SUPPORT FOR SELECTION OF A CLEANUP LEVEL FOR METHAMPHETAMINE AT CLANDESTINE DRUG LABORATORIES

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of Public Health
and Environment

February 2005

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Acknowledgements

The Colorado Department of Public Health and Environment wishes to thank, in particular: Dr Susan Griffin (US EPA Region 8) for her assistance in developing the technical approach utilized in this report, Deputy Caoimhín P. Connell (Park County Sheriff's Office and Consulting Forensic Industrial Hygienist for Forensic Applications, Inc.) for his input on multiple review drafts; and the many stakeholders and reviewers who provided constructive and insightful comments to early drafts of this document. This document would not have been possible without their invaluable advice and assistance.

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1.0 Introduction

Methamphetamine (referred to as "meth") is a powerful, highly toxic, addictive drug that is illegally "cooked" in makeshift labs. Meth can be found in the form of pills, capsules, powder or chunks. It can be smoked, snorted, injected or eaten. Meth is also called crank, speed, crystal or ice. Meth laboratories have been a growing problem throughout Colorado and across the United States. In Colorado alone, the number of meth lab seizures reported by the Colorado Bureau of Investigation has increased dramatically over the past several years: 150 in 1999, 264 in 2000, 452 in 2001, and the number exceeded 700 in 2002 (CDPHE 2003).

In accordance with House Bill 04-1182, the Colorado Department of Public Health and Environment (CDPHE) is developing regulations for the cleanup of properties used as meth labs. One goal is to develop re-occupation standards that will protect the occupants (mainly children) from residual chemicals left from the production of illicit drugs.

Methamphetamine production is associated with the release of numerous chemicals, such as volatile organic compounds (VOCs), acids, bases, metals and chemical salts, in addition to methamphetamine itself. Specific chemical residues may vary depending on the cooking process that is utilized. Airborne contaminants are absorbed or deposited onto surfaces such as rugs, furniture, drapes, and walls and may also enter and contaminate heating, ventilation, and air conditioning (HVAC) systems. Chemical spills are not uncommon and may also impact residential surfaces. Presence of these chemicals may pose a health-risk to residents who reoccupy these structures after seizure (CDPHE 2003).

In order to determine acceptable risk-based concentrations for meth lab related chemicals, CDPHE has previously reviewed human exposure reference values for chemicals commonly associated with meth production (CDPHE 2003). Many of these chemicals are well studied and have established concentrations that are thought to be protective under a residential exposure scenario. However, to date, no health-based value for methamphetamine has been developed.

Several states have established cleanup standards specifically for the residue of methamphetamine. After communicating with some of these state health departments, it was learned that these levels are not health-based, but are rather based on analytical detection limits. Health-based values could not be established due to deficiencies in the toxicity database. These current meth cleanup levels are instead based on what is believed to be conservative and protective, while at the same time achievable by clean-up contractors.

Although numerous states have adopted these detection based cleanup standards for methamphetamine, none have tried to correlate these levels to known health-effect-based concentrations. This paper attempts to reconcile what is known about methamphetamine health effects with those levels currently being used as cleanup standards in order to support selection of a Colorado standard for methamphetamine cleanup. Analytical methods are constantly being refined and detection limits lowered. Simply setting a cleanup standard based on the current detection limit does not provide information on potential health effects. The information summarized in this document will provide Colorado with a balanced approach for weighing these lower detection limits against practicability and cost considerations.

In addition to this introduction, this report is organized into the following sections:

Section 2 This section provides a brief overview of the toxicity of methamphetamine.

Section 3 This section reviews the current methamphetamine cleanup standards established by various States.

Section 4 This section discusses how humans may be exposed to residual methamphetamine and provides equations for quantifying the level of exposure anticipated via oral ingestion and dermal absorption at concentrations equivalent to the cleanup standards discussed in Section 3.

Section 5 This section correlates the estimated exposure doses calculated in Section 4 with known health effects of methamphetamine. The toxicity literature for methamphetamine was reviewed in order to derive interim reference dose (RfD) values to provide a foundation for evaluating the health protectiveness of the proposed technology cleanup standards. Additionally, knowledge of therapeutic and illicit methamphetamine use was incorporated into this section.

Section 6 This section reviews the sources of uncertainty in the exposure estimates for humans.

Section 7 This section summarizes the findings of this document.

Section 8 This section provides full citations for guidance documents and scientific publications referenced in the report.

2.0 General Human Toxicity of Methamphetamine

The toxicity of methamphetamine is covered here in brief to provide a general background to the reader. Overall, the potential health effects of methamphetamine depend on several factors, including:

- how much methamphetamine a person is exposed to,
- how long a person is exposed, and
- the health condition of the person being exposed.

The primary effect of methamphetamine is as a stimulant to the central nervous system. Exposure to even small amounts of methamphetamine can produce euphoria, increased alertness, paranoia, decreased appetite and increased physical activity. Other central nervous system effects include writhing, jerky, or flailing body movements, irritability, insomnia, confusion, tremors, anxiety, aggression, hyperthermia, and convulsions. Death may sometimes result from hyperthermia (a condition where the body temperature increases) and convulsions (NIDA 2002).

Methamphetamine exposure causes cardiovascular effects including chest pain and hypertension and sometimes can result in cardiovascular collapse and death. Additionally, methamphetamine

increases heart rate, blood pressure and risk of stroke, and may cause irreversible damage to blood vessels in the brain (NIDA 2002).

The psychological symptoms observed with prolonged methamphetamine abuse can resemble those of schizophrenia and are characterized by paranoia, hallucinations, repetitive behavior patterns, and delusions of parasites or insects on the skin. Methamphetamine-induced paranoia can result in homicidal or suicidal thoughts, with drug abusers often exhibiting violent tendencies (NIDA 2002).

There are a few accepted medicinal usages of methamphetamine, such as the treatment of narcolepsy, attention deficit disorder, and for short-term use for obesity; but these therapeutic uses are limited. The trade name of the drug currently used is DESOXYN (methamphetamine hydrochloride tablets, USP). There are no clinical reasons for prescribing methamphetamine to infants or children less than 6 years of age (Abbott, 1995).

The majority of our knowledge of methamphetamine toxicity in humans is derived from drug abuse and overdose scenarios. Low-level, chronic exposures to methamphetamine have not been well studied. However, information from high dose studies and clinical case reports allows us to better understand the mechanisms by which methamphetamine may exert its toxicity. The target population of concern in establishing a cleanup standard is residents who may reoccupy the structure after seizure. Health impacts on infants and young children raised in areas that were formerly used as clandestine labs, are of particular concern. Children are often more susceptible to hazards due to their physiologic status (rapid growth, incomplete development, and rapid metabolism requiring more air and water per body weight than adults) and behaviors (crawling, hand to mouth activity, gnawing on furniture, window sills, toys). However, specific risks to infants and children associated with chronic low-level exposure to methamphetamine encountered by infants or children in a former drug lab site have not been studied.

In parallel with increasing trends in methamphetamine usage, the incidence of infants born with evidence of illicit drug exposure has been increasing. Methamphetamine has been described as readily crossing the placenta, therefore resulting in intrauterine exposure (Williams et al., 2003). Studies on methamphetamine use during pregnancy illustrate an increased incidence of intrauterine growth retardation, prematurity, and perinatal complications (Oro and Dixon, 1987). The use of amphetamines in the first trimester of pregnancy has been associated with an increased risk of malformations, including heart defects, cleft palate, exencephaly, microcephaly, mental retardation, and biliary atresia (Plessinger, 1998). In infants exposed gestationally, body weight, length, and head circumference changes have been documented. At birth, methamphetamine withdrawal symptoms may include abnormal sleep patterns, tremors, hypertonicity, a high-pitched cry, poor feeding patterns, sneezing, frantic sucking, and tachypnea (Acuff-Smith et al., 1992). During the first year, the infant may exhibit signs of lethargy, poor feeding, poor alertness, and severe lassitude (HSDB, 2004). In some cases, methamphetamine use during pregnancy has resulted in death to the developing fetus. Methamphetamine is also readily excreted in breast milk and nursing infants may be exposed as a result of maternal environmental exposure.

3.0 Current Methamphetamine Cleanup Standards

The methamphetamine cooking process can release as much as 5,500 micrograms of methamphetamine per cubic meter into the air, and deposit as much as 16,000 micrograms per

100 square centimeters onto surfaces (Martyny et al., 2003). There are concerns that residual methamphetamine generated during the manufacturing process may indeed pose a threat to human health, and render the property 'Unsafe for Human Use' until decontamination has occurred.

Based on the fact that no formal health-based cleanup standards have been derived for methamphetamine, CDPHE concurs with the conclusion that use of an alternative standard is necessary. In support of this conclusion, a request to the Superfund Technical Support Center for assistance in deriving a health-based toxicity value resulted in a response confirming that data were insufficient for such an undertaking.

A very small percentage of states within the U.S. have adopted methamphetamine cleanup standards for reoccupation. The initial efforts in establishing surface contamination standards were conducted by the State of Washington, where the state imposed a cleanup level of 5 ug/ft^2 (0.5 ug/100 cm^2) in buildings known to have been used to manufacture methamphetamine. This standard was not based on the toxicity of methamphetamine, but rather on the belief that this concentration was an achievable standard of cleanliness (Martyny et al., 2004). Due to lower detection limits, the State of Washington recently lowered its acceptable level of surface contamination to 0.1 ug/100 cm^2. Again, health information was not utilized to set this standard. Rather the thinking was that in the face of an unknown risk to crawling infants, known contaminants should be reduced to the lowest practical levels using current available methods and processes (Martyny et al., 2004).

Many states have followed Washington's lead in establishing methamphetamine standards. Current cleanup standards by state are summarized below.

Alaska
Based on preliminary research and the fact that no health-based standards exist for methamphetamine, the Alaska Department of Environmental Conservation recommends adopting a 'fit for use' cleanup standard of 0.1 ug/100cm^2. (Personal communication with Leslie Pearson – Alaska Division of Spill Prevention and Response)

Arizona
All remediated areas and materials shall meet a post-remediation clearance level of 0.1 ug/100cm^2 for methamphetamine. http://www.btr.state.az.us/

Arkansas
The Arkansas Department of Health recommends use of 0.5 µg /ft^2 as the acceptable methamphetamine post cleanup re-occupancy level.
http://www.healthyarkansas.com/pdf/adh_methguidelines_2004.pdf

Minnesota
Minnesota has established a provisional cleanup level of <1 ug/ft^2 for methamphetamine based on best judgment and current practices.
http://www.health.state.mn.us/divs/eh/meth/lab/cleanup0903.pdf

Oregon

Oregon has established a programmatic methamphetamine cleanup concentration of 0.5 ug/ft^2. (personal communication with Brett Sherry – Oregon Clandestine Drug Lab Cleanup Program)

Tennessee

Tennessee rule 1200-1-19 establishes in its standard of cleanliness for sites used to manufacture methamphetamine that methamphetamine shall not exceed 0.1 micrograms /100 square centimeters.
http://www.state.tn.us/environment/dsf/meth/pdfs/Meth%20RAP%20Guidance%20published%208-20-04.pdf

Washington

Acknowledging that the standard is not a health-based standard but one that is based upon achievable and measurable results, the Washington Office of Environmental Health assessments recommended the current decontamination standard for methamphetamine at 0.1µg/100cm^2. Additionally, it is assumed that the cleanup processes necessary to reduce the levels of methamphetamine to 0.1µg/100cm^2 should be sufficient to reduce the concentrations of other methamphetamine manufacturing precursors to acceptable levels. Unfortunately, no study or evidence to support this assumption has been located.

Because the values presented above did not use consistent units of measurement, the values have been converted to units of ug/100 cm^2 and are summarized below.

State	Original Units	Cleanup Standard (ug/100 cm^2)
Alaska	0.1 ug/100 cm^2	0.1
Arizona	0.1 ug/100 cm^2	0.1
Arkansas	0.5 ug/ft^2	0.05
Minnesota	<1 ug/ft^2	<0.1
Oregon	0.5 ug/ft^2	0.05
Tennessee	0.1 ug/100 cm^2	0.1
Washington	0.1 ug/100 cm^2	0.1

As seen, the cleanup standards tend to be fairly consistent across states, with values ranging from 0.05 to 0.1 ug/100 cm^2. It is important to note that several local health departments within Colorado have established their own methamphetamine cleanup standards as follows: Tri-County Health Department and Denver County Health Department are using 0.5 ug/100cm^2.

4.0 Extrapolation of Cleanup Standards to Dose Levels

Although it may not be feasible presently to derive a health-based standard for methamphetamine that can be used to establish a cleanup concentration, it is possible to estimate what sort of dose might be anticipated from exposure to concentrations left in place at the technology-based levels that are in current use. The intent of the exposure calculations presented below is to estimate a high end or upper bound (reasonable maximum) exposure to the individuals of concern. These exposure estimates may then be compared to what is known about methamphetamine health effects, in order to provide further support for setting a reoccupancy standard for methamphetamine.

Although in theory, any person who is exposed to residual methamphetamine is of concern, there are several populations that are considered to be sensitive and have been selected for evaluation. Exposure estimates were made for three categories of individuals: infant (age 1), child (age 6), and adult female (childbearing age).

Infant: The infant was selected based on their distinct exposure patterns, which may result in them having the highest exposure levels to methamphetamine in a household. Infants may be more highly exposed to environmental toxicants through dermal and oral ingestion routes than are adults or older children. For example, young children often play and crawl on the floor and are more likely to wear less clothing than do adults. Infants who are not yet walking may employ various means of transportation such as crawling, rolling or scooting across floor surfaces. These behavioral distinctions are likely to result in noticeably higher dermal contact with residual methamphetamine on household surfaces. Additionally, because infants have an urge to place fingers and objects into their mouths while exploring their environment (mouthing), they have a higher potential for exposure to methamphetamine through ingestion of residues that have been transferred from treated surfaces to the hands or objects that are mouthed. An infant (age 1) was selected to represent this group, as they may not yet be walking (therefore having more floor surface contact), and there are more readily available exposure factors available for one-year olds than there are for children under one.

Child: Although the child may not have as much physical exposure to residual methamphetamine as does an infant, it was determined that exposure to a six-year old child should be evaluated. The rationale behind selection of this age was that the therapeutic usage of methamphetamine in the treatment of Attention Deficit Disorder is indicated beginning at age six. Therefore, the estimated exposure to this age child can be compared to levels used therapeutically. Additionally, the exposure factors for a six-year old child are relatively well defined and calculations can be performed with fewer uncertainties.

Adult Female: As discussed previously, exposure to methamphetamine has been correlated with adverse reproductive outcomes. Therefore, the adult female (childbearing age) was selected as a population of concern. Methamphetamine exposures predicted in the mother can be compared to doses associated with these outcomes to assess the likelihood of the developing fetus being adversely impacted.

There is no consistent, established national guidance for the estimation of risks from wipe samples. The most commonly used estimation method involves treating wipe samples as indicative of the contaminant source, estimating exposure parameters to determine dose, and using this information to estimate risk. The general guidelines used in this document were modeled using a document entitled “Wipe Sample Assessment” that was developed from the expertise of USEPA scientists throughout the country (specifically NCEA and Superfund Regional risk assessors) (USEPA 2003). These equations can be used to estimate exposure via oral ingestion and dermal absorption.

The approach used in this model attempts to evaluate exposure that is representative of a “daily” dose to methamphetamine. This model does not attempt to calculate a chronic exposure nor reduce anticipated exposure by assuming that the populations of concern may spend some

portion of the time outside of the household. Rather, the exposure value calculated in this assessment represents the dose that someone could be anticipated to receive based on a day spent in the home environment. The actual dose received may be higher or lower than that calculated.

All models are based on foundational assumptions. The assumptions used are, in turn, based on objective observations and other parameters generally considered reasonable by the scientific community and are typically found within peer-reviewed literature.

Several assumptions are incorporated into these equations. Based on the chemical properties of the contaminants of concern, it is assumed that volatilization of the chemical on the surface is negligible, and that the chemical is available on the surface for the entire exposure duration (that is, that a previous transfer of contaminant from surface to skin would not deplete the amount of surface contamination. It is assumed that there is an amount of chemical deposited on skin (known as the maximum "Ds"); that is, that there would be a limit on how much contaminant could be transferred to the skin in a single day. Therefore, this method tends to be conservatively biased with respect to oral and dermal exposure (USEPA, 2003).

4.1 Oral Exposure Equation

Daily oral exposure to a contaminant on a household surface can be estimated as follows:

$Do = (C \times SAh \times CFh \times FTSH \times FTHM \times ABSo)/BW$

Do =Oral dose (mg/kg/day)
C = Concentration of chemical on contaminated surface (mg/cm^2)
SAh =Exposed hand surface area (cm^2)
CFh =Contact frequency of hand against surface (times/day)
FTSH= Fraction transferred from surface to hand
FTHM= Fraction transferred from hand to mouth
ABSo= Oral absorption fraction
BW =Body weight (kilograms)

4.2 Dermal Exposure Equation

To estimate the daily dermal exposure to a contaminated household surface, the following equation can be used:

$Dd = (C \times SAs \times CFs \times FTSS \times ABSd)/BW$

Dd =Dermal dose (mg/kg/day)
C = Concentration of chemical on contaminated surface (mg/cm^2)
SAs =Exposed skin surface area (cm^2)
CFs =Contact frequency of skin against surface (times/day)
FTSS= Fraction transferred from surface to skin
ABSd= Dermal absorption fraction
BW =Body weight (kilograms)

4.3 Exposure Parameters

Although these equations are limited by the above-mentioned assumptions, they are basically sound in theory and generally accepted as reasonable by the scientific community (USEPA, 2003). The difficulty is in defining the specific inputs to the equations, since some of the input parameters have very little or no experimentally determined values in the literature; thus the need for reliance upon professional judgment.

This section contains the exposure parameters used in the dermal and oral exposure equations. Values are summarized in Attachment 1. Although efforts were made to locate measured values for these parameters, in many cases use of professional judgment was required. The rationale for selection of each value is provided below.

4.3.1 Shared Exposure Parameters

The following summarizes exposure parameters that are the same for both the oral and dermal exposure models. These parameters include, surface concentration and body weight.

- **Concentration of Chemical on Surface (C)**

Currently, there are two clean-up levels most commonly used by various states: 0.1 micrograms per 100 square centimeters (0.1 µg/100cm^2) and 0.5 micrograms per square foot (0.5 µg/ft^2). A concentration of 0.5 µg/ft^2 is approximately equal to 0.05 µg/100 cm^2.[1] Additionally, some local health departments within the state of Colorado have established cleanup standards of 0.5 ug/100 cm^2. In this model, the concentration of the chemical on a surface was set according to one of three scenarios: 0.5ug/100cm^2, 0.1ug/100cm^2, or 0.05 ug/100cm^2.

Note: 1 square foot = 929.0304 square centimeters

- **Body Weight (BW)**

Body weights have been fairly well defined in the experimental literature. USEPA's Exposure Factors handbook was consulted to identify appropriate body weights for use in these calculations:

Infant: A one-year-old child was assumed to have a body weight of 11.2 kg based on an average of the 50th percentile of males (11.7 kg) and females (10.7 kg) as listed in Tables 11-2 and 11-3 of the Child Specific Exposure Factors Handbook (EPA 2002a).

Child: A six-year-old child was assumed to have a body weight of 21.7 kg based on an average of the 50th percentile of males (22.0 kg) and females (21.3 kg) as listed in Tables 11-2 and 11-3 of the Child Specific Exposure Factors Handbook (EPA 2002a). [Note: The EPA recommended default of 15 kg for a child's body weight was not used as this may underestimate

[1] 0.1 µg/100cm2 equals 0.929 µg/ft2; and 0.5 µg/ft2 equals 0.0538 µg/100cm2

the body weight of a six year old, as it is intended to represent the weight for all children ranging up to age six.]

Adult Female: The EPA default value of 70 kg was used as the body weight for adult females.

4.3.2 Oral Exposure Parameters

The following summarizes exposure parameters that are specific to the oral exposure model.

- **Exposed Hand Surface Area (SAh)**

Ingestion of residual methamphetamine is considered to be a result of hand to mouth activities. Therefore, knowledge of the exposed hand surface area is key in evaluating exposure via this route. Because the palm-side of the hand is typically used for contacting surfaces, this area was considered to be the exposed area for this assessment. In order to estimate the area specific to the palm-side, the value for the total hand area was divided by a factor of two.

Infant: Assuming that hands comprise approximately 5.3% of the total body area (5110 cm^2), using a value of 270 cm^2 for total hand area (both hands), the exposed area (palm side) would be approximately 135 cm^2.

Child: The average total body surface area for a six-year-old child is 8,200 cm^2. This value was derived by averaging the data for both males and females for children ages 5-6 and ages 6-7 (USEPA 2002a).

Age (years)	Males	Females	Average
5<6	7930 cm^2	7790 cm^2	7860 cm^2
6<7	8660 cm^2	8430 cm^2	8550 cm^2
			8200 cm^2

Assuming that hands comprise approximately 4.7% of the total body area, a value of 385 cm^2 for total hand area (both hands) can be derived. Dividing this value by two, results in a value of 192.5 cm^2 for the exposed (palm-side) hand surface area.

Adult Female: Based on a value of 820 cm^2 for total hand area (Table 6-3, EPA 1997), the exposed hand surface area for the adult female is 410 cm^2.

- **Contact Frequency of Hand to Surface (CFh)**

According to a study summarized in the Child Specific Exposure Factors Handbook (USEPA, 2002a) children were observed to contact smooth surfaces an average of 83.7 times per hour and textured surfaces an average of 22.1 times per hour. On average, children ages 0 to 48 months are awake approximately 8.9

hours per day (USEPA, 2002a). This results in a potential for exposure to both smooth and textured surfaces to occur an average of 942 times daily.

However, it is not thought that each "contact" is equivalent to a loading event, whereby methamphetamine will be lodged onto the skin surface. Although specific data do not exist, it is highly unlikely that residual methamphetamine will be "loaded" onto hand surfaces 942 times a day. Therefore, rather than using an estimate of surface contact frequency, a loading frequency was developed for use in this parameter. The loading frequency was based on estimates developed by USEPA for soil ingestion rates. Using an estimate of soil adherence to a hand surface, calculations can be performed to estimate how many hand to mouth transfers would be necessary to result in an intake equivalent to an assumed soil ingestion rate.

Infant: The USEPA recommends 200 mg per day as reasonable maximum exposure estimate for soil (and dust) intakes for children aged 1-6. For the purposes of this modeling effort, it is assumed that all soil/dust exposure results from contact with indoor dust. The dermal guidance (USEPA 2004) recommends a soil adherence factor of 0.2 mg soil per cm^2 skin for children aged 1-6. [This is based on the 95^{th} percentile adherence factor in children playing both indoors and outdoors at a daycare center (USEPA 2004).] Assuming that an infant's hand surface area is 135 cm^2 then this would be 27 mg soil adhering to the hand when placed in the soil. If 10% of this soil on the hand was transferred to the mouth, then it would take approximately 74 hand to mouth transfers to reach 200 mg/day

Child: As for the infant, these assumptions can be used to estimate contact frequencies for a child. Assuming ingestion of 200 mg per day of soil, a soil adherence factor of 0.2 mg soil per cm^2 skin and a child's hand surface area of 192.5 cm^2 , this would result in 38.5 mg soil adhering to the hand when placed in the soil. If 10% of this soil on the hand was transferred to the mouth, then it would take approximately 52 hand to mouth transfers to reach 200 mg/day.

Adult: A similar approach can be used to estimate contact and transfer frequencies for an adult. EPA assumes a soil/dust ingestion rate of 100 mg per day for adults. Using a soil adherence factor 0.07 mg soil per cm^2 skin (USEPA 2004) and an adult's hand surface area of 410 cm^2, this would result in 29 mg soil adhering to the hand when placed in the soil. If 10% of this soil on the hand was transferred to the mouth, then it would take approximately 35 hand to mouth transfers to reach 100 mg/day

Therefore, the values used for contact frequency of hand to surface are 74, 52 and 35 events per day for the infant, child and adult female, respectively.

Fraction Transferred from Surface to Hands (FTSH)

This parameter is also difficult to estimate. Obviously, the worst-case assumption would be an FTSH of 1, or 100% transfer. However, for some chemicals, the range may be narrowed even beyond that. FTSH is assumed to be chemical-specific.

The following are excerpts from the Wipe Assessment Guidance, which discusses past derivation of transfer values:

> *'USEPA has previously assumed transfer of 0.5 for PCBs (USEPA, 1987) based on an Office of Toxic Substances (OTS) assessment. Michaud et al (1994) assumed 0.5 for PCBs and dioxins, but stated that 0.1 might be more realistic. In developing re-entry guidelines for an office building after a fire, a panel of assessors used ranges of 0.1, 0.25, and 0.5 of the arm surface area for PCBs and dioxins (New York State Dept. of Health, 1985). However, that actually assumed 100% transfer over a smaller surface area (that is, these percentages were technically used to adjust the exposed skin surface area rather than attempting to estimate a transfer rate).*
>
> *In a study of malathion uptake from different surfaces, USEPA-EMSL found that FTSS of malathion from painted sheetrock to human hands was only 0.0003. (Mean transfer from vinyl flooring to hands was 0.0018, and from carpet to hands was 0.0152.) Malathion is a pesticide assumed to have lipophilicity more similar to PCBs than to volatiles or metals. However, the representativeness of such a number for PCBs and dioxins is unknown. PCBs are more lipophilic (have higher Kows) than malathion.'*

For the purposes of this assessment, it was determined that a transfer factor of 0.5 to hands would be acceptable.

Fraction Transferred from Hands to Mouth (FTHM)

This factor represents the total fraction of material that is removed from the skin via ingestion. Ingestion typically occurs via hand to mouth activities. Mouthing behavior includes all activities in which objects, including fingers, are touched by the mouth or put into the mouth except for eating and drinking. Mouthing is the process whereby contaminants from surfaces may be ingested. According to USEPA (2002a), children's contact with surfaces is intermittent and non-uniform over different parts of the body and the nature of the mouthing itself is intermittent and non-uniform, making this pathway difficult to model. Additionally, little is known about mouthing tendencies in adults.

For the purposes of this assessment, it was assumed that 10% of the total amount of methamphetamine transferred to the exposed hand surface would be ingested. This assumption applies to infants, children and adult females, and reflects the assumptions used above to identify contact frequency rates.

Oral Absorption Fraction (ABSO)

Therapeutic information for methamphetamine indicates that this drug is rapidly absorbed from the gastrointestinal tract in humans (Abbott, 1995; Makalinao and Aguirre, 1993). Therefore, an oral absorption fraction of 1 was assumed for the calculations. This assumes that all ingested methamphetamine will be absorbed.

4.3.3 Dermal Exposure Parameters

The following summarizes exposure parameters that are specific to the dermal exposure model.

Exposed Skin Surface Area (SAs)

Children may be more highly exposed to environmental toxicants through dermal routes than are adults. For instance, children often play and crawl on contaminated surfaces and are more likely to wear less clothing than do adults. These factors result in higher dermal contact with contaminated media. In addition, children have a higher body surface area relative to body weight.

Skin surface areas have been fairly well defined in the experimental literature. USEPA's Exposure Factors handbook (EPA 1991) and the Child Specific Exposure Factors Handbook (USEPA 2002a) were consulted to identify appropriate skin surface areas for use in these calculations:

Infant: Surface areas for children under two years of age are not provided in the Exposure Factors Handbooks, due to a lack of information on height in that age group. However, Costeff (1996, as cited in USEPA 2002a) developed an empirical formula for calculating the surface area of children. This formula applies to the weight range between 1.5 and 100 kg.

$$\mathbf{SA = (4W + 7)/(W+90)}$$

Where:

SA = surface area (m^2);
Constants = 4, 7, and 90; and
W = weight (kg).

Using this equation, it can be determined that a one year old child with a body weight of 11.2 kg has a corresponding surface area of 0.511 m^2.

However, it is not assumed that the entire surface area of the infant will be exposed. For a one year old, it is assumed that the child is allowed to crawl around the floor in only a diaper. Therefore assuming that the torso, upper appendages, and lower appendages could be exposed in a diapered child, these areas correlate to approximately 84% of the total body surface area. Therefore the surface area used to estimate exposure to methamphetamine is 0.429 m^2 (4290 cm^2).

Child: The surface area input for a residential child as recommended in EPA's 2004 Dermal Risk Assessment Guidance is 2,800 cm^2.

Adult Female: The surface area input for a residential adult as recommended in EPA's 2004 Dermal Risk Assessment Guidance is 5,700 cm^2 .

- **Contact Frequency of Skin to Surface (CFs)**

This parameter is one of the most difficult to estimate. Previous assessments have usually assumed 1 contact per day. Often, this assumption is made with little discussion, as if multiple contacts with the surface were not considered. One contact per day may not be a realistic assumption when modeling residential scenarios, especially with children who have been observed to have frequent contact with surface materials within a household.

It was assumed that infants, children and adults have a contact frequency of 2 events per day. This assumes that the individual gets one bath a day and then recoats his/her exposed body surface with residue.

- **Fraction Transferred from Surface to Skin (FTSS)**

The worst-case assumption would be an FTSS of 1, or 100% transfer. As determined above for the fraction transferred from surface to hands (FTSH) for the purposes of this assessment, it was determined that a transfer factor of 0.5 to skin would be acceptable.

- **Dermal Absorption Fraction (ABSD)**

This parameter is assumed to be chemical-specific. However, no information was located pertaining to the dermal absorption of methamphetamine. A research study on the dermal absorption of cocaine was identified, in which 1.2% of the dose was absorbed from a 5 mg dose of cocaine freebase applied to the forearm skin surface of a volunteer (Baselt et al., 1990).

The value selected for use in these equations was 0.1 (10%). This is equivalent to the default value recommended by USEPA for the dermal absorption fraction of semi-volatile organic compounds, and is the highest default value for dermal absorption currently recommended by USEPA. Although the dermal absorption of cocaine is an order of magnitude lower than the value selected for use in the equations, it is not known how similar the absorption characteristics are between these two drugs. Additionally, it is assumed that the research on cocaine was conducted using an adult volunteer and there is evidence that children (especially young infants) may have greater dermal absorption rates than adults (USEPA, 1997).

4.4 Total Estimated Doses

Using the above equations and input parameters, the following estimated daily doses (mg/kg-day) of methamphetamine were calculated:

Methamphetamine Cleanup Standard	Target Population	Oral Dose (Do) mg/kg-day	Dermal Dose (Dd) mg/kg-day	Total Dose mg/kg-day
0.5ug/100 cm^2	Infant	2.23E-04	1.92E-04	**4.15E-04**
	Child	1.15E-04	6.45E-05	**1.80E-04**
	Adult	5.13E-05	4.07E-05	**9.20E-05**
0.1ug/100 cm^2	Infant	4.46E-05	3.83E-05	**8.29E-05**
	Child	2.31E-05	1.29E-05	**3.60E-05**
	Adult	1.03E-05	8.14E-06	**1.84E-05**
0.05 ug/100 cm^2 (0.5ug/ft^2)	Infant	2.23E-05	1.92E-05	**4.15E-05**
	Child	1.15E-05	6.45E-06	**1.80E-05**
	Adult	5.13E-06	4.07E-06	**9.20E-06**

As seen, the infant is predicted to receive the highest daily dose of methamphetamine on a body weight basis.

5.0 Correlation of Estimated Exposure Doses to Known Health Effects Ranges

The estimated doses presented above can be compared to what is known about health effects from methamphetamine exposure. As discussed previously, the majority of toxicity information for humans comes from illicit users and therapeutic approved uses. There are also several animal studies from which health effects and corresponding doses can be derived. The following subsections contain information on methamphetamine doses associated with therapeutic treatments, illicit use, and research studies.

5.1 Therapeutic

Therapeutic use of DESOXYN (methamphetamine hydrochloride tablets, USP) is indicated for use in the treatment of attention deficit disorder in children (age 6 and older), narcolepsy and short-term treatment of obesity. According to product insert information (Abbott, 1995), the following dosing regimen is prescribed:

> *Attention Deficit Disorder with Hyperactivity:* For treatment of children 6 years or older with a behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity: an initial dose of 5 mg DESOXYN once or twice a day is recommended. Daily dosage may be raised in increments of 5 mg at weekly intervals until an optimum clinical response is achieved.

> The usual effective dose is 20 to 25 mg daily. The total daily dose may be given in two divided doses daily.
>
> *For Obesity:* One 5 mg tablet should be taken one-half hour before each meal. Treatment should not exceed a few weeks in duration. Methamphetamine is not recommended for use as an anorectic agent in children under 12 years of age

As seen, dosing with DESOXYN begins at 5 mg daily and is not indicated for children less than 6 years of age, as the long-term effects of methamphetamine in children have not been established. For a six-year old child, a 5 mg intake is equivalent to a dose of 0.23 mg/kg-day (assuming a body weight of 21.7 kg). In an adult female (70 kg), this 5 mg intake is equivalent to a dose of 0.07 mg/kg-day.

5.2 Illicit Use

The average amount of methamphetamine taken during illicit use is estimated at 20-40 mg (Madden et al., 2004), which for a 70 kg female is equivalent to a dose of 0.29 to 0.57 mg/kg. The corresponding daily dose would be dependent on how frequently an individual used methamphetamine throughout the course of a day. A positive drug effect (euphoria, enhanced wakefulness, increased physical activity, decreased appetite, and increased respiration) in subjects has been noted at doses as low as 5mg (0.07 mg/kg). Although it is unclear as to exactly how much methamphetamine is consumed by drug abusers, it has been reported that among the chronic methamphetamine abusers attending drug dependence clinics the levels range from 150–250 mg a day (2.14-3.57 mg/kg-day) (Cheung, date unspecified). Other reports suggest that substance dependent users may consume 700 – 1,000 mg/day (10-14.3 mg/kg-day) (Makalinao and Aguirre, 1993). This wide range in reported doses is attributable in part to the fact that response is variable among users and tolerance develops in chronic abusers, requiring increased usage to obtain the desired effect.

It is possible that infants are more susceptible to the toxicity of methamphetamine, although there is little data to fully substantiate this assumption. One report details the death of a two-month old infant who was exposed to a lethal quantity of methamphetamine via breast-feeding (Washington, 2000). Upon autopsy, the methamphetamine blood level of the infant was 39 ng/mL. This blood level seen in the infant is comparable with levels seen in adults undergoing narcolepsy therapy with methamphetamine. Patients receiving methamphetamine in a therapeutic dose of 10 to 12.5 mg have had peak blood levels of 20 to 30 ng/mL (INFOTEXT, 2004). Additionally, according to at least one website, a ten-fold difference in the estimated lethal dose of methamphetamine is identified (100 mg in children and 1 g (1000 mg) in adults) (SDRL, 2004).

5.3 Laboratory Studies

Numerous research studies have been conducted in laboratory animals to assess the effects of methamphetamine exposure. The majority of these studies deal with high methamphetamine doses in the range of 20-40 mg/kg-day, or approximately an order of magnitude higher than doses thought to be typical of drug abusers entering treatment clinics. Neurological, developmental and reproductive effects have been identified as the most sensitive endpoints from methamphetamine exposure (NIDA 2002). A brief review of this research is provided below.

5.3.1 Neurotoxicity

Because methamphetamine's primary effect is as a central nervous system stimulant, there have been a large number of laboratory studies conducted to assess neurotoxicity. A select few of these representative studies have been summarized below.

Gomes-Da-Silva et al. (1998). Methamphetamine effects were evaluated in the rat during the first month of life by administering 10 mg/kg-day of (+) meth-amphetamine hydrochloride, subcutaneously, twice daily, from postnatal day 1 until the day before sacrifice (either postnatal day 5, 7 or 30). Rats exposed to methamphetamine were observed to have increased occurrences of retinal hemorrhages (18, 7 & 11% on postnatal days 5, 7 and 30, respectively) compared to control groups (2, 0 & 0% on postnatal days 5, 7 and 30, respectively). On postnatal day 30, the mean body weights of rats treated with methamphetamine were 75% (males) and 70% (females) that of controls.

Ricaurte et al. (1980). Repeated administration of methylamphetamine produced long-term depletions of both dopamine (DA) and serotonin (5-HT) in the rat brain. Male Sprague-Dawley rats were assigned to one of three dosing groups: control, 25 mg/kg-day, 100 mg/kg-day and were dosed twice daily via injection for a total of 4 days. Mortality was observed at 7% (1/15) and 43% (13/30) in the 25 and 100 mg/kg-day dose groups, respectively. None of the rats receiving the saline control died. After the treatment period, the mean body weights for the control, 25 and 200 mg/kg-day dosing groups were 230$\pm$15, 208$\pm$12, and 190$\pm$9 grams, respectively. Rats were sacrificed either 3 or 6 weeks after the final injection. At the three-week point, rats treated with 25 mg/kg-day methylamphetamine showed no significant depletion of DA in any of the brain regions examined, whereas rats treated with 100 mg/kg-day showed significant reductions in several brain areas. The 5-HT levels at three weeks were significantly reduced in both dosing groups, with the 100 mg/kg-day treatment affecting all brain regions examined. At six weeks post treatment, rats treated with 25 and 100 mg/kg-day displayed a 29 and 51% decrease in 5-HT uptake, respectively.

Ricaurte et al. (1984). Using subcutaneously implanted osmotic minipumps, male Sprague Dawley rats were exposed for 3 days to approximately 1, 2 or 4 mg/day of methamphetamine. The authors reported starting body weights of 250 g (0.25 kg) which correlates to tested doses of 4mg/kg-day, 8 mg/kg-day and 16 mg/kg-day. Two weeks following exposure, a selective striatal dopamine depletion associated with striatal nerve fiber degeneration was observed in the rats that had received the 4 mg/day (16 mg/kg-day) dose The lower daily doses (1 and 2 mg/day) failed to result in a similar response, even when administered for up to 12 days.

Villemagne et al. (1998). The purpose of this study was to evaluate brain dopamine neurotoxicity in baboons experimentally exposed to doses of methamphetamine in the range of those used recreationally by humans. Baboons were treated with saline or one of three doses of methamphetamine (0.5 mg/kg, 1 mg/kg, and 2 mg/kg), each of which was administered intramuscularly four times

daily for a total dose of 2 mg/kg-day, 4 mg/kg-day or 8 mg/kg-day. Animals were sacrificed for neurochemical studies 2-3 weeks after methamphetamine treatment. Methamphetamine produced long-term decreases on brain dopamine axonal markers at all doses tested.

Vorhees et al. (1994). In this experiment, Sprague-Dawley CD rats were injected subcutaneously with d-methamphetamine (30 mg/kg b.i.d.) early in postnatal development (days 1-10), later (postnatal days 11-20), or with water during both of these periods. Both methamphetamine treated groups exhibited reduced locomotor activity, with the effect most evident during the evaluation conducted at 30 days of age.

Vorhees et al. (2000). This study investigated the effects of neonatal D-methamphetamine treatment on cued and spatial learning and memory as adults. Methamphetamine was administered to neonatal Sprague-Dawley CD rats on postnatal days 11-20. Group MA40-4 received 40 mg/kg-day of methamphetamine in four doses of 10 mg/kg per injection. Group MA40-2 received the same total dose divided into two daily 20 mg/kg injections with saline for the other two injections during the day. Control animals received saline for four injections daily. As adults, the groups were evaluated using several behavioral methods including the straight swimming channel, Morris water maze, cued learning, and spatial learning (acquisition, reversal, and reduced platform variants). Both the MA40-4 and MA40-2 groups had significantly increased mortality of 15% and 21%, respectively compared to saline controls (1.7%). Additionally, both methamphetamine treated groups weighed less than the saline group beginning on postnatal day 13 and continuing throughout the remainder of treatment on postnatal day 20. No differences in swimming ability were noted for either group using a straight swimming channel. The MA40-4 group was impaired in hidden platform learning in the Morris water maze, and also showed reduced memory performance on probe trials. The MA40-2 group was slower at finding the visible platform during cued learning and were also impaired during acquisition and memory trials in the Morris hidden platform maze.

Williams et al. (2003). This study explored the spatial learning ability of Sprague-Dawley CD rats treated four times daily with a 5 mg/kg dose of methamphetamine (20 mg/kg-day) during postnatal days 11-20. Treated rats had significantly lower body weights than did the corresponding saline treated controls. Tests included a Barnes maze apparatus (aversive and appetitive version), a forced swim assessment (30 days following Barnes maze testing), and adult methamphetamine neurotoxicity and cliff avoidance. Under the aversive scenario of the Barnes maze, the authors demonstrated that the neonatally methamphetamine treated rats had deficits in learning the maze and that these deficits were more pronounced when the DEEP goal box was used, suggesting that the more aversive the testing environment, the greater the learning deficits. When the animals were tested in an appetitive version (food reward) of the Barnes maze, no differences were observed between the treatment groups in latency to the goal or number of errors. Following the forced swim, the animals that had been treated neonatally with methamphetamine had lower levels of corticosterone relative to animals treated with saline. Following acute methamphetamine

administration in adulthood, the animals that had been previously exposed neonatally displayed longer latencies to fall from a cliff than did the neonatally saline treated rats. The authors indicated that the ability of a re-exposed rat to remain on a platform 42% longer than animals receiving a first time dose of methamphetamine supports the position that the neonatally methamphetamine exposed animals may exhibit hypoactivity.

As seen, methamphetamine has recognized damaging effects on brain dopamine (DA) and serotonin (5-HT) neurons. However, it is difficult to identify at what point dopamine depletion or fiber degeneration becomes an adverse effect. This is similar to the issue that toxicologists struggle with when trying to correlate reductions in serum enzymes to potential health consequences. It is unclear as to how much of a reduction is necessary before an adverse effect is exhibited.

Learning deficits, such as those investigated in Vorhees et al (2000) and Williams et al. (2003) are easier to define as adverse effects. The spatial learning effects caused by developmental methamphetamine treatment have been observed in multiple studies, suggesting that these effects may be of concern for humans exposed to this drug during stages of early brain development. The Williams study appears to use the lowest dose that elicits these effects in spatial learning ability (i.e., 20 mg/kg-day). Therefore this study was identified as a critical study from which to derive a reference dose.

In general, a reference dose (RfD) is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of harmful effects during a lifetime. It is derived from a benchmark dose level (BMDL), a no observable adverse effect level (NOAEL), a lowest observable adverse effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used [2]. The RfD is generally expressed in units of milligrams per kilogram of bodyweight per day (mg/kg/day). The RfD is useful as a reference point from which to gauge the potential effects of the chemical at other doses. Usually, doses less than the RfD are not likely to be associated with adverse health risks. As the frequency and/or magnitude of the exposures exceeding the RfD increase, the probability of adverse effects in a human population increases. However, it should not be unconditionally concluded that all doses below the RfD are "acceptable" (or will be risk-free) and that all doses in excess of the RfD are "unacceptable" (or will result in adverse effects) (IRIS, 1993).

An uncertainty factor (UF) is one of several, generally 10-fold, default factors used in deriving an RfD from experimental data. The factors are intended to account for (1) the variation in sensitivity among the members of the human population (i.e., inter-individual variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-

[2] The LOAEL is the lowest dose for a given chemical at which adverse effects have been detected, while the NOAEL is the highest dose at which no adverse effects have been detected. A benchmark dose (BMD) is and alternative to the NOAEL/LOAEL approach and represents an exposure due to a dose of a substance associated with a specified low incidence of risk.

than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation when the database is incomplete (USEPA 2002b).

The intraspecies UF is applied to account for variations in susceptibility within the human population (interhuman variability) and the possibility (given a lack of relevant data) that the database available is not representative of the dose/exposure-response relationship in the subgroups of the human population that are most sensitive to the health hazards of the chemical being assessed. Because the RfD is defined to be applicable to "susceptible subgroups," this UF was established to account for uncertainty in that regard. The database UF is intended to account for the potential for deriving an underprotective RfD as a result of an incomplete characterization of the chemical's toxicity.

For the critical study identified above for neurotoxic effects of methamphetamine (Williams et al., 2003) where adverse effects were observed at a dose of 20 mg/kg-day, applying an uncertainty factor of 3000 (10 for LOAEL to NOAEL X 10 for intraspecies X 10 for interspecies X 3 for database deficiencies) would result in an RfD of 0.007 mg/kg-day.

5.3.2 Developmental Toxicity

For an excellent review on developmental toxicity of amphetamines (including methamphetamine), the reader is encouraged to consult the following recently released draft report entitled:

> Draft National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) Expert Panel Report On The Reproductive And Developmental Toxicity Of Amphetamine And Methamphetamine. November 2004.

According to the NTP-CERHR website, the National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences established the NTP Center for the Evaluation of Risks to Human Reproduction in 1998 to serve as an environmental health resource to the public and to regulatory and health agencies. The Center provides scientifically-based, uniform assessments of the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed. This is accomplished through rigorous evaluations of the scientific literature by independent panels of scientists. The amphetamines are currently undergoing review by an expert panel and the draft report summarizes their preliminary findings. A meeting of the expert panel has been scheduled for January 2005 in order to:

- Evaluate the evidence that a chemical is a reproductive or developmental toxicant;
- Determine patterns of chemical use and human exposure(s);
- Reach a scientific consensus of the potential for known or estimated human exposures to result in adverse effects on reproduction and/or development and

- Identify needs for additional research and testing to improve the scientific certainty of a chemical's hazard or risk.

As part of their draft report, the NTP-CERHR panel calculated benchmark doses for various studies investigating reproductive and developmental effects of methamphetamine exposure. The benchmark dose approach involves modeling the dose-response curve in order to determine, as accurately as possible, the relationship between a given exposure level and the likelihood of its detrimental effects. The output of the modeling is used to yield a 'benchmark dose' or BMD: this is the dose that corresponds with a given statistical likelihood of health impairment in the exposed population—for instance, 1 per cent or 10 per cent. The BMD is then divided by an uncertainty factor to yield a health-based recommended exposure limit. In order to account for the variation of the research data, the BMD is not taken as the point of departure for the determination of a recommended exposure limit. The preferred point of departure is the value that corresponds to the lower 90% or 95% confidence interval for the BMD: the BMDL. As with the NOAEL method, the health-based recommended exposure limit is obtained by dividing the BMDL by one or more uncertainty factors.

The NTP-CERHR expert panel stresses that calculation of a benchmark dose in their draft report does not mean that regulation based on the underlying data is recommended, or even that the underlying data are suitable for regulatory decision-making. It is hoped by CDPHE and other methamphetamine stakeholders that the results of the upcoming expert panel meeting can be used to establish an accepted RfD for methamphetamine that can be used as the foundation for clean-up standards at illicit drug labs. In the interim, the toxicity data summarized in the draft report are being used here to provide a comparison with detection-based cleanup levels.

Prenatal Studies: Two methamphetamine studies were identified as multiple-dose experimental animal prenatal developmental toxicity studies: Yamamoto et al (1992) and Kasirsky and Tansy (1971). The following summaries were taken directly from the NTP-CERHR report.

> *Kasirsky and Tansy (1971):* '.... iv dosed 50 mice/group with 5.0 or 10.0 mg/kg bw/day methamphetamine HCl **[purity not specified]** on GD 9–11, 9–12, 12–15, or 9–15 (plug day = GD 1). One control group of 50 mice was not treated and a second group of controls was given saline on GD 9–15. Maternal weights were significantly reduced in every treatment group and feed and water intake were decreased on the first 2–3 days of exposure **[data not shown]**. Fetal weights were significantly decreased in all treatment groups, but there were no significant effects on resorptions. **[The Expert Panel calculated a BMD10 of 2.1 mg/kg bw/day and BMDL of 1.5 mg/kg bw/day for fetal body weights on GD 9–15.]** The only significant increases in malformations (exencephaly, cleft palate, microphthalmia, and anophthalmia) occurred in fetuses from the group treated with 10.0 mg/kg bw/day methamphetamine on GD 9–15 (rate was13.6 vs. 1% in either control group). **[The Expert Panel estimated a BMD10 of 9.2 mg/kg bw/day and BMDL of 8.4 mg/kg bw/day for malformations/live implant].** The Expert Panel noted that this study is relevant for evaluation of abuse scenarios but is limited by incomplete reporting and lack of litter-based analyses.'

Yamamoto et al. (1992): '…..administered mice (n=10–26/group) a single ip dose of methamphetamine HCl **[purity not indicated]** in saline on GD 8 (plug = GD 0) at dose levels of 0, 11, 13, 14, 15, 17, 19, or 21 mg/kg bw. Larger numbers of animals were used for the higher dose groups in anticipation of treatment-induced maternal death, which occurred in 3/16 dams at 15 mg/kg bw, 5/14 dams at 17 mg/kg bw, 6/17 dams at 19 mg/kg bw, and 13/26 dams at 21 mg/kg bw. Maternal feed consumption and weight gain were not reported. Fetal body weights and mortality were not affected by treatment. External and skeletal malformations (visceral malformations not examined) occurred at doses ≥14 mg/kg bw. **[The Expert Panel calculated BMD10s of 14.6 for fetal death, 16.1 for external malformations, and 15.5 for skeletal malformations; BMDLs were estimated at 10.3 for fetal death, 12.2 for external malformations, and 12.4 for skeletal malformations.]**. The Expert Panel noted that the ip dose is not relevant for human therapeutic exposures and that result interpretation is very limited by unconventional group housing of dams.'

Study	Exposure	Endpoint	Developmental		Comments
			NOAEL	LOAEL	
Yamamoto et al. (1992) Jc1:ICR mouse	Methamphetamine. Intraperitoneal 11,13,14,15,17,19, or 21 mg/kg bw on gestational day 8.	Fetal death	21 mg/kg bw		BMD_{10} = 14.6 mg/kg bw BMDL = 10.3 mg/kg bw
		External malformations	17 mg/kg bw	19 mg/kg bw	BMD_{10} = 16.1 mg/kg bw BMDL = 12.2 mg/kg bw
		Skeletal malformations	13 mg/kg bw	14 mg/kg bw	BMD_{10} = 15.5 mg/kg bw BMDL = 12.4 mg/kg bw
Kasirsky and Tansy (1971) CF1 mouse	Methamphetamine. Intravenous 5.0 or 10.0 mg/kg bw/day on GD 9-11, 9-12, 12-15, or 9-15	Resorptions Decreased Fetal Weight		5 mg/kg-day	BMD_{10} = 2.1 mg/kg-day BMDL = 1.5 mg/kg-day
		Increased malformations	5 mg/kg-day	10 mg/kg-day	BMD_{10} = 9.2 mg/kg-day BMDL = 8.4 mg/kg-day

As seen, the lowest calculated benchmark dose for prenatal developmental effects reported by the expert panel was 1.5 mg/kg-day based on resorptions and decreased fetal weights. Using the expert panel's recommendations for BMDs, we applied an uncertainty factor of 300 (10 for intraspecies, 10 for interspecies, and 3 for database deficiencies) resulting in an RfD of 0.005 mg/kg-day.

Postnatal Studies: Three methamphetamine studies were identified as multiple-dose experimental animal postnatal developmental toxicity studies: Martin (1975), Cho et al. (1991) and Acuff-Smith et al. (1996). The expert panel notes that the remaining studies examined effects in offspring of rats dosed sub-cutaneously during gestation with multiple dose levels. Though the route is not relevant to therapeutic human exposure and limitations were noted in most studies (e.g., analysis on a per fetus versus per litter basis), the studies do provide qualitative information and allow an assessment of dose response.

These studies suggest that the types and magnitude of effects can vary according to the period of gestational methamphetamine exposure. Therefore, the expert panel found a direct comparison of studies to be difficult. However, the studies do suggest that prenatal methamphetamine exposure can result in decreased litter size (≥ 2 mg/kg bw/day), delayed eye opening (≥ 2 mg/kg bw/day), reduced postnatal body weight gain (≥ 3 mg/kg bw/day), and increased still birth or postnatal mortality (≥ 20g/kg bw/day). One study demonstrated that increases in still births and postnatal mortality are greater with late- (gestational day (GD) 13–18) versus mid- (GD 7–12) gestational exposures (Acuff-Smith et al. 1996). Reductions in the number of dams delivering litters and increases in eye defects were noted at higher doses. A delay in testicular descent was noted in one study where pups had other evidence of development delays *(Cho et al. 1991*) but none of the reliable studies reported delays in vaginal opening.

Study	**Exposure**	**Endpoint**	**Developmental**		**Comments**
			NOAEL	**LOAEL**	
Martin (1975) Sprague-Dawley Rat	Methamphetamine. Subcutaneous 0, 2, 6 or 10 mg/kg bw/day on GD 1-21.	Decreased Litter size and delayed eye opening		2 mg/kg-day	
Choe et al. (1991) Wistar Rat	Methamphetamine. Subcutaneous 0,1,2,3, or 4.5 mg/kg bw/day on GD 7-20.	Decreased male pup body weight gain during lactation and post-weaning; delayed testicular descent, incisor eruption, and eye opening	2 mg/kg-day	3 mg/kg-day	Testicular Descent: BMD_{10} = 3.8 mg/kg-day BMDL = 3.3 mg/kg-day Incisor eruption: BMD_{10} = 5.1 mg/kg-day BMDL = 3.1 mg/kg-day Eye opening: BMD_{10} = 15.7 mg/kg-day BMDL = 3.2 mg/kg-day
Acuff-Smith et al. (1996) Sprague Dawley Rat	Methamphetamine. Subcutaneous 0, 10, 20, 30, or 40 mg/kg bw/day on GD 7-12 or GD 13-18.	Decreased litter size (GD 13-18 exposure).		10 mg/kg-day	BMD_{10} = 38 mg/kg-day BMDL = 20 mg/kg-day
		Increased stillbirth and postnatal mortality on PND 1-3 (GD 13-18 exposure).	10 mg/kg-day	20 mg/kg-day	Stillborn/pup: BMD_{10} = 36 mg/kg-day BMDL = 31 mg/kg-day Postnatal mortality/live born pup: BMD_{10} = 53 mg/kg-day BMDL = 40 mg/kg-day
		Increased stillbirth and postnatal mortality on PND 1-3 (GD 7-12 exposure).	30 mg/kg-day	40 mg/kg-day	Stillborn/pup: BMD_{10} = 91 mg/kg-day BMDL = 58 mg/kg-day Postnatal mortality/live born pup: BMD_{10} = 48 mg/kg-day BMDL = 40 mg/kg-day

As seen, the lowest calculated benchmark dose for postnatal developmental effects reported by the expert panel was 3.1 mg/kg-day based on incisor eruption. Using the

expert panel's BMD, we applied an uncertainty factor of 300 (10 for intraspecies, 10 for interspecies, and 3 for database deficiencies) resulting in an RfD of 0.01 mg/kg-day.

5.3.3 Reproductive Toxicity

As for developmental toxicity, the reader is encouraged to consult the NTP-CERHR expert panel report on the reproductive and developmental toxicity of methamphetamine for a review of the associated reproductive effects from exposure to methamphetamine. A summary of the reproductive effects noted in this draft expert panel report are provided below for use in comparison of doses associated with detection-based cleanup standards with doses known to result in adverse outcomes.

The NTP-CERHR report identified three multiple-dose methamphetamine studies that evaluated reproductive toxicity. These were studies by Saito et al (1991), Yamamoto et al. (1999), and Kasirsky and Tansy (1971). The following summaries were taken directly from the NTP-CERHR report.

> *Saito et al. (1991):* '…..dosed male Wistar-Imamichi rats with a single ip dose of methamphetamine 0, 1, 2, or 4 mg/kg bw and immediately tested copulatory behavior with a sexually receptive female. At 4 mg/kg bw, the number of mounts, intromissions, and ejaculations over a 90-minute period was significantly reduced compared to the control group. Frequency of spontaneous motion increased at 2 and 4 mg/kg bw and stereotypic behavior increased at 4 mg/kg bw group. In a second experiment, rats were ip administered 0 (n = 7) or 1 (n = 5) mg/kg bw methamphetamine HCl once/week for 8 weeks. Copulatory behavior was observed 5 times at 2-week intervals. In the 1 mg/kg bw group, percentage of rats ejaculating reached statistical significance during the 4th and 5th testing and percentage of treated rats intromitting was reduced during the 5th test. **[Based on proportion of males ejaculating, the NOAEL is 2 mg/kg bw and the LOAEL is 4 mg/kg bw according to the authors results. Benchmark dose calculations by CERHR using the EPA Benchmark Dose Software give a BMD10 of 2.0 mg/kg bw and a BMDL of 1.1 mg/kg bw.]'**
>
> Yamamoto et al. *(1999)*: '…..treated mice with a single ip injection of *d*-methamphetamine HCl in saline at 0 (n = 30), 3.75 (n = 20), 7.5 (n = 20), or 15 (n = 60) mg/kg bw. **[It is not clear if numbers are for total numbers treated or evaluated.]** Twenty-four hours after injection, mice were paired 1:1 with untreated female mice until a plug was detected or for 14 days. The same mating procedure was conducted in half the mice from the 15 mg/kg bw/day group 48 hours following injection. Dams were allowed to litter and at birth, litter size was noted, and pups were weighed and examined for external malformations. Clinical signs were observed in the 15 mg/kg bw/day group and about 37% of the animals died within 20 hours of treatment. The number of vaginal plugs and births were significantly reduced in the 15 mg/kg bw/day group mated 24 hours after treatment, but the effects were not observed 48 hours after treatment. There were no significant effects on litter size, pup body weight, sex ratio, or postnatal mortality at any dose level. Additional mice (5–7/group) were treated with 0 or 15 mg/kg bw *d*-methamphetamine and evaluated for testicular and epididymal weight, serum testosterone level, sperm motility, and serum methamphetamine

and amphetamine levels. Weights of testes and epididymides were described as "slightly lower" in the 15 mg/kg bw/day group 24 hours after treatment. **[*t*-Test by CERHR showed no significant difference in weights of the caudae epididymides or left testis. There was a significant 7% decrease in right testis weight in the 24-hour 15-mg/kg bw group. Variances were not specified but were assumed to be SEM.]** Sperm motility was lower in males treated with 15 mg/kg bw/day and examined 24 and 48 hours later. Serum testosterone level was higher in the 15 mg/kg bw/day males examined at 24 hours, but lower in males examined at 48 hours. The Expert Panel noted that reproductive competency of untreated female rats was not verified and measurements of testosterone levels were inadequate since factors such as diurnal variations were not considered.'

Kasirsky and Tansy (1971): 'In a study that provided limited protocol details, 6 male rabbits were iv treated with methamphetamine HCl in saline at doses of 0, 1.5, 3.0, or 5.0 mg/kg bw/day for 3 months prior to mating *(190*). The rabbits were mated with untreated females, who were killed on GD 30 for examination of fetuses. There were no significant effects on whole litter resorptions, offspring survival, malformations, or fetal weight.'

Study	Exposure	Endpoint	NOAEL	LOAEL	Comments
Saito et al. Male Wistar-Imamichi rats	Methamphetamine HCl. Ip 0, 1, 2, or 4 mg/kg bw, single dose	Decreased number of mounts, intromissions and ejaculations over a 90-minute period.	2 mg/kg bw	4 mg/kg bw	BMD_{10} = 2.0 mg/kg bw BMDL = 1.1 mg/kg bw
Yamamoto et al. ICR Mice	d-Methamphetamine HCl Ip 0, 3.75, 7.5, or 15 mg/kg bw, single injection	Decreased vaginal plugs and births in mice mated 24 hours after treatment. Decreased sperm motility at 24 and 48 hours after treatment (only evaluated for mice treated with 15 mg/kg bw)	7.5 mg/kg bw	15 mg/kg bw	
		No significant effects on litter size, pup bw, sex ratio, or postnatal mortality.	15 mg/kg bw		
Kasirsky and Tansy Male rabbit	Methamphetamine HCl. Iv 0, 1.5, 3.0, or 5.0 mg/kg bw/day for 3 months prior to mating.	No significant effects on whole litter resorptions, offspring survival, malformations or fetal weight	5 mg/kg - bw/day		

For reproductive toxicity, the lowest benchmark dose value is 1.1 mg/kg-day. This was a one-time dose that did not elicit changes in reproductive measures. Using this benchmark dose derived by the expert panel, we applied an uncertainty factor of 300 (10 for intraspecies, 10 for interspecies, and 3 for database deficiencies) resulting in an RfD of 0.004 mg/kg-day.

5.4 Comparison

The RfD values that have been derived above and summarized below were not intended to establish a state approved toxicity standard, but to provide a credible basis for

evaluating the health protectiveness of the proposed technology cleanup standards. The table below shows the RfDs or health based intakes that are protective of neurological, reproductive, and developmental effects for sensitive individuals in a population. They are shown in comparison to the intakes that an infant would be expected to receive following cleanup to three proposed technology standards. As seen, each of the proposed technology standards would be protective of these health-based endpoints.

Dose mg/kg-day	Basis
0.00004	Calculated daily dose to an infant exposed at 0.05 ug/100 cm^2 wipe concentration
0.00008	Calculated dose to an infant exposed at 0.1 ug/100 cm^2 wipe concentration
0.0004	Calculated dose to an infant exposed at 0.5 ug/100 cm^2 wipe concentration
0.004	Calculated RfD based on reproductive endpoints (Section 5.3.3)
0.005	Calculated RfD based on prenatal developmental endpoints (Section 5.3.2)
0.007	Calculated RfD based on neurotoxicity endpoints (Section 5.3.1)
0.01	Calculated RfD based on postnatal developmental endpoints (Section 5.3.2)
0.07	Lowest therapeutic level of methamphetamine assuming 5 mg dose for a 70 kg adult
2.14	Illicit usage assuming a 150 mg daily dose for a 70 kg adult

The following calculations further emphasize the importance of remediating properties used to manufacture methamphetamine. Martyny et al. (2003) reported surface methamphetamine concentrations up to 16,000 ug/sample at former drug laboratories. Based on a total of 97 samples collected at these locations, the average concentration was determined to be 499 ug/sample (Note: The authors indicated that they attempted to collect samples from 100 cm^2 areas whenever possible). When estimates of 499 ug/100cm^2 for average exposures and 16,000 ug/100 cm^2 for maximum exposures at an unremediated property are entered into the exposure model developed above, the resulting dose to an infant is 0.41 and 13.3 mg/kg-day, respectively. These numbers highlight the importance of remediation at former methamphetamine laboratories as the

predicted exposures are well within a range where health effects would be expected to be observed.

6.0 Uncertainties

It is important to recognize that the exposure calculations presented in this document are based on a number of assumptions, and that these assumptions introduce uncertainty into the dose estimates. Assumptions are required because of data gaps in our knowledge of true environmental concentrations, in our understanding of the toxicity of chemicals, and in our ability to estimate the true level of human exposure to chemicals. In many cases, assumptions employed in the process to deal with uncertainties are intentionally conservative; that is, they are more likely to lead to an overestimate than an underestimate of exposure. However, some data gaps can result in an underestimation of exposure, and in other cases it is not possible to judge whether an approach is more likely to overestimate or underestimate exposure.

Because of these numerous sources of uncertainty, none of the dose estimates should be considered to be precise, but rather should be thought of as approximations. It is important for risk managers, stakeholders and the public to take these uncertainties into account when interpreting these results and ultimately adopting a methamphetamine cleanup standard.

6.1 Uncertainties in Concentration Data

Measured concentrations of chemicals in environmental media are the foundation of determining the dose to an exposed individual, but there are a number of uncertainties inherent in these data. For this modeling, the concentration was set equivalent to one of several potential cleanup levels to estimate doses resulting from exposure to these concentrations. These dose estimates are based on the assumption that a person is exposed to an average concentration equal to the cleanup standard. It has been stated by risk management personnel within CDPHE that the standard that is adopted is intended to be implemented on a "not to exceed" basis. Therefore, estimated doses based on exposure at concentrations equivalent to the cleanup standard will tend to be conservative (error on the high side). In other words, by applying a cleanup standard as a "not to exceed" standard, the average concentration of methamphetamine that may be present after cleanup would be anticipated to be lower than the cleanup standard itself. Composition of the building materials in the affected area, air exchanges and ventilation-heating/cooling system, area of the room or rooms in the concentration area, and the room(s) height are significant factors when setting a concentration level to the data.

6.2 Uncertainty in Human Exposure

6.2.1 Uncertainty in Exposure Parameters

Even if there were no uncertainty in the concentration of chemicals in environmental media to which humans are exposed, there would still be considerable uncertainty in the calculated estimates of actual exposure levels. This is because there is very wide variation between different people in the amount of contact they have with different media. Human exposure estimates were based on national statistics or on professional judgment, which may or may not provide reasonable estimates of human exposure. To account for the uncertainty that is inherent in this approach, most of the default human exposure parameters recommended by EPA tend to be somewhat conservative (i.e., on

the high side). However, the possibility always remains that a few individuals at a residence may be exposed for a longer duration and/or at a higher exposure rate than was assumed. In such cases, the estimates of dose may be too low. However, for most people, it is believed that the exposure and dose estimates for oral ingestion and dermal absorption are more likely to be too high than too low.

6.2.2 Uncertainty From Pathways Not Quantified

Exposure was not assessed in detail for several potential exposure pathways, including inhalation of dislodged methamphetamine residue and ingestion of methamphetamine in breast milk by nursing infants related to environmental maternal exposure. Omission of these exposure pathways introduces some uncertainty into this evaluation, and will presumably tend to result in an underestimation of exposure. However, it is believed that the additional level of exposure contributed by these exposure pathways is probably low compared to oral and dermal exposure. This uncertainty should be considered when selecting a methamphetamine cleanup standard.

6.3 Uncertainty in Toxicity Values

Even if accurate information were available for a person or a population on the true intake rates of each chemical in each medium, there would still be considerable uncertainty in the predicted health consequences of those exposures.

EPA has not established toxicity values for methamphetamine via any exposure route. For the purposes of this assessment, this data gap was filled by using interim values developed by extrapolating data from the peer-reviewed literature, pharmaceutical product information sheets, and knowledge of methamphetamine abuse scenarios. These un-validated values are subject to considerable uncertainty, but were intended to encompass endpoints that are sensitive to the effects of methamphetamine. Despite these uncertainties, it was determined that it was important to attempt to weigh potential health effects from exposure to methamphetamine with the technology based cleanup standards.

The majority of the available toxicity data are based on shorter-term (subchronic or acute) studies with limited dosing levels. Although it would be desirable to have more data from chronic studies, it is advantageous that many of the studies were conducted during critical developmental periods (e.g., gestation, organogenesis, early development), which are expected to be sensitive to the effects of methamphetamine. No evidence was located to indicate that methamphetamine may be a carcinogen.

Uncertainty in toxicity factors also arises from lack of knowledge on the potential interactive effects of different chemicals. This review focused on exposure to only methamphetamine. Under laboratory research conditions, it is possible to expose receptors to one chemical under controlled conditions. Exposure to only methamphetamine is not anticipated to be the case in situations where individuals may occupy former methamphetamine laboratories. The process of manufacturing methamphetamine uses a wide variety of chemicals and may introduce a wide suite of chemical contamination to a residential property. Therefore, it is assumed that individuals may be exposed to more than just methamphetamine under these conditions. Most risk assessments evaluate the toxicity of, or risk associated with, individual chemicals, and then combine them by simple addition to estimate risk related to chemical mixtures. However, adding

risks ignores potential synergistic or antagonistic interactions that could lead to underestimation or overestimation of total risk, respectively. Knowledge of mechanisms of action can guide judgments of whether risks related to combinations of particular chemicals will be additive or independent.

It is also quite possible that the cooking process may not always result in the production of a "pure" methamphetamine compound. Because this cooking process is often accomplished using a variety of household products under less than ideal conditions, it is possible that impurities may be introduced into the methamphetamine, or that alternate forms of methamphetamine may be produced. The toxicity associated with alternate forms or introduction of impurities is not accounted for in this review and may result in more or less toxic forms of methamphetamine residue.

7.0 Summary of Findings

The purpose of this report was to evaluate whether the technology based cleanup standards for methamphetamine would be anticipated to be health protective to residents of former drug laboratories. It is acknowledged that a technology-based standard can not be viewed as a "safe level" standard, since no one truly knows how much an infant or child would absorb via skin, or get as an oral dose from putting hands that have been in contact with the contaminant in his/her mouth. However, rather than just accepting a technology-based standard at face value, it is important to at least attempt to compare concentrations of methamphetamine that would be acceptable under residual conditions to better assess whether these concentrations are below those known to have health consequences.

Three technology based concentrations that are currently being used in the United States as methamphetamine cleanup standards were evaluated in this report:

- 0.5 ug/100 cm^2
- 0.1 ug/100 cm^2
- 0.05 ug/100 cm^2

Using a model developed to assess the exposure dose correlated with a known wipe concentration, it was predicted that a one-year old infant would have the highest daily dose on a body weight basis to residual methamphetamine on household surfaces. These doses were predicted to range from 0.00004 to 0.0004 mg/kg-day depending on which cleanup standard was input into the exposure model

Reference doses were provisionally identified from the available toxicity literature for use in comparing the estimated intake to an infant. The RfDs based on endpoints varying from neurotoxicity to developmental and reproductive toxicity ranged from 0.004 to 0.01 mg/kg-day. As stated previously, it is important to recognize that the RfDs developed in this report are not intended to represent state approved RfDs, but are merely presented to provide a frame of reference for potential health effects from exposure to methamphetamine.

Based on the evaluation presented in this document, it appears that all three of the technology based cleanup standards for methamphetamine that were evaluated in this document are anticipated to be health protective of residents of former drug laboratories. The level of

protectiveness demonstrated in this effort ranges from 10 to 100-fold at cleanup concentrations of 0.5 ug/100 cm^2 and 0.05 ug/100 cm^2, respectively. Allowing for an extra measure of protectiveness can help account for some of the uncertainties that are inherent in the process (Section 6) and should be considered by risk managers when establishing a cleanup standard.

This effort was not intended to result in the derivation and documentation of a specific cleanup value for methamphetamine in the state of Colorado. Rather, the results from this evaluation will be used to support, in conjunction with other risk management considerations, the selection of a numeric cleanup criteria for methamphetamine.

8.0 References and Additional Resources

Abbott. 1995. DESOXYN Package Insert. 03-4653-R4 ABBOTT LABORATORIES NORTH CHICAGO, IL 60064, U.S.A. December, 1995

Acuff-Smith, KD., George, M., Lorens, SA, and CV. Vorhees. 1992. Preliminary Evidence for Methamphetamine-Induced Behavioral and Ocular Effects in Rat Offspring Following Exposure During Early Organogenesis. Psychopharmacology (1992) 109:255-263.

Baselt, RC. et al. 1990. On the Dermal Absorption of Cocaine. J Anal Toxicol. Nov-Dec; 14(6):383-4.

CDPHE. 2003. Cleanup of Clandestine Methamphetamine Labs Guidance Document. Colorado Department of Public Health and Environment. Hazardous Materials and Waste Management Division. July 2003. http://www.cdphe.state.co.us/hm/methlab.pdf

Cheung, B. Lecture Notes. Patterns of Use. http://www.hkma.com.hk/download/lecturenote/BenCKL-Eng.pdf

HSDB. 2004. Hazardous Substances Database. Accessed online November 2004.

INFOTEXT ®. 2004 - Regulations, Standards and General Information) (METHAMPHETAMINE - MEDICAL REVIEW OFFICER INFORMATION

IRIS. 1993. Reference Dose (RfD): Description and Use in Health Risk Assessments. Background Document 1A. March 15, 1993 http://www.epa.gov/iris/rfd.htm

Madden, LJ., Flynn, CT., Zandonatti, MA., May M., Parsons, LH., Katner, SN., Henriksen, SJ., and HS Fox. 2004. Modeling Human Methamphetamine Exposure in Non-Human Primates: Chronic Dosing in the Rhesus Macaque Leads to Behavioral and Physiological Abnormalities. Neuropsychopharmacology. (2004) 1-10. http://www.nature.com/npp/journal/vaop/ncurrent/pdf/1300575a.pdf

Makalinao, I and AA Aguirre. Methamphetamine. International Programme on Chemical Safety Poison Information Monograph 334. Pharmaceutical http://www.inchem.org/documents/pims/pharm/pim334.htm

Martyny, J. et al. 2003. Chemical Exposures Associated with Clandestine Methamphetamine Laboratories. National Jewish Medical and Research Center.

Martyny, J. Arbuckle, SL., McCammon, CS. and N. Erb. 2004. Methamphetamine Contamination on Environmental Surfaces Caused by Simulated Smoking of Methamphetamine. National Jewish Medical and Research Center. http://www.colodec.org/medical/documents/Meth%20smoking%20experiment.pdf

NIDA. 1996. National Institute on Drug Abuse. *NIDA NOTES, November/December, 1996.* Facts about Methamphetamine. http://www.nida.nih.gov/NIDA_Notes/NNVol11N5/Tearoff.html

NIDA. 2002. National Institute on Drug Abuse. Research Report Series. Methamphetamine Abuse and Addiction. NIH Publication Number 02-4210. January 2002 Reprint. http://www.drugabuse.gov/ResearchReports/methamph/methamph.html

NTP-CERHR. 2004. Draft NTP-CERHR EXPERT PANEL REPORT on the REPRODUCTIVE and DEVELOPMENTALTOXICITY of AMPHETAMINE AND METHAMPHETAMINE. NATIONAL TOXICOLOGY PROGRAM. US Department of Health and Human Services. November 2004.

Oro, AS. And SD Dixon. 1987. Perinatal Cocaine and Methamphetamine Exposure: Maternal and Neonatal Correlates. J. Pediatr. 1987 Oct; 111(4):571-8.

Plessinger MA. Prenatal exposure to amphetamines. Obs Gyn Clin North Am. 1998;25(1):119-138. http://www.erowid.org/references/refs_view.php?A=ShowDoc1&ID=314

Ricaurte, GA, Schuster CR, and Seiden LS. 1980. Long-Term Effects of Repeated Methylamphetamine Administration on Dopamine and Serotonin Neurons in the Rat Brain: A Regional Study. Brain Research. 193: 153-163.

Ricaurte GA, Seiden LS, and Schuster CR. 1984. Further Evidence that Amphetamines Produce Long-Lasting Dopamine Neurochemical Deficits by Destroying Dopamine nerve Fibers. Brain Research. 303: 359-364.

SDRL. 2004. Methamphetamine. San Diego Reference Laboratory http://www.sdrl.com/druglist/methamphetamine.html

Smith, L. et al. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. J Develop Behav Pediat, 2003;24(1):17-23)

USEPA. 1991. Human Health Evaluation Manual, Supplemental Guidance: Standard Default Exposure Factors. OSWER Directive 9285.6-03. Office of Solid Waste and Emergency Response, Washington, D.C. March 25.

USEPA. 1997. Exposure Factors Handbook. EPA/600/P-95/002Fa. August 1997 http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12464&CFID=915001&CFTOKEN=75731168

USEPA. 2002a. Child-specific exposure factors handbook. National Center for Environmental Assessment, Washington, DC; EPA/600/P-00/002B.
http://fn.cfs.purdue.edu/fsq/WhatsNew/KidEPA.pdf

USEPA. 2002b. A Review of the Reference Dose and Reference Concentration Processes EPA/630/P-02/002F. December 2002.

USEPA. 2003. Wipe Sample Assessment. Internal Draft Document developed by USEPA Region III.

USEPA. 2004. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). EPA/540/R/99/005, OSWER 9285.7-02EP, PB99-963312, July 2004.
http://www.epa.gov/superfund/programs/risk/ragse/

Villemagne, V, Yuan J, Wong DF, Dannals RF, Hatzidimitriou G, Mathews VB, Ravert HT, Musachio J, McCann UD, and Ricaurte GA. 1998. Brain Dopamine Neurotoxicity in Baboons Treated with Doses of Methamphetamine Comparable to Those Recreationally Abused by Humans: Evidence from [^{11}C]WIN-35,428 Positron Emission Tomography Studies and Direct *In Vitro* Determinations. The Journal of Neuroscience. 18(1): 419-427.

Vorhees CV, Ahrens KG, Acuff-Smith KD, Schilling MA, Fisher JE. 1994. Methamphetamine Exposure During Early Postnatal Development in Rats: II. Hypoactivity and Altered Responses to Pharmacological Challenge. Psychopharmacology. 114: 402-408.

Vorhees, C.V., Inman-Wood SL, Morford LL, Broening HW, Fukumura M, and Moran MS. 2000. Adult Learning Deficits After Neonatal Exposure to d-Methamphetamine: Selective Effects on Spatial Navigation and Memory. The Journal of Neuroscience. 20(12): 4732-4739.

Washington. 2000. State of Washington. Review of Contaminant Levels: Guidelines for Clandestine Drug Lab Cleanup.
http://www.colodec.org/medical/documents/Clean%20Up%20Stds%20Toxicology%20Report-Washington.pdf

Williams, MT., Blankenmeyer TL, Schaefer TL, Brown CA, Budelsky GA, and Vorhees CV. 2003. Long-term Effects of Neonatal Methamphetamine Exposure in Rats on Spatial Learning in the Barnes Maze and on Cliff Avoidance, Corticosterone Release, and Neurotoxicity in Adulthood. Developmental Brain Research 147: 163-175.

Attachment 1
Exposure Parameters for Intake Models

Exposure Parameter	Abbreviation	Units	Values		
			Infant	Child	Adult
Assumed Age	--	years	1	6	Childbearing
Concentration of Chemical on Surface	C	mg/cm^2	5E-06, 1E-06 or 5E-07		
Body Weight	BW	kg	11.2	21.7	70
Exposed Hand Surface Area	SAh	cm^2	135	192.5	410
Contact Frequency of Hand to Surface	CFh	times/day	74	52	13
Fraction Transferred from Surface to Hands	FTSH	unitless	0.5	0.5	0.5
Fraction Transferred from Hands to Mouth	FTHM	unitless	0.1	0.1	0.1
Oral Absorption Fraction	ABSO	unitless	1	1	1
Exposed Skin Surface Area	SAs	cm^2	4290	2800	5700
Contact Frequency of Skin to Surface	CFs	times/day	2	2	2
Fraction Transferred from Surface to Skin	FTSS	unitless	0.5	0.5	0.5
Dermal Absorption Fraction	ABSD	unitless	0.1	0.1	0.1