%	0.0%	15.7%
Terminal Rate	0/28 (0%)	1/30 (3%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First Incidence (days)	---	729 (T)	---	---	543
Poly-3 test	P<0.001	P=0.487	---	---	P=0.007
Female					
Number Necropsied	50	50	50	50	50
Oral Mucosa					
Squamous Cell Carcinoma[j]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	11/50 (22%)
Adjusted Rate	0.0%	0.0%	0.0%	4.6%	23.9%
Terminal Rate	0/33 (0%)	0/32 (0%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First Incidence (days)	---	---	---	646	506
Poly-3 test	P<0.001	---	---	P=0.233	P<0.001
Tongue					
Squamous Cell Papilloma	1	1	0	0	0
Squamous Cell Carcinoma	0	0	0	1	0

Table 2. Incidences of Neoplasms of the Oral Cavity in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate – Continue (Page 54, NTP, 2007a, Table 6)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female (continued)					
Oral Mucosa or Tongue					
Squamous Cell Papilloma or Squamous Cell Carcinoma[k]					
Overall Rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	11/50 (22%)
Adjusted Rate	2.2%	2.3%	0.0%	4.6%	23.9%
Terminal Rate	0/33 (0%)	1/32 (3%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First Incidence (days)	618	729 (T)	.....	646	506
Poly-3 test	P<0.001	P=0.756	P=0.503N	P=0.491	P=0.002

(T)Terminal sacrifice
[a] Number of animals with neoplasm
[b] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 0/350; all routes: 5/1,499 (0.3% ± 0.7%), range 0%-2%
[c] Number of animals with neoplasm per number of animals necropsied
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by N
[g] Not applicable; no neoplasms in animal group
[h] Value of statistic cannot be computed.
[i] Historical incidence for drinking water studies: 1/300 (0.3% ± 0.8%), range 0%-2%; all routes: 10/1,449 (0.6% ± 0.8%), range 0%-2%
[j] Historical incidence for drinking water studies: 0/300; all routes: 5/1,400 (0.4% ± 0.8%), range 0%-2%
[k] Historical incidence for drinking water studies: 3/250 (1.2% ± 1.1%), range 0%-2%; all routes: 14/1,350 (1.1% ± 1.6%), range 0%-6%

C. Non-Neoplastic Lesions

Incidences of nonneoplastic lesions of the liver in rats are summarized in Table 3. Concentration-related non-neoplastic liver lesions were observed in males and females exposed to 57.3 mg/L or greater. These included histiocytic cellular infiltration, chronic inflammation, fatty change (females), and clear cell focus (females). As summarized in Table 4, increased incidences of histiocytic infiltration also occurred in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females exposed to 57.3 mg/L or greater.

Table 3. Incidences of Nonneoplastic Lesions of the Liver in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 55 NTP, 2007a, Table 7)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Number Examined Microscopically	50	50	49	50	49
Infiltration Cellular, Histiocyte[a]	1 (1.0)[b]	0	2 (1.0)	5 (1.4)	34** (1.4)
Inflammation, Chronic	19 (1.1)	25 (1.2)	21 (1.3)	28* (1.1)	26 (1.3)
Basophilic Focus	22	28	29*	32*	30
Female					
Number Examined Microscopically	50	50	50	50	50
Infiltration Cellular, Histiocyte	1 (1.0)	5 (1.0)	21** (1.3)	42** (2.0)	47** (2.6)
Inflammation, Chronic	12 (1.3)	21* (1.2)	28** (1.3)	35** (1.6)	39** (2.1)
Fatty Change	3 (3.3)	7 (3.6)	10* (2.5)	13** (2.5)	16** (2.8)
Clear Cell Focus	7	5	7	20**	7

* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Table 4. Incidence of Selected Nonneoplastic Lesions in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (page 57, NTP 2007a, Table 8)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Small Intestine, Duodenum[a]	48	48	47	46	48
Infiltration Cellular, Histiocyte[b]	0	0	6* (1.2)[c]	36** (1.1)	47** (1.5)
Lymph Node, Mesenteric	49	50	49	50	49
Infiltration Cellular, Histiocyte	13 (2.0)	11 (1.5)	30** (1.9)	39** (2.1)	41** (2.1)
Hemorrhage	2 (1.5)	7 (1.1)	9* (1.3)	8* (1.1)	17** (1.3)
Lymph Node, Pancreatic	33	34	34	38	35
Infiltration Cellular, Histiocyte	17 (2.0)	22 (1.6)	17 (1.9)	17 (2.1)	25 (2.1)
Female					
Small Intestine, Duodenum	46	49	48	46	50
Infiltration Cellular, Histiocyte	0	0	1 (1.0)	30** (1.0)	47** (1.2)
Lymph Node, Mesenteric	50	50	50	50	50
Infiltration Cellular, Histiocyte	21 (1.7)	18 (1.4)	27 (1.5)	36** (2.0)	42** (2.4)
Hemorrhage	11 (1.1)	13 (1.3)	16 (1.3)	14 (1.1)	21* (1.3)
Lymph Node, Pancreatic	31	37	31	34	36
Infiltration Cellular, Histiocyte	17 (2.0)	20 (1.9)	23 (2.6)	32** (2.8)	27 (3.0)
Salivary Gland	50	50	50	50	50
Atrophy	9 (1.3)	7 (1.4)	10 (1.2)	17* (1.4)	17 (2.1)

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC considered dosing at the top dose of 516 mg/L sodium dichromate dihydrate to be adequate, but not excessive, in both sexes for the assessment of carcinogenicity of Cr(VI) in rats. This was based on non-neoplastic liver lesions (including histiocytic cellular infiltration, chronic inflammation, fatty change (females)) and histiocytic infiltration in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females. In addition, there was decreased body weight seen in high dose males (6-9%) and females (4-10%) compared to the controls throughout the study and by the end of the study were 88% and 89% that of the respective controls (Tables 5 and 6). According to the NTP report, the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 172 and 516 mg/L rats was less than that by the controls throughout the study.

Table 5. Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 44-45, NTP, 2007a, Table 3)

Days on Study	0 mg/L		14.3 mg/L			57.3 mg/L			172 mg/L			516 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	118	50	117	99	50	117	99	50	117	99	50	118	100	50
8	151	50	149	99	50	146	97	50	147	97	50	143	95	50
15	185	50	183	99	50	181	98	50	180	97	50	173	93	50
22	218	50	215	99	50	213	98	50	210	97	50	201	93	50
29	243	50	240	99	50	239	99	50	235	97	50	225	93	50
36	261	50	257	99	50	257	99	50	254	97	50	243	93	50
43	275	50	271	99	50	272	99	50	267	97	50	257	93	50
50	289	50	286	99	50	285	99	50	279	96	50	270	93	50
57	305	50	301	99	50	302	99	50	295	96	50	285	93	50
64	317	50	312	99	50	313	99	50	304	96	50	295	93	50
71	334	50	329	98	50	331	99	50	321	96	50	311	93	50
78	345	50	340	99	50	339	98	50	330	96	50	320	93	50
85	351	50	345	98	50	348	99	50	338	96	50	324	92	50
113	387	50	381	98	50	383	99	50	373	96	50	363	94	50
141	410	50	404	99	50	407	99	50	395	96	50	386	94	50
169	434	50	427	98	50	431	99	50	418	96	50	407	94	50
197	451	50	443	98	50	448	99	50	437	97	50	424	94	50
225	468	50	458	98	50	464	99	50	449	96	50	437	94	50
253	480	50	471	98	50	477	99	50	462	96	50	447	93	50
281	488	50	478	98	50	483	99	49	469	96	50	454	93	50
309	490	50	485	99	50	488	100	49	477	97	50	461	94	50
337	501	50	495	99	48	497	99	48	486	97	50	468	94	50
365	511	50	502	98	47	505	99	48	490	96	50	475	93	50
393	515	50	507	98	47	512	99	48	496	96	50	479	93	50
421	523	50	515	98	47	519	99	48	503	96	49	485	93	50
449	524	50	515	98	47	519	99	48	504	96	49	484	92	50
477	525	50	516	98	45	518	99	48	503	96	49	484	92	50
505	525	48	517	98	45	520	99	46	501	96	49	483	92	50
533	530	47	519	98	45	525	99	45	508	96	47	487	92	50
561	532	47	518	97	44	525	99	44	507	95	46	483	91	48
589	531	46	515	97	42	522	98	43	506	95	44	473	89	47
617	529	45	519	98	40	519	98	40	502	95	42	480	91	41
645	526	44	517	98	38	520	99	36	501	95	39	474	90	39
673	513	41	515	100	36	517	101	32	500	97	39	462	90	36
701	515	32	503	98	33	514	100	31	500	97	38	455	88	32
Mean for weeks														
1-13	261		257	99		257	99		252	97		243	94	
14-52	457		449	98		453	99		441	96		427	94	
53-101	523		514	98		518	99		502	96		477	91	

Table 6. Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 46-47, NTP, 2007a, Table 4)

Days on Study	0 mg/L		14.3 mg/L			57.3 mg/L			172 mg/L			516 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	100	50	99	99	50	100	99	50	99	99	50	99	98	50
9	122	50	120	99	50	121	99	50	119	98	50	115	94	50
16	135	50	132	98	50	134	99	50	131	97	50	129	95	50
23	150	50	146	97	50	147	98	50	145	97	50	144	96	50
30	157	50	154	98	50	154	98	50	153	97	50	152	97	50
37	164	50	161	98	50	162	98	50	161	98	50	159	97	50
44	170	50	168	99	50	167	98	50	166	98	50	165	97	50
51	175	50	172	98	50	172	98	50	171	97	50	170	97	50
58	180	50	178	99	50	177	98	50	175	97	50	175	97	50
65	183	50	180	99	50	180	98	50	178	97	50	178	97	50
72	188	50	184	98	50	185	98	50	183	98	50	182	97	50
79	193	50	189	98	50	188	97	50	186	97	50	186	96	50
86	198	50	193	97	50	192	97	50	192	97	50	190	96	50
114	208	50	203	97	50	202	97	50	201	97	50	199	96	50
142	217	50	211	97	50	209	96	50	206	95	50	207	95	50
170	229	50	223	98	50	221	97	50	218	95	50	215	94	50
198	237	50	229	97	50	229	97	50	226	95	50	222	94	50
226	246	50	239	97	50	237	96	50	235	96	50	230	94	50
254	255	50	248	97	50	246	97	50	242	95	50	237	93	50
282	263	50	255	97	50	253	96	50	248	94	50	242	92	50
310	272	50	261	96	50	262	96	50	256	94	50	248	91	50
338	281	50	271	96	50	271	96	50	265	94	50	254	90	50
366	289	50	279	97	50	278	96	50	272	94	50	263	91	50
394	297	50	288	97	49	287	97	50	279	94	49	268	90	50
422	309	50	297	96	49	297	96	50	290	94	49	275	89	50
450	314	50	302	96	49	304	97	50	296	94	48	281	89	50
478	317	50	307	97	48	310	98	49	302	95	48	284	90	48
506	323	49	312	97	48	315	98	49	308	95	47	290	90	47
534	332	48	323	97	48	322	97	48	318	96	46	298	90	47
562	337	48	328	98	46	325	97	47	319	95	45	300	89	46
590	341	46	332	97	46	333	98	44	325	95	42	307	90	42
618	336	42	332	99	43	333	99	43	326	97	40	314	93	40
646	348	40	336	96	41	340	98	43	333	96	39	315	90	40
674	350	39	339	97	37	346	99	38	337	96	37	318	91	36
702	351	35	338	96	34	346	98	34	340	97	36	312	89	35
Mean for weeks														
1-13	163		160	98		160	98		158	97		157	96	
14-52	245		238	97		237	96		233	95		228	93	
53-101	326		316	97		318	98		311	95		294	90	

2. 2-Year Carcinogenicity Study in Mice (NTP 2007a)

Reference:
National Toxicology Program (NTP) (2007a) NTP Draft Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS No. 7789-12-0) in F344 Rats and B6C3F1 Mice (Drinking Water Studies). Southern Research Institute, Birmingham, AL. NTP TR 546 (NIH Publication No. 07-5887), 2007. Published by the National Institutes of Health, U.S. Department of Health and Human Services.

A. Experimental Design

In this B6C3F1 mouse oncogenicity study, groups of 50 male mice were exposed to drinking water containing 0,14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0, 0.45, 0.9, 2.4, or 5.7 mg Cr(VI) /kg body weight for males). Groups of 50 female mice were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0, 0.3, 1.2, 3.2 or 8.8 mg Cr(VI)/kg body weight for females).

B. Discussion of Tumor Data

Survival Analysis

As summarized in Table 7, survival of the exposed groups was similar to that of the control groups.

Table 7. Survival of Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate (Page 59, NTP, 2007a, Table 9)

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Animals initially in study	50	50	50	50	50
Moribund	7	5	5	4	3
Natural deaths	10	10	10	8	15
Animals surviving to study termination	33[a]	35	35	38	32[a]
Percent probability of survival at end of study[b]	66	70	70	76	64
Mean survival (days)[c]	700	694	682	708	689
Survival analysis[d]	P=0.724	P=0.949N	P=0.982N	P=0.387N	P=0.918
	0 mg/L	**14.3 mg/L**	**57.3 mg/L**	**172 mg/L**	**516 mg/L**
Female					
Animals initially in study	50	50	50	50	50
Moribund	5	0	2	2	3
Natural deaths	8	11	3	6	5
Animals surviving to study termination	37[e]	39[a]	45[a]	42[e]	42
Percent probability of survival at end of study	74	78	90	84	84
Mean survival (days)	696	705	714	709	709
Survival analysis	P=0.504N	P=0.780N	P=0.068N	P=0.333N	P=0.285N

[a] Includes one animal that died during the last week of the study
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposed group is indicated by N.
[e] Includes two animals that died during the last week of the study

Tumor Analysis

As summarized in Table 8, the incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum combined) were increased in exposed groups of male and female mice. Male mice had a statistically significant trend, and statistically significant pair-wise comparison of the 257.4 mg/L (5.7 mg/kg/day Cr(VI)) dose group with the controls, for duodenum adenomas, combined small intestine, duodenum, jejunum and ileum adenomas, and combined adenomas and carcinomas, all at $p < 0.01$. There was also a statistically significant trend, and a statistically significant pair-wise comparison of the 257.4 mg/L (5.7 mg/kg/day Cr(VI)) dose group with the controls, for combined small intestine, duodenum, jejunum and ileum carcinomas, both at $p < 0.05$. There was a statistically significant pair-wise comparison of the 2.4 mg/kg/day Cr(VI) dose group with the controls for combined small intestine, duodenum, jejunum and ileum combined adenomas and carcinomas at $p < 0.05$. There was a statistically significant trend for duodenum carcinomas at $p < 0.05$. There was a statistically significant trend for jejunum adenomas at $p < 0.01$.

Female mice had statistically significant trends, and statistically significant pair-wise comparisons of the 172 and 516 mg/L (3.2 and 8.8 mg/kg/day Cr(VI)) dose groups with the controls, for combined small intestine, duodenum, jejunum and ileum adenomas, and combined adenomas and carcinomas, all at $p < 0.01$. There was also a statistically significant trend at $p < 0.01$, and a statistically significant pair-wise comparison of the 8.8 mg/kg/day Cr(VI) dose group with the controls at $p < 0.05$, for combined small intestine, duodenum, jejunum and ileum carcinomas.

The incidences in the ≥85.7 mg/L males and ≥57.3 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration.

C. Non-Neoplastic Lesions

In the small intestine, as summarized in Table 8, the incidences of diffuse epithelial hyperplasia were significantly increased in the duodenum of all exposed groups of male and female mice. The incidences of cellular histiocytic infiltration were significantly increased in the duodenum of 85.7 and 257.4 mg/L males and in 172 and 516 mg/L females. In the jejunum, the incidences of diffuse epithelial hyperplasia and histiocytic cellular infiltration were significantly increased in 516 mg/L females.

As summarized in Table 9, the incidences of histiocytic cellular infiltration of the liver in all exposed groups of females, of the mesenteric lymph node in all exposed groups of males and females, and of the pancreatic lymph node of 85.7 and 257.4 mg/L males and 172 and 516 mg/L females were significantly increased.

Table 8. Incidences of Neoplasms and Nonneoplastic Lesions in the Small Intestine of Mice (Page 70, NTP, 2007a, Table 13)

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Number Necropsied	50	50	50	50	50
Duodenum					
Epithelium, Hyperplasia, Focal[a]	0	0	0	1 (3.0)[b]	2 (3.5)
Epithelium, Hyperplasia, Diffuse	0	11** (2.0)	18** (1.6)	42** (2.1)	32** (2.1)
Infiltration Cellular, Histiocytes	0	2 (1.0)	4 (1.0)	37** (1.2)	35** (1.7)
Adenoma, Multiple	0	0	0	0	6*
Adenoma (includes multiple)[c]					
Overall Rate[d]	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)	15/50 (30%)
Adjusted Rate[e]	2.2%	0.0%	2.3%	10.8%	32.9%
Terminal Rate[f]	0/33 (0%)	0/35 (0%)	1/35 (3%)	5/38 (13%)	10/32 (31%)
First Incidence (days)	665	—[h]	729 (T)	729 (T)	451
Poly-3 test[g]	P<0.001	P=0.505N	P=0.751	P=0.106	P<0.001
Carcinoma[i]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rate	0.0%	0.0%	0.0%	4.3%	6.8%
Terminal Rate	0/33 (0%)	0/33 (0%)	0/35 (0%)	2/38 (5%)	3/32 (9%)
First Incidence (days)	—	—[j]	—	729 (T)	729 (T)
Poly-3 test	P=0.011	—	—	P=0.243	P=0.113
Jejunum					
Adenoma[k]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rate	0.0%	0.0%	0.0%	0.0%	6.8%
Terminal Rate	0/33 (0%)	0/35 (0%)	0/35 (0%)	0/38 (0%)	2/32 (6%)
First Incidence (days)	—	—	—	—	714
Poly-3 test	P=0.002	—	—	—	P=0.114
Carcinoma, Multiple	0	1	0	0	0
Carcinoma (includes multiple)[l]	0	2	0	1	2
Duodenum, Jejunum, or Ileum					
Adenoma[m]					
Overall Rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)	17/50 (34%)
Adjusted Rate	2.2%	2.3%	2.3%	10.8%	37.2%
Terminal Rate	0/33 (0%)	1/35 (3%)	1/35 (3%)	5/38 (13%)	11/32 (34%)
First Incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 test	P<0.001	P=0.755	P=0.751	P=0.106	P<0.001
Carcinoma[n]					
Overall Rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rate	0.0%	4.5%	2.3%	6.5%	11.4%
Terminal Rate	0/33 (0%)	2/35 (6%)	1/35 (3%)	3/38 (8%)	5/32 (16%)
First Incidence (days)	—	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.014	P=0.233	P=0.492	P=0.123	P=0.028
Adenoma or Carcinoma[o]					
Overall Rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	7/50 (14%)	20/50 (40%)
Adjusted Rate	2.2%	6.8%	4.6%	15.1%	43.8%
Terminal Rate	0/33 (0%)	3/35 (9%)	2/35 (6%)	7/38 (18%)	14/32 (44%)
First Incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 test	P<0.001	P=0.296	P=0.485	P=0.032	P<0.001

Table 8. Incidences of Neoplasms and Nonneoplastic Lesions in the Small Intestine of Mice - Continue (Page 71, NTP, 2007a, Table 13)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female					
Number Necropsied	50	50	50	50	50
Duodenum					
Epithelium, Hyperplasia, Focal	0	0	1 (2.0)	2 (3.0)	0
Epithelium, Hyperplasia, Diffuse	0	16** (1.6)	35** (1.7)	31** (1.6)	42** (2.2)
Infiltration Cellular, Histiocyte	0	0	4 (1.3)	33** (1.2)	40** (2.0)
Adenoma, Multiple	0	0	0	1	6*
Adenoma (includes multiple)[p]					
Overall Rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	13/50 (26%)	12/50 (24%)
Adjusted Rate	0.0%	0.0%	4.2%	27.8%	25.2%
Terminal Rate	0/37 (0%)	0/39 (0%)	2/45 (4%)	13/42 (31%)	11/42 (26%)
First Incidence (days)	—	—	729 (T)	729 (T)	693
Poly-3 test	P<0.001	—	P=0.251	P<0.001	P<0.001
Carcinoma[q]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rate	0.0%	0.0%	0.0%	2.1%	12.6%
Terminal Rate	0/37 (0%)	0/39 (0%)	0/45 (0%)	1/42 (2%)	5/42 (12%)
First Incidence (days)	—	—	—	729 (T)	625
Poly-3 test	P<0.001	—	—	P=0.507	P=0.019
Jejunum					
Epithelium, Hyperplasia, Diffuse	0	2 (2.0)	1 (2.0)	0	8** (1.9)
Infiltration Cellular, Histiocyte	0	0	0	2 (1.0)	8** (1.6)
Adenoma, Multiple	0	0	0	0	1
Adenoma (includes multiple)[r]					
Overall Rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rate	0.0%	2.2%	0.0%	4.3%	10.6%
Terminal Rate	0/37 (0%)	1/39 (3%)	0/45 (0%)	2/42 (5%)	5/42 (12%)
First Incidence (days)	—	729 (T)	—	729 (T)	729 (T)
Poly-3 test	P=0.002	P=0.504	—	P=0.246	P=0.035
Carcinoma[s]	1	0	2	2	1
Duodenum, Jejunum, or Ileum					
Adenoma[t]					
Overall Rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	15/50 (30%)	16/50 (32%)
Adjusted Rate	0.0%	2.2%	4.2%	32.0%	33.7%
Terminal Rate	0/37 (0%)	1/39 (3%)	2/45 (4%)	15/42 (36%)	15/42 (36%)
First Incidence (days)	—	729 (T)	729 (T)	729 (T)	693
Poly-3 test	P<0.001	P=0.504	P=0.251	P<0.001	P<0.001
Carcinoma[u]					
Overall Rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted Rate	2.2%	0.0%	4.2%	6.4%	14.7%
Terminal Rate	1/37 (3%)	0/39 (0%)	2/45 (4%)	3/42 (7%)	6/42 (14%)
First Incidence (days)	729 (T)	—	729 (T)	729 (T)	625
Poly-3 test	P<0.001	P=0.496N	P=0.521	P=0.319	P=0.037

Table 8. Incidences of Neoplasms and Nonneoplastic Lesions in the Small Intestine of Mice - Continue (Page 72, NTP, 2007a, Table 13)

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female (continued)					
Adenoma or Carcinoma[v]					
Overall Rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	17/50 (34%)	22/50 (44%)
Adjusted Rate	2.2%	2.2%	8.3%	36.3%	45.9%
Terminal Rate	1/37 (3%)	1/39 (3%)	4/45 (9%)	17/42 (41%)	20/42 (48%)
First Incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)	625
Poly-3 test	P<0.001	P=0.756N	P=0.198	P<0.001	P<0.001

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 6/299 (2.0% ± 2.2%), range 0%-6%; all routes: 9/1,549 (0.6% ± 1.3%), range 0%-6%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by N
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for drinking water studies: 1/299 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,549 (0.2% ± 0.8%), range 0%-4%
[j] Value of statistic cannot be computed.
[k] Historical incidence for drinking water studies: 0/299; all routes: 1/1,549 (0.1% ± 0.4%), range 0%-2%
[l] Historical incidence for drinking water studies: 5/299 (1.7% ± 1.5%), range 0%-4%; all routes: 25/1,549 (1.6% ± 2.2%), range 0%-8%
[m] Historical incidence for drinking water studies: 6/299 (2.0% ± 2.2%), range 0%-6%; all routes: 10/1,549 (0.7% ± 1.3%), range 0%-6%
[n] Historical incidence for drinking water studies: 6/299 (2.0% ± 1.8%), range 0%-4%; all routes: 30/1,549 (2.0% ± 2.2%), range 0%-8%
[o] Historical incidence for drinking water studies: 11/299 (3.7% ± 3.7%), range 0%-10%; all routes: 39/1,549 (2.6% ± 2.7%), range 0%-10%
[p] Historical incidence for drinking water studies: 1/350 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,648 (0.2% ± 0.6%), range 0%-2%
[q] Historical incidence for drinking water studies: 0/350; all routes: 1/1,648 (0.1% ± 0.4%), range 0%-2%
[r] Historical incidence for drinking water studies: 0/350; all routes: 0/1,648
[s] Historical incidence for drinking water studies: 2/350 (0.6% ± 1.0%), range 0%-2%; all routes: 5/1,648 (0.3% ± 0.7%), range 0%-2%
[t] Historical incidence for drinking water studies: 1/350 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,648 (0.2% ± 0.6%), range 0%-2%
[u] Historical incidence for drinking water studies: 3/350 (0.9% ± 1.1%), range 0%-2%; all routes: 8/1,648 (0.5% ± 0.8%), range 0%-2%
[v] Historical incidence for drinking water studies: 4/350 (1.1% ± 1.6%), range 0%-4%; all routes: 11/1,648 (0.7% ± 1.1%), range 0%-4%

Table 9. Incidence of Selected Nonneoplastic Lesions in Mice in the 2-Year Drinking Water study of Sodium Dichromate Dihydrate. (Page 76, NTP, 2007a, Table 14)

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Liver[a]	50	50	50	50	50
Clear Cell Focus[b]	20	17	19	16	7**
Eosinophilic Focus	27	26	19	21	12**
Lymph Node, Mesenteric	47	47	49	49	46
Infiltration Cellular, Histiocyte	14 (1.2)[c]	38** (1.1)	31** (1.2)	32** (1.5)	42** (2.5)
Lymph Node, Pancreatic	12	16	15	12	20
Infiltration Cellular, Histiocyte	0	2 (1.0)	2 (1.0)	5* (1.4)	12** (2.3)
Pancreas	49	49	50	49	48
Acinus, Cytoplasmic Alteration	0	1 (3.0)	1 (3.0)	9** (2.1)	8** (2.6)
	0 mg/L	**14.3 mg/L**	**57.3 mg/L**	**172 mg/L**	**516 mg/L**
Female					
Liver	49	50	50	50	50
Infiltration Cellular, Histiocyte	2 (1.0)	15** (1.1)	23** (1.0)	32** (1.0)	45** (1.9)
Inflammation, Chronic	16 (1.1)	21 (1.1)	22 (1.1)	27* (1.1)	24 (1.0)
Eosinophilic Focus	14	18	8	5*	4**
Lymph Node, Mesenteric	46	48	46	50	50
Infiltration Cellular, Histiocyte	3 (1.0)	29** (1.3)	26** (1.1)	40** (1.9)	42** (2.7)
Lymph Node, Pancreatic	21	15	17	18	16
Infiltration Cellular, Histiocyte	0	1 (1.0)	2 (1.5)	7** (1.9)	8** (2.5)
Pancreas	48	50	49	50	50
Acinus, Cytoplasmic Alteration	0	6* (2.5)	6* (2.0)	14** (2.4)	32** (2.6)

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

D. Adequacy of Dosing for Assessment of Carcinogenicity

Dosing at the high dose (257.4/516 mg/L, males/females) was considered adequate, but not excessive in male and female mice. This was based on the presence of diffuse epithelial hyperplasia and cellular histiocytic infiltration in the duodenum and jejunum of male and/or female mice. Histiocytic cellular infiltration was also seen in the liver, and mesenteric and pancreatic lymph nodes. In addition, mean body weights of 257.4 mg/L males were less than controls for the first 4 months of the study, but by the end of the study, the mean body weight of 257.4 mg/L males was only slightly less than that of the control group. Mean body weights of 172 and 516 mg/L females were less than those of the controls for the first 8 months of the study. By the end of the study, the mean body weight of 172 mg/L females was 8% less than that of the controls, and the mean body weight of 516 mg/L females was 15% less than that of the control group. The NTP report stated that the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 85.7 and 257.4 mg/L males and 172 and 516 mg/L females was less than that by the controls throughout the study.

IV. TOXICOLOGY

1. Metabolism

Orally administered chromium compounds are relatively poorly absorbed, with most estimates in the range of 0.5 to 2%. Trivalent chromium is absorbed about one quarter as well as the hexavalent form, but hexavalent chromium is reduced to trivalent chromium in the stomach, potentially limiting the systemic availability of hexavalent chromium ingested orally. Gastrointestinal absorption of Cr(VI) occurs with greater efficiency than absorption of Cr(III), though absorption of ingested hexavalent chromium is estimated to be less than 5%. There is rapid extracellular reduction of Cr(VI) to Cr(III) in acidic environments. There is greater absorption of Cr(VI) than Cr(III) because it readily enters cells by facilitated diffusion via anion channels in contrast to Cr(III) which enters by passive diffusion or phagocytosis. Intracellular reduction of Cr(VI) to Cr(III) occurs by ascorbate and GSH. To study the tissue distribution of chromium, additional groups of male F344/N rats and female B6C3F1 mice were treated the same as the core cancer study (NTP, 2007a). The total chromium concentrations were determined in selected tissues, including erythrocytes, plasma, liver, kidney, glandular stomach, and forestomach and excreta at multiple time points in the study (days 6, 13, 182, and 371). In addition, there was a 48-hour washout period to allow excretion of unabsorbed Cr. The results are shown in Figures 1 and 2. In general, Cr concentrations tended to increase with increasing exposure concentration and duration of exposure. In the liver, the chromium concentration was not proportional to exposure concentration indicating saturation of the active uptake mechanism for Cr (Figure 1). The highest Cr concentrations were in the kidney, glandular stomach, and liver (Figure 2). Therefore, the study demonstrated that following oral exposure, Cr(VI) is absorbed and distributed to different tissues in the body.

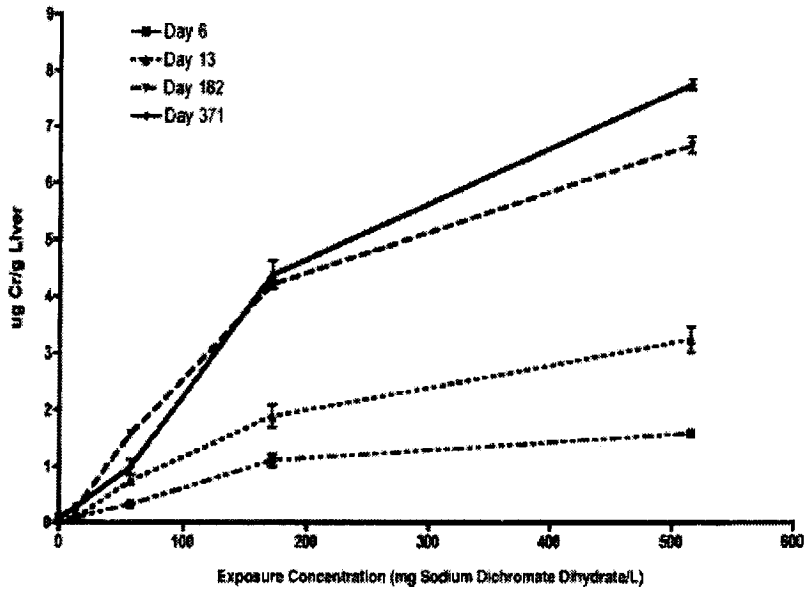


Figure 1. Chromium Concentrations on Days 6, 13, 182, and 371 in the Liver of Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water (Page 79, NTP, 2007a, Figure 5)

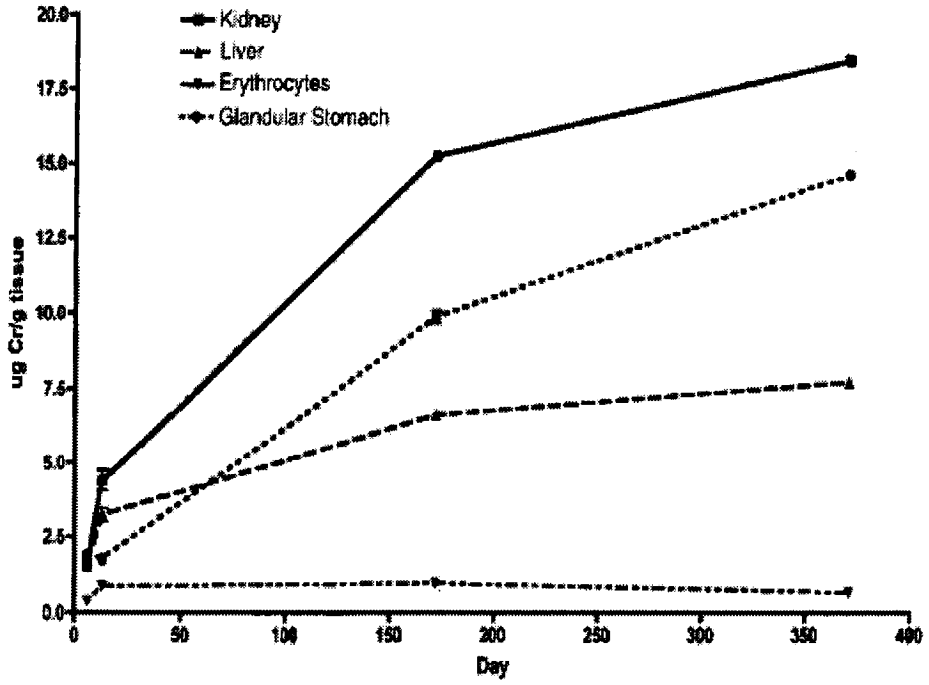
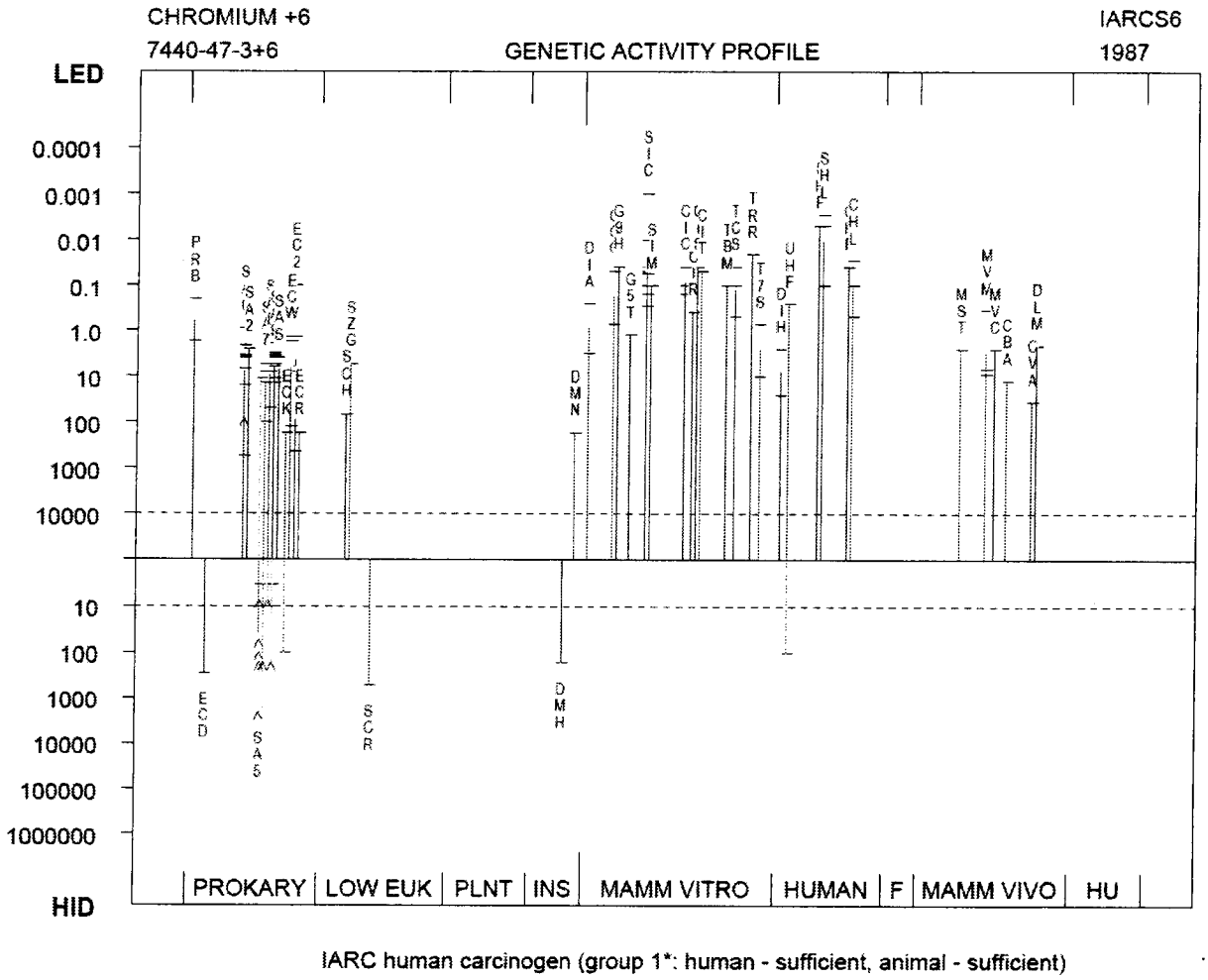


Figure 2. Chromium Concentrations in the Kidney, Liver, Erythrocytes, and Glandular Stomach of Male Rats Exposed to 516 mg/L Sodium Dichromate Dihydrate in Drinking Water (Page 79, NTP, 2007a, Figure 6)

2. Mutagenicity

The genetic activity profiles (GAP) for Cr(VI) and Cr (III) were developed jointly with the International Agency for Research on Cancer (IARC) to graphically display genetic toxicology data as a function of concentration or dose (GAP 2000). Details for the schematic representation of the GAP for Cr(VI), depicted in Figure 3, and the GAP for Cr (III), depicted in Figure 4, can be found in Waters et al. (1988).

Chromium has been extensively studied for DNA damage, mutagenicity, and other mechanisms involved in genotoxic effects (reviewed in Bianchi and Levis, 1984, 1988; DeFlora et al., 1990; Alcedo and Wetterhahn, 1990; IARC, 1990; ATSDR, 1993, 2000; Klein, 1996). For Cr(VI), there is clear evidence of mutagenicity both *in vitro* and *in vivo* in animals and humans. Some of the mutagenic studies were reviewed in this section. In acceptable assays, Cr(VI) is active in bacteria, yeast, insects, mammalian cells and whole animals in inducing a variety of genotoxic effects. The in vitro response was largely observed in the absence of S9 activation. Whereas, Cr(III) compounds gave negative or weakly positive results with or without S9 activation.



IARC human carcinogen (group 1*: human - sufficient, animal - sufficient)

Figure 3. The Genetic Activity Profile (GAP) of Hexavalent Inorganic Chromium (VI)

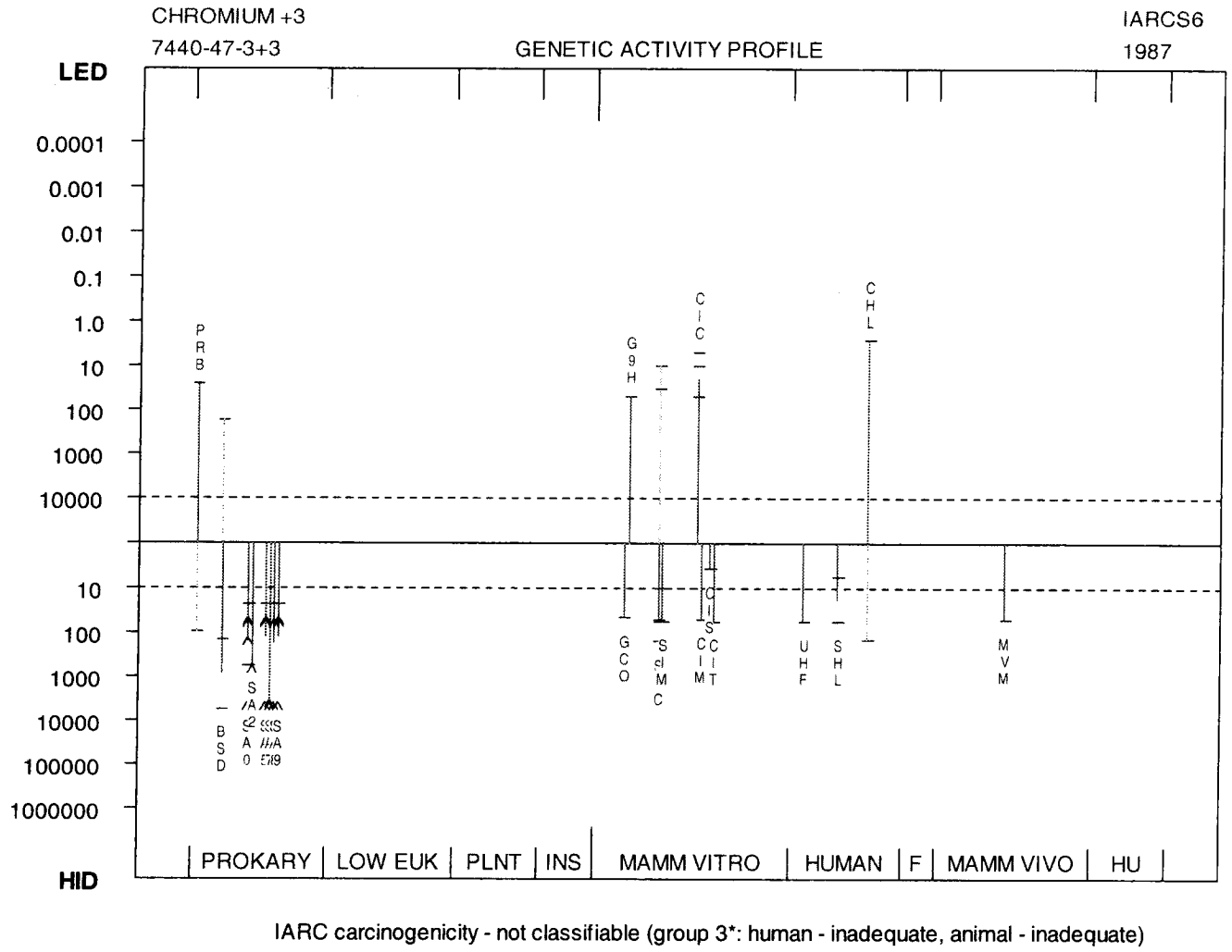


Figure 4. The Genetic Activity Profile (GAP) of Hexavalent Inorganic Chromium (III)

Bacterial reverse mutation test (§870. 5100)

Four Cr(VI) compounds (sodium dichromate, chromic acid, calcium chromate and potassium chromate) and two Cr(III) compounds (chromium potassium sulfate and chromium chloride) were tested for mutagenicity by means of the Ames Assay. Strains (TA1535, TA1537, TA98 and TA100) of *Salmonella typhimurium* were exposed for 48 hours to the chromium compounds (Petrilli and De Flora 1977). Throughout a series of experiments, Cr(VI) compounds (sodium dichromate, chromic acid, calcium chromate and potassium chromate) consistently produced a marked increase in His + revertants at concentrations of 10 to 200 µg/plate. On the average, 1 µmol of Cr(VI) yielded approximately 500 revertants of TA100 strain, irrespective of the compound tested (sodium dichromate, chromic acid, calcium chromate and potassium chromate). The mutagenic potency of the Cr(VI) was not enhanced by adding the metabolic activation system (S9 fraction of rat, induced either with sodium barbital or with Aroclor 1254). The two Cr(III) compounds (chromium potassium sulfate and chromium chloride), with or without the S9 fraction, were neither toxic nor mutagenic to the bacterial tester strains. This study is considered as an acceptable guideline study.

Venitt and Levis (1974) reported that the soluble chromates of sodium, potassium and calcium (Cr(VI), at doses of 0.05, 0.10, and 0.20 µmol/agar plate, caused reversion of *E. coli* WP2 (trp-) to prototrophy. The soluble trivalent compound (chromium potassium sulfate) was not mutagenic in the testing system.

In the *E. coli* Hs_3OR test system (which utilizes arginine revertants), Nakamuro et al. (1978) found that the Cr(VI) salts potassium dichromate and potassium chromate and the trivalent chromium triacetate produced significant ($p<0.01$) numbers of chromosomal aberrations following treatment at concentrations of 0.5×10^{-6}M, 4×10^{-6}M and 1.6×10^{-5}M, respectively.

Sodium dichromate dihydrate (5 to 300 µg/plate) was mutagenic in *Salmonella typhimurium* strains TA100 and TA98 and in *E. coli* strain WP2 uvrA pKM101 with and without 10% induced rat liver S9 enzymes (NTP, 2007b). Responses were stronger in the strains that mutate via base substitution (TA100, E. coli WP2); in all three tester strains, mutagenicity was more pronounced in the absence of S9, based on the lowest concentration that elicited a significant mutagenic response.

***In vitro* mammalian cell gene mutation (§870. 5300)**

The mutagenic effects of chromium compounds have been studied in mammalian cells. In a study by Nishimura and Umeda (1978), FM3A cells derived from C3H mouse mammary carcinomas were exposed *in vitro* to potassium dichromate, chromic acid, potassium chromate or chromium sulfate (doses not stated). Of the Cr(VI) compounds, potassium dichromate and chromic acid induced both chromosomal aberrations and 8-azaguanine-resistant mutations, whereas potassium chromate enhanced only chromosomal changes; chromium sulfate (Cr(III)) had no effect.

Newbold et al. (1979) have exposed Chinese hamster cells to potassium dichromate (Cr(VI) (0.35 to 0.78 μg/mL) and zinc chromate (Cr(VI) (1 to 4 pg/mL) using 8-azaguanine-resistance to measure mutagenicity. Both compounds were mutagenic in a dose-dependent manner at all levels tested. Chromic acetate (Cr(III) (50 to 200 pg/mL) and the relatively insoluble lead chromate (Cr(VI) (5 to 10 pg/mL) were not mutagenic, however, even at doses that were approximately 200 and 10 times higher, respectively, than the maximum dose at which cell survival was measurable with potassium dichromate. The mutation frequency in the presence of potassium dichromate increased in a linear fashion with increasing lethality when only subthreshold (minimally lethal) doses were considered. At higher doses it became harder to recover mutants due to the increased incidence of cell death.

***In vitro* mammalian chromosome aberration test (§870. 5375)**

Tsuda and Kato (1976) detected chromosomal aberrations in Chinese hamster embryo cells that had been exposed *in vitro* to potassium dichromate ($K_2Cr_2O_7$) (Cr(VI)) (0.1 to 0.5 μg/mL culture medium). The chromosomal lesions produced included abnormal metaphases, gaps, chromatid breaks and exchanges, as well as deletions and fragmentations.

Raffetto et al. (1977) examined the changes produced in tertiary mouse fetal cell cultures following exposure to equitoxic doses of chromium chloride (Cr(III)) (0.4 μg/mL) and potassium dichromate (Cr(VI)) (0.1μg/mL). Both compounds produced similar morphological changes, and more chromosomal aberrations were noted in cells treated with Cr(VI) than in those treated with Cr(III). Cells treated with Cr(VI) also exhibited unscheduled DNA synthesis whereas those treated with Cr(III) did not.

Nakamuro et al. (1978) compared the chromosomal aberration effects of trivalent and hexavalent chromium salts. Five chromium compounds, potassium dichromate ($K_2Cr_2O_7$) and potassium chromate (K_2CrO_4) containing Cr(VI), and chromium triacetate ($Cr(CH_3COO)_3$), chromium nitrate ($Cr(NO_3)_3$, and chromium trichloride ($CrCl_3$) containing Cr(III), were studied for their ability to induce chromosomal damage in cultures of human leukocytes. In the study, the chromosome-breaking activity was significantly higher for the compounds with hexavalent than trivalent chromium compounds. The efficiency was in the decreasing order $K_2Cr_2O_7 > K_2CrO_4 >$ $>Cr(CHCOO)_3 > Cr(NO_3)_3$, $CrCl_3$. The last three trivalent chromium compounds were significantly less efficient as compared with the first two hexavalent chromium compounds.

Majone and Levis (1979) have evaluated the clastogenicity of hexavalent potassium dichromate and sodium dichromate in Chinese hamster cells *in vitro.* Both compounds induced mitotic delays that were proportional to the dose of chromium. Chromosomal aberrations were also produced; these were primarily chromatid gaps, breaks, and interchanges and were dose dependent over a range of 0.1 to 1.0 μg Cr(VI) /mL. Sister chromatid exchanges were used as an index of chromosomal damage. Both Cr(VI) compounds increased the frequency of chromosomal aberrations but were weak inducers of sister chromatid exchange.

Both potassium chromate (Cr(VI)) (0.15 pg/mL) and chromium chloride (Cr(III)) (50 pg/mL) induced chromosomal aberrations and mitotic alterations in the pseudodiploid Chinese hamster ovary cell line (Majone and Rensi 1979). Levis and Majone (1979), also using the pseudodiploid line, evaluated 11 water-soluble salts of Cr(III) and Cr(VI). Giant cells were produced by exposure to both Cr(VI) and Cr(III) compounds. The frequency of chromosomal aberrations was increased tenfold after exposure to 1.0 pg/mL Cr(VI) as sodium chromate, but only doubled after treatment with 50 to 150 pg/mL Cr(III) as chromium nitrate. A significant number ($p<0.001$) of sister chromatid exchanges were seen after exposure to 0.1 pg/mL of the Cr(VI) compounds potassium dichromate, sodium dichromate and chromic acid, but not in response to 150 pg/mL of trivalent chromium nitrate or chromium potassium sulfate.

Mitotic gene conversion in *Saccharomyces cerevisiae*

Galli et al. (1985) studied the ability of potassium dichromate ($K_2Cr_2O_7$) (Cr(VI)) and chromium chloride ($CrCl_3$) (Cr(III)) to induce gene conversion and point reverse mutation in D_7 diploid strain of *S. cerevisiae*. It was confirmed that $K_2Cr_2O_7$ will induced mutation in the testing cells from the stationary phase of growth with and without metabolic activation (S9 hepatic fraction) and cells from the logarithmic phase without metabolic activation were used in this study. In contrast, $CrCl_3$ will increase the genetic toxicity in the presence of sulfate buffer, but not with Tris-HCl buffer. Galli et al.(1985) suggested that the phosphate ion may be the carrier responsible of the entrance of Cr(III) in the cells.

Kirpnick-Sobol et al. (2006) determined the effects of Cr(VI) as potassium dichromate and Cr(III) as chromium(III) chloride on the frequencies of DNA deletions measured with the deletion assay in *Saccharomyces cerevisiae*. It was confirmed that both Cr(VI) and Cr(III) significantly increased the frequency of DNA deletions. Kirpnick-Sobol et al. (2006) quantified intracellular chromium concentrations in yeast. It revealed that Cr(III) is a more potent inducer of DNA deletions than Cr(VI) once Cr(III) is absorbed.

Cell transformation

DiPaolo and Casto (1979) have also demonstrated morphological transformations (e.g., crisscrossing and piling up of cells) using cultured Syrian, hamster embryo cells exposed to sodium chromate (Cr(VI)) at 0.1, 0.5 and 1.0 pg/mL. The frequencies of transformation were 0.7%, 2.10% and 3.48%, respectively.

***In Vivo* studies**

Gene Mutations (Non-Guideline)

Itoh and Shimada (1998) studied the mutagenic effects of potassium chromate (K_2CrO_4) (Cr(VI)) in *lacZ* transgenic mice (muta™ Mouse). At a single dose of 40mg/kg, K_2CrO_4 was administered

intraperitoneally to five male mice per treatment group. The animals were sacrificed on days 1 and 7 after the treatment. Mutant frequencies in the bone marrow and liver were analyzed by the positive selection method using *E. coli* C (*galE*) Strain and phenyl -D-galactoside. Potassium chromate induced a significant increase in mutant frequency in the bone marrow on day 1, but not on day 7 after the treatment. In the liver, on the other hand, a significant induction in the mutant frequency was seen on day 7, while no induction was observed on day 1. Ito and Shimada (1998) suggested the reason for the different responses to the mutagenic activity of K_2CrO_4 between these organs may be related to the cell turnover rates of these organs. The mutations induced by K_2CrO_4 in the bone marrow may have occurred in more differentiated cells than stem cells, and the rapid proliferative activity may have caused a rapid decrease in mutated cells by day 7. This study is considered as non-guideline but acceptable study.

Mammalian chromosomal aberration test (§870. 5385)

The effects of two Cr(VI) compounds, potassium chromate (K_2CrO_4) and potassium dichromate ($K_2Cr_2O_7$), on bone marrow cells have been studied in mice and white, non-inbred rats, respectively (Wild 1978; Bigaliev and Elemesova 1978). Two intraperitoneal injections, 24 hours apart, of 24.25 and 48.5 mg of K_2CrO_4 (Cr(VI))/kg body weight in mice (both sexes; weight 26 to 35 g) produced a significant increase (alpha <0.01) in the number of micronucleated polychromatic erythrocytes, whereas two intraperitoneal injections, 24 hours apart, of 12.12 mg K_2CrO_4 (Cr(VI))/kg had no significant effect (Wild 1978). A single dose of potassium dichromate (Cr(VI)) administered intraperitoneally to rats at 15 mg/kg (weight of rats not stated) produced a significant increase in the number of bone marrow cells with metaphasic chromosomal aberrations (Bigaliev and Elemesova 1978).

In NTP study (2007b), the results of four micronucleus tests conducted in three strains of mice were mixed. In one study, micronucleus frequencies were determined in peripheral blood erythrocytes of male and female B6C3F1 mice administered sodium dichromate dihydrate over an exposure concentration range of 62.5 to 1,000 mg/L for 3 months. No significant increases were seen in micronucleated normochromatic erythrocytes in male or female mice over the exposure concentration range tested; there was a decrease in the percentage of polychromatic erythrocytes among total erythrocytes (an indication of bone marrow toxicity), but the changes were small and not well correlated with exposure concentrations. In the second study, micronucleus frequencies were evaluated in male B6C3F1, BALB/c, and am3-C57BL/6 mice administered sodium dichromate dihydrate over an exposure concentration range of 62.5 to 250 mg/L in drinking water for 3 months. An increase in micronucleated erythrocytes that was judged to be equivocal was noted in male B6C3F1 mice based on the trend test ($p=0.031$), which showed an increase in micronucleated normochromatic erythrocytes that did not reach statistical significance (required p value of 0.025); no exposed groups were significantly increased over the control group in this study. No increase in micronucleated normochromatic erythrocytes was observed in male BALB/c mice. A significant exposure concentration-related increase ($p<0.001$) in micronucleated erythrocytes was noted in male am3-C57BL/6 mice. In this study, two of three dose groups were significantly ($p<0.008$) elevated over the control group. No significant effect of

chemical exposure on the percentage of polychromatic erythrocytes was observed in any of the three micronucleus tests conducted in the second study.

Other Studies

Cr(VI) can be absorbed by animal and further pass the placental barrier to the embryo. Kirpnick-Sobol et al. (2006) reported that exposure of pregnant mice (C57BL/6J p^{un}/p^{un}) to either potassium dichromate (Cr VI; 62.5 or 125.0 mg/L) or chromium (III) chloride (1,875 or 3,750 mg/L) in drinking water during gestational days 10 to 20 resulted in significant increases in the frequencies of large-scale DNA deletions in their pups examined at 20 days of age. Kirpnick-Sobol et al. (2006) reported that in comparing the embryo chromium concentrations to DNA deletion frequency revealed that Cr(III) exposure lead to induction of DNA deletions at an ~3-fold lower embryo chromium concentration than dose exposure to Cr(VI).

3. Structure-Activity Relationship

According to the Oncologic Cancer Expert System report, in general, virtually all Cr-containing compounds are of some carcinogenicity concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route. The carcinogenic potential of inorganic chromium compounds is affected by their oxidation state, crystallinity, and solubility, which affect the extent of compound uptake by cells. Hexavalent compounds are more easily taken up by cells than trivalent; and crystalline compounds are more easily taken up than amorphous compounds. Sparingly soluble and insoluble compounds are more likely than soluble compounds to be retained at the site of exposure, and thus have more of an opportunity to be taken up by the cells. Organic chromium compounds containing a Cr-C covalent bond are treated as inorganic compounds because the Cr-C covalent bond is expected to be easily hydrolyzed in aqueous solution. Since the substance is a(an) inorganic or organic compound, and the oxidation state of chromium is hexavalent, and exposure to this soluble substance is expected to be by the oral route, the level of carcinogenicity concern is MODERATE. The final level of concern for this Cr-containing inorganic or organic compound, when the anticipated exposure is via the oral route, is MODERATE.

4. Subchronic and Chronic Toxicity

90 Days Rat and Mouse Study – (NTP 2007b Study 1)

In a 90-day subchronic study by the National Toxicology Program (2007b), sodium dichromate dihydrate (>99.7% a.i., Lot no. 062001) was administered to 10 F344/N rats/sex/dose and 10 B6C3F1 mice/sex/dose (core study animals) via drinking water at dose levels of 0, 62.5, 125, 250, 500, or 1,000 mg sodium dichromate dihydrate/L for 3 months (14 weeks) (equivalent to average daily doses of approximately 0, 5, 10, 17, 32, or 60 mg sodium dichromate dihydrate/kg body weight for rats and 0, 9, 15, 26, 45, or 80 mg/kg for mice and on a molecular basis,

equivalent to approximately 0, 1.7, 3.5, 5.9, 11.2, and 20.9 mg hexavalent chromium/kg body weight per day for rats and 0, 3.1, 5.2, 9.1, 15.7, and 27.9 mg/kg per day for mice). In addition, groups of 10 rats/sex (clinical pathology rats) were exposed to the same concentrations of sodium dichromate dihydrate for 4 weeks for clinical pathology studies.

In the core study animals, mean body weight gains of the 1,000 mg/L F 344/N rats at the end of the study were significantly lower than those of the controls for males and females (89% and 94%, respectively, of the control. Additionally, the mean body weight gain for the 500 mg/L male rats was significantly different from the control group (95% of the control). Final mean body weights and overall body weight gain of the male and female B6C3F1 mice exposed to 125 mg/L of sodium dichromate dihydrate and higher were significantly less than those of the control animals, as well as the overall body weight gain in the 62.5 mg/L male mice.

Water consumption by both male and female rats exposed to at least 250 mg/L and mice exposed to 125 mg/L or higher sodium dichromate dihydrate was generally less than that of the controls. Decreases in urine volume and increases in urine specific gravity in the clinical pathology rats were also observed and attributed to the reduced water consumption.

Signs of microcytic hypochromic anemia were observed at all dose levels and represented by lower automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts. These results were considered to be treatment-related in both rats and mice, with lower severity in mice. Additionally, increased neutrophil lymphocyte, leukocyte, and monocyte counts, mostly observed at the higher dose levels, were attributed to inflammatory response related to the inflammatory lesions observed during the histopathological examination (e.g., gastric lesions). For the clinical chemistry analyses, serum cholesterol and triglyceride concentrations were decreased and considered to be related to muscle injury. Increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations may have resulted from altered hepatic function. However, the only liver lesions reported in rats were chronic focal inflammation in females, and this lesion was also observed in the controls.

Only nonneoplastic lesions were found in the animals, with the incidences of histiocytic cellular infiltration generally significantly increased in the duodenum of rats and mice, the liver of female rats, and the mesenteric lymph node of mice exposed to levels about 125 mg/L. In male and female rats exposed to 1,000 mg/L of sodium dichromate dihydrate, there was increased focal ulceration, regenerative epithelial hyperplasia, and squamous epithelia metaplasia in the glandular stomach. Incidences of epithelia hyperplasia was also significantly increased in the duodenum of all exposed groups of mice.

Based on the findings, treatment-related effects were observed in both rats and mice at 62.5 mg/L (equivalent to an average daily dose of approximately 5 mg sodium dichromate dihydrate/kg body weight for rats and 9 mg/kg for mice and on a molecular basis, equivalent to approximately 1.7 mg hexavalent chromium/kg body weight per day for rats and 3.1 mg/kg per day for mice). Treatment-related effects at this dose included the following:

Treatment-related effects at 62.5 mg/L				
	F334/N Rats Male	F334/N Rats Female	B6C3F$_1$ Mice Male	B6C3F$_1$ Mice Female
Decrease in body weight and body weight gain			X	
Decrease in mean cell volume	X		X	
Decrease in mean cell hemoglobin	X	X	X	X
Decrease in erythrocytes	X	X		
Increase in alanine aminotransferase and sorbitol dehydrogenase (rats only)	X	X		
Increased incidence of epithelium hyperplasia in the duodenum, small intestine			X	X

Based on these results, the LOAEL is 5 mg (LDT) sodium dichromate dihydrate/kg body weight for F334/N rats and 9 mg/kg (LDT) for B6C3F$_1$ mice based on the effects noted above. A NOAEL could not be determined due to toxicological effects noted at the lowest dose tested.

90 Days Mouse Study – (NTP 2007b Study 2)

In 90 day subchronic mice study, sodium dichromate dihydrate (>99%; lot 13822LI) was administered to 10 B6C3F$_1$ mice/dose, 10 BALB/c mice/dose, and 5 *am3*-C57BL/6 mice in water at dose levels of 0, 62.5, 125, or 250 mg/L (approximately equivalent to 0, 8, 15, and 26 mg/kg/day, respectively, for B6C3F$_1$ mice; 0, 9, 14, and 24 mg/kg/day, respectively for BALB/c mice; and 0, 8, 15, and 25 mg/kg/day, respectively for *am3*-C57BL/6 mice) for 3 months. Only male mice were used in this study.

This study was conducted in order to confirm and expand upon findings reported in an NTP reproductive toxicity study in which BALB/c mice showed an adverse effect on the liver (increased hepatocyte vacuolization) when administered sodium dichromate dihydrate. Consequently, the effect of sodium dichromate dihydrate was examined in three strains of mice: B6C3F$_1$, BALB/c, and *am3*-C57BL/6 mice. *Am3*-C57BL/6 mice were selected because they are thought to be relatively insensitive to many hepatoxicants. Results from the study indicated that there were little differences between the three strains. All strains showed the following treatment-related effects: decreased body weight and body weight gains; decreased water consumption; increased erythrocytic microcytosis; increased incidence of histiocytic infiltration of the small intestines; and increased incidence of pancreatic secretory depletion. An increased incidence of glycogen depletion in the liver was observed in B6C3F$_1$ and *am3*-C57BL/6 mice but not in the BALB/c mice and is attributed to decreased food consumption. BALB/c and *am3*-C57BL/6 mice displayed increased serum alanine aminotransferase levels. Based on these results, this study did not confirm the hepatotoxic effects (with the exception of the minor alanine aminotransferase response) earlier observed in BALB/c mice.

Based on the findings, treatment-related effects were observed at 62.5 mg/L (or 8 mg/kg/day for $B6C3F_1$ and *am3*-C57BL/6 mice and 9 mg/kg/day for BALB/c mice) for all strains. Treatment-related effects at this dose included the following:

Treatment-related Effects at 62.5 mg/L			
	$B6C3F_1$	**BALB/c**	***am3*-C57BL/6**
Decreased body weight and body weight gain			X
Decreased mean cell volume (RBC)	X	X	
Decreased mean cell hemoglobin (RBC)	X	X	X
Increased incidence of histiocytic infiltration of the small intestines	X	X	
Increased incidence of mucous cells in epithelium	X		X
Increased incidence of glycogen depletion in the liver			X
Increased incidence of secretory depletion in the pancreas			X

Consequently, the LOAEL is 8 mg/kg/day for $B6C3F_1$ and *am3*-C57BL/6 mice and 9 mg/kg/day for BALB/c mice based on the effects noted above. A NOAEL could not be determined due to toxicological effects noted at the lowest dose tested.

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on the toxicological effects observed at the low dose.

5. Human Epidemiological Studies

The carcinogenic activity of chromium has been known since the late 19th century when the first cases of nasal tumors were reported in Scottish chrome pigment workers (Costa and Klein 2006). Sedman et al. (2006) concluded from their review of several occupational studies that human exposure to Cr(VI) by inhalation has been linked to increased rates of cancer in several occupational studies. A number of retrospective analyses have associated significant increases in respiratory cancer to Cr(VI) worker exposure in the chromate and chromate pigment production industry. The Gibb et al. (2000) investigation of 2,357 chrome production workers is considered to be the most comprehensive and firmly established Cr(VI) as a human lung carcinogen (Costa and Klein 2006).

While several studies of human ingestion of chromium exist in the open literature, these investigations do not provide strong causal support for an association between Cr(VI) and cancer. However, one study was found in which oral ingestion has been implicate as an exposure route associated with Cr(VI)-induced cancer. In the study of Zhang and Li (1986), 155 subjects were exposed to $\approx$ 20 mg/L Cr(VI) through drinking water in the Liaoning Province of northeastern China. The source of contamination was a chromium ore smelting facility located in a rural area outside of Jinzhou; Cr(VI) was detected in 28% of the area wells in 1965. Contamination levels in 55% of these wells were >20 mg/L Cr(VI). Higher per capita rates of cancers,

including lung and stomach cancers were found. In a retrospective analysis of the Zhang and Li study, Beaumont et al. (2008) confirmed that there was a substantial association between stomach cancer and mortality and Cr(VI) contaminated drinking water compared to a nearby uncontaminated area.

6. Mutagenic Mode of Action

In response to the 2005 revised U.S Environmental Protection Agency (EPA) Cancer Guidelines, a strategy is in place to combine genetic toxicology data with other information to determine whether a carcinogen operates through a mutagenic mode of action (MOA). This information is necessary for EPA to decide whether age-dependent adjustment factors (ADAFs) should be applied to the cancer risk assessment. A decision tree has been developed as part of this approach and outlines the critical steps for analyzing a compound for carcinogenicity through a mutagenic MOA (*e.g.,* data analysis, determination of mutagenicity in animals and in humans). Agents showing mutagenicity in animals and/or humans proceed through the Agency's framework analysis for MOAs. Chromium (VI) is carcinogenic in animals and humans via both the inhalation and oral routes. Chromium VI induced oral cavity tumors in male and female rats and tumors of the small intestine in male and female mice. Cr(VI) is also mutagenic, producing consistent positive results for mutagenic activity in numerous *in vitro* assays, in animals (mice and rats) and in humans (lipid peroxidation in blood, micronuclei induction in buccal cells) occupationally exposed to Cr(VI). Accordingly, Cr(VI) was processed through the framework analysis and key steps leading to tumor formation were identified and include: interaction of cellular components (DNA) with Cr(VI), mutagenesis, hyperplasia and tumor formation. Within the timeframe and tumorigenic dose range for early events, genetic changes in mice (single/double-stranded DNA breaks, Comet assay at 0.59 to 9.5 mg/kg) can commence within 24 hours of treatment. Supporting evidence is also found for cell proliferation, indicating that mutagenicity, associated with oxidative damage, DNA adduct formation and cytotoxicity, leads to a proliferative response, which occurs early (90 days) in the process of tumor induction. Overall, the weight of evidence evaluation supports Cr(VI) acting through a mutagenic MOA. In addition, no data were found that an alternative MOA might be operative. Therefore, the Cancer Guidelines recommend a linear extrapolation for the oral exposure risk assessment. Data also exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus, it is recommended that the ADAFs be applied. Details will be provided in the MOA document currently in preparation.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

Rat

Oral Mucosa and Tongue Tumors:

- *Male rats:*

The incidences of oral mucosa and tongue tumors for average daily doses of 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 0.21, 0.77, 2.10, or 5.95 mg Cr(VI)/kg body weight/day, respectively) were as follows:

Squamous Cell Papilloma or Squamous Cell Carcinoma:

0/50 (0%), 1/50 (2%), 0/49 (0%), 0/50 (0%), 7/49 (12%)

Male rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 516 mg/L dose group with the controls, for combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, both at $p<0.01$. When compared to historical control data (1/300 (0.3%), with a range of 0-2% for drinking water), the incidence of squamous cell papillomas or carcinomas in the high dose (12%) exceeded the historical control group range (0–2%). **Therefore, the CARC considered the oral mucosa and tongue tumors seen in males at the high dose to be treatment-related. In addition, these tumors are considered to be rare.**

- *Female rats*:

The incidences of combined oral mucosa and tongue tumors for average daily doses of 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (equivalent to 0, 0.26, 0.95, 2.45 or 7 mg Cr(VI) /kg body weight for females) were as follows:

Squamous Cell Papilloma and Squamous Cell Carcinoma:

1/50 (2%), 1/50 (2%), 0/50 (0%), 2/50 (4%), 11/50 (22%)

Female rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 516 mg/L dose group with the controls, for combined oral mucosa and tongue squamous cell combined papillomas and carcinomas, at $p<0.01$. In the 172 mg/L dose group, the incidence of 2/50 (4%), while not statistically significant by a pair-wise comparison, was considered to be biologically significant. When compared to historical control data (3/250 (1.2%) for drinking water), the incidence of oral or tongue squamous cell papillomas or

squamous cell carcinomas in the two high dose groups (4% and 22%) exceeded the historical control group range (0 – 2%). **Therefore, the CARC considered the oral mucosa and tongue tumors seen at both the 172 and 516 mg/L dose groups to be treatment-related. In addition, these tumors are considered to be rare.**

• *Adequacy of Dosing*: The CARC considered dosing at the top dose of 516 mg/L sodium dichromate dihydrate to be adequate, but not excessive, in both sexes for the assessment of carcinogenicity of Cr(VI) in rats. This was based on non-neoplastic liver lesions (including histiocytic cellular infiltration, chronic inflammation, fatty change (females)) and histiocytic infiltration in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females. In addition, there was decreased body weight seen in high dose males (6-9%) and females (4-10%) compared to the controls throughout the study and by the end of the study were 88% and 89% that of the respective controls. According to the NTP report, the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 172 and 516 mg/L rats was less than that by the controls throughout the study.

Mouse

Tumors of the Small Intestine (Duodenum, Jejunum, or Ileum)

- *Male mice:*

The incidences of small intestine tumors (duodenum, jejunum, or ileum) for the control, 14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate groups (0, 0.45, 0.9, 2.4, or 5.7 mg Cr(VI) /kg body weight /day, respectively), were as follows:

Adenoma:	1/50 (2%),	1/50 (2%),	1/50 (2%),	5/50 (10%),	17/50 (34%)
Carcinoma:	0/50 (0%),	2/50 (4%),	1/50 (2%),	3/50 (6%),	5/50 (10%)
Combined:	1/50 (2%),	3/50 (6%),	2/50 (4%),	7/50 (14%),	20/50 (40%)

Male mice had a statistically significant trend, and statistically significant pair-wise comparisons of the 257.4 mg/L dose group with the controls, for combined small intestine, duodenum, jejunum and ileum adenomas, and combined adenomas and carcinomas, all at $p < 0.01$. There was also a statistically significant trend, and a statistically significant pair-wise comparison of the 257.4 mg/L dose group with the controls, for combined small intestine, duodenum, jejunum and ileum carcinomas, both at $p < 0.05$. There was a statistically significant pair-wise comparison of the 85.7 mg/L dose group with the controls for combined small intestine, duodenum, jejunum and ileum combined adenomas and carcinomas, at $p < 0.05$. At the top two doses, the incidences of all tumor types (adenomas (34%), carcinomas (10%), and combined (40%)) exceeded the historical controls ranges (0-6% for adenoma, 0-4% for carcinoma, and 0-10% for adenoma or carcinoma combined). **Therefore, the CARC concluded that the small intestine tumors seen in male mice at both the 85.7 and 257.4 m/L dose groups were**

treatment-related. These are considered to be rare tumors. This decision was supported by the presence of nonneoplastic hyperplasia in the small intestine in both the chronic and subchronic mouse studies.

- *Female mice*:

The incidences of small intestine tumors (Duodenum, Jejunum, and Ileum) for the control, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dehydrate (0, 0.3, 1.2, 3.2 or 8.8 mg Cr(VI) /kg body weight /day) groups respectively, were as follows:

Adenoma:	0/50 (0%),	1/50 (2%),	2/50 (4%),	15/50 (30%),	16/50 (32%)
Carcinoma:	1/50 (2%),	0/50 (0%),	2/50 (4%),	3/50 (6%),	7/50 (14%)
Combined:	1/50 (2%),	1/50 (2%),	4/50 (8%),	17/50 (34%),	22/50 (44%)

Female mice had significant increasing trends for adenomas, carcinomas and combined, all at $p<0.01$. There were also significant differences in the pair-wise comparisons of the 172 and 516 mg/L sodium dichromate dehydrate dose groups with the controls for adenoma and combined adenomas or carcinomas, both at $p<0.01$. In addition, there was a significant difference in the pair-wise comparison of the high dose group with the controls for carcinomas, at $p<0.05$. In the 57.3 mg/L dose group, the incidences of adenomas (4%), carcinomas (4%) and combined (8%), while not statistically significant, were considered to be biologically significant. The tumor responses at the top three doses exceeded the spontaneous tumor incidence rates of historical control ranges (0-2% for adenoma, 0-2% for carcinoma, and 0-4% for adenoma/carcinoma combined). **Therefore, the CARC concluded that the increased incidence of small intestine tumors at the top three doses in female mice were treatment related. These are considered to be rare tumors. This decision was supported by the presence of non-neoplastic hyperplasia in the small intestine in both the chronic and subchronic mouse studies.**

• *Adequacy of Dosing*: Dosing at the high dose (257.4/516 mg/L, males/females) was considered adequate, but not excessive in male and female mice. This was based on the presence of diffuse epithelial hyperplasia and cellular histiocytic infiltration in the duodenum and jejunum of male and/or female mice. Histiocytic cellular infiltration was also seen in the liver, and mesenteric and pancreatic lymph nodes. In addition, mean body weights of 257.4 mg/L males were less than controls for the first 4 months of the study, but by the end of the study, the mean body weight of 257.4 mg/L males was only slightly less than that of the control group. Mean body weights of 172 and 516 mg/L females were less than those of the controls for the first 8 months of the study. By the end of the study, the mean body weight of 172 mg/L females was 8% less than that of the controls, and the mean body weight of 516 mg/L females was 15% less than that of the control group. The NTP report stated that the lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 85.7 and 257.4 mg/L males and 172 and 516 mg/L females was less than that by the controls throughout the study.

2. Structure-Activity Relationship

According to the Oncologic Cancer Expert System report, in general, virtually all Cr-containing compounds are of some carcinogenicity concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route. The carcinogenic potential of inorganic chromium compounds is affected by their oxidation state, crystallinity, and solubility, which affect the extent of compound uptake by cells. Hexavalent compounds are more easily taken up by cells than trivalent; and crystalline compounds are more easily taken up than amorphous compounds. Sparingly soluble and insoluble compounds are more likely than soluble compounds to be retained at the site of exposure, and thus have more of an opportunity to be taken up by the cells. Organic chromium compounds containing a Cr-C covalent bond are treated as inorganic compounds because the Cr-C covalent bond is expected to be easily hydrolyzed in aqueous solution. Since the substance is a(an) inorganic or organic compound, and the oxidation state of chromium is hexavalent, and exposure to this soluble substance is expected to be by the oral route, the level of carcinogenicity concern is MODERATE. The final level of concern for this Cr-containing inorganic or organic compound, when the anticipated exposure is via the oral route, is MODERATE.

3. Mutagenicity

There is clear evidence that Cr(VI) is a mutagen, including positive results from *in vitro* mutagenicity studies and from *in vivo* animal studies, as well as data showing lipid peroxidation in blood and micronuclei induction in the buccal epithelial cells of humans. For this reason, a mutagenic mode of action (MOA) analysis is under way. It is briefly described below and will be the subject of a later document.

4. Mutagenic Mode of Action

In response to the 2005 revised U.S Environmental Protection Agency (EPA) Cancer Guidelines, a strategy is in place to combine genetic toxicology data with other information to determine whether a carcinogen operates through a mutagenic mode of action (MOA) (USEPA, 2005a,b). This information is necessary for EPA to decide whether age-dependent adjustment factors (ADAFs) should be applied to the cancer risk assessment. A decision tree has been developed as part of this approach and outlines the critical steps for analyzing a compound for carcinogenicity through a mutagenic MOA (*e.g.,* data analysis, determination of mutagenicity in animals and in humans). Agents showing mutagenicity in animals and/or humans proceed through the Agency's framework analysis for MOAs. Chromium (VI) is carcinogenic in animals and humans via both the inhalation and oral routes. Following oral exposure, Cr(VI) induced oral cavity tumors in male and female rats and tumors of the small intestine in male and female mice. Cr(VI) is also mutagenic, producing consistent positive results for mutagenic activity in numerous *in vitro* assays, in animals (mice and rats) and in humans (lipid peroxidation in blood, micronuclei induction in buccal cells) occupationally exposed to Cr(VI). Accordingly,

Cr(VI) was processed through the framework analysis and key steps leading to tumor formation were identified and include: interaction of cellular components (DNA) with Cr(VI), mutagenesis, hyperplasia and tumor formation. Within the timeframe and tumorigenic dose range for early events, genetic changes in mice (single/double-stranded DNA breaks, Comet assay at 0.59 to 9.5 mg/kg) can commence within 24 hours of treatment. Supporting evidence is also found for cell proliferation, indicating that mutagenicity, associated with oxidative damage, DNA adduct formation and cytotoxicity, leads to a proliferative response, which occurs early (90 days) in the process of tumor induction. Overall, the weight of evidence evaluation supports Cr(VI) acting through a mutagenic MOA. In addition, no data were found that an alternative MOA might be operative. Therefore, the Cancer Guidelines recommend a linear extrapolation for the oral exposure risk assessment. Data also exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus, it is recommended that the ADAFs be applied. Details will be provided in the MOA document currently in preparation.

5. Human Epidemiological Studies

The carcinogenic activity of chromium has been known since the late 19th century when the first cases of nasal tumors were reported in Scottish chrome pigment workers (Costa and Klein 2006). Sedman et al. (2006) concluded from their review of several occupational studies that human exposure to Cr(VI) by inhalation has been linked to increased rates of cancer in several occupational studies. A number of retrospective analyses have associated significant increases in respiratory cancer to Cr(VI) worker exposure in the chromate and chromate pigment production industry. The Gibb et al. (2000) investigation of 2,357 chrome production workers is considered to be the most comprehensive and firmly established Cr(VI) as a human lung carcinogen (Costa and Klein 2006).

While several studies of human ingestion of chromium exist in the open literature, these investigations do not provide strong causal support for an association between Cr(VI) and cancer. However, one study was found in which oral ingestion has been implicate as an exposure route associated with Cr(VI)-induced cancer. In the study of Zhang and Li (1986), 155 subjects were exposed to $\approx$ 20 mg/L Cr(VI) through drinking water in the Liaoning Province of northeastern China. The source of contamination was a chromium ore smelting facility located in a rural area outside of Jinzhou; Cr(VI) was detected in 28% of the area wells in 1965. Contamination levels in 55% of these wells were > 20 mg/L Cr(VI). Higher per capita rates of cancers, including lung and stomach cancers were found. In a retrospective analysis of the Zhang and Li study, Beaumont et al. (2008) confirmed that there was a substantial association between stomach cancer and mortality and Cr(VI) contaminated drinking water compared to a nearby uncontaminated area.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified hexavalent chromium, Cr(VI), as **"Likely to be Carcinogenic to Humans"** based on the presence of oral mucosa and tongue tumors in male and female rats and tumors of the small intestine in male and female mice at doses that were adequate, but not excessive, to assess carcinogenicity. There is clear evidence that Cr(VI) is mutagenic and convincing evidence supporting a mutagenic mode of action. The decision is also qualitatively supported by human epidemiological data which indicates an association between exposure and increased stomach tumor incidence.

VII QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended using a linear low-dose extrapolation approach (Q_1*) for estimating the human cancer risk based on the most potent tumor type. Data also exist showing that Cr(VI) induces mutagenicity in germinal cells and passes through the placental barrier causing DNA deletions and teratogenicity in developing embryos. Additionally, there is concern that older children are at risk because of the ability of Cr(VI) to penetrate cellular membranes and interact with intracellular mechanism leading to mutations; thus, it is recommended that the ADAFs be applied.

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