Support for selection of a methamphetamine cleanup standard in Colorado

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Abstract

Methamphetamine production for illicit use occurs in makeshift labs and is associated with the release of numerous chemicals, including methamphetamine residues. These methamphetamine residues may pose a health risk to residents who reoccupy these structures after property seizures. Several states have established technology-based cleanup standards for methamphetamine, but none have examined the health-protectiveness of these standards. In response to Colorado House Bill 04-1182, exposure intakes correlated with three technology-based standards were calculated for various groups of individuals. Intakes were assessed for a 1-year-old infant, 6-year-old child, and a female of childbearing age. Exposure intakes were compared to toxicity reference values developed from developmental endpoints following methamphetamine exposure from the available literature. Uncertainty factors were applied to the lowest adverse effect levels observed in these studies to arrive at the toxicity reference values. These reference values were greater than the calculated intakes from each proposed technology standard, suggesting that all of the proposed standards would be protective of human health exposure. The cost and practicality of attaining each of the proposed standards was also factored into the decision making process. In their final regulation (6 CCR 1014-3), the CDPHE selected 0.5 \( \frac{\text{g}}{100 \text{ cm}^2} \) as the final cleanup standard for methamphetamine residues.

Keywords: Clandestine drug lab; Methamphetamine contamination of homes; Exposure assessment from wipe samples; Regulatory cleanup standard; Adverse health effects; Risk assessment

1. Introduction

Methamphetamine is a powerful, highly toxic, addictive drug that is illegally “cooked” in makeshift labs. Methamphetamine can be found in the form of pills, capsules, powder or chunks. It can be smoked, snorted, injected or eaten. Methamphetamine is often referred to as “meth” and is also called crank, speed, crystal or ice. Methamphetamine laboratories have been a growing problem throughout Colorado and across the United States. In Colorado alone, the number of methamphetamine 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 the introduction of House Bill 04-1182, the Colorado Department of Public Health and Environment (CDPHE) developed regulations for the cleanup of properties used as methamphetamine labs. A primary goal of this regulation was to develop re-occupation standards that would be protective of future occupants (mainly children) of seized properties. This effort was achieved through the input of a large stakeholder group represented by EPA, fire departments, law enforcement, local industrial hygienists, property owners, and others.

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. The two most common methods currently used in Colorado include the Red phosphorus and Birch methods (CDPHE, 2003). Both use ephedrine or pseudoephedrine as a primary ingredient.

### 1.1. Red phosphorus method

This method is also called the “Red P.” “HI” Method, or the Red, White and Blue Method. There are several chemicals commonly associated with this method including hydriodic acid, hydrochloric acid, sulfuric acid, sodium hydroxide, sodium chloride, red phosphorus, iodine, isopropyl alcohol, ethyl alcohol, methyl alcohol, hydrogen peroxide, naphtha, charcoal lighter fluid, acetone, benzene, toluene, ethyl ether, freon, hydrogen chloride gas, and chloroform.

### 1.2. Birch method

This method is also known as the “Ammonia” or “Nazi” Method. The chemicals associated with the birch method include anhydrous ammonia, lithium metal, sodium metal, isopropyl alcohol, ethyl alcohol, methyl alcohol, hydrogen chloride gas, hydrochloric acid, sulfuric acid, sodium chloride (salt), toluene, naphtha, freon, ethyl ether, chloroform, and methyl-ethyl-ketone.

### 1.3. Other methods

Other methods to manufacture methamphetamine include the amalgam method, which primarily uses phenyl-2-propanone (P2P) and methylamine. This P2P method may result in mercury and lead contamination at a property. Chemicals also associated with this manufacturing method are mercuric chloride, aluminum, hydrochloric acid, isopropyl alcohol, methanol, ethanol, acetone, benzene, chloroform, and ether.

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).

To determine acceptable risk-based concentrations for chemicals associated with methamphetamine labs, CDPHE had previously reviewed human exposure reference values for chemicals commonly associated with methamphetamine 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. A table summarizing the chemical exposure limits for select chemicals associated with clandestine methamphetamine labs can be found in the CDPHE guidance document (CDPHE, 2003). However, to date, no health-based value for methamphetamine has been developed.

Therefore, an evaluation specific to methamphetamine is the focus of this paper.

Several states have established cleanup standards specifically for the residue of methamphetamine (Table 1). After communicating with some of these state health departments, it was learned that these levels do not represent health-based values, but were based on analytical detection limits. Health-based values could not be established due to deficiencies in the toxicity database. These current state-specific methamphetamine cleanup levels are instead based on what is believed to be conservative and protective, while at the same time achievable by cleanup 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. We attempted to reconcile what was known about methamphetamine health effects with those levels currently being used as cleanup standards to support selection of a Colorado state 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. Our approach provided us with a balanced means of weighing these lower detection limits against practicability and cost considerations.

### 2. General exposure assessment

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 was to estimate a high end or upper bound exposure (or dose) to the individuals of concern. These exposure estimates may then be compared to what is known about methamphetamine health effects, to provide further support for setting a re-occupancy standard for methamphetamine.

Although in theory, any person who is exposed to residual methamphetamine is of concern, several discrete populations were selected for evaluation. Exposure estimates were made for three categories of individuals: infant (age
1) and child (age 6) because their behaviors, such as crawling and playing on the floor, and increased mouthing activities may expose them to more contaminated media within a home; and the adult female of childbearing age because of the susceptibility of the fetus to contaminants during critical stages of early development.

Exposure to methamphetamine residues and dust on indoor surfaces was estimated using the USEPA guidance Standard Operating Procedures (SOPs) for Residential Exposure Assessment (hereafter referred to as the SOP guidance) originally published by the Office of Pesticides for estimating exposure to pesticides (USEPA, 1997a, 2001). Pesticides are typically applied to indoor surfaces as liquid or aerosol formulations and consequently, some of the parameters are based on application rates. Since pesticide application rates are not applicable to methamphetamine deposition, we also utilized information on assessing exposures to indoor surfaces from the World Trade Center Indoor Environment Assessment (USEPA/NYCDHMH, 2003) which used a wipe sample methodology in lieu of application rates. The equations and assumptions used to estimate oral and dermal dose from methamphetamine exposures are discussed below.

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.

2.1. Estimation of dermal dose

The following equation from the SOP guidance was used to estimate dermal contact with residues and contaminated dust on indoor surfaces:

\[
PDR = \frac{(ISR \times TC \times ET \times ABSD)}{BW}
\]

where PDR is the potential dose rate (mg/kg/day), ISR is the indoor surface transferable residue (mg/cm²), CSL is the contaminant surface load (mg/cm²), FTSS is the fraction transferred from surface to skin (unitless fraction).

When this substitution is made and the equation is adjusted to allow for varying exposure times for carpeted and hard indoor surfaces, the equation is as follows:

\[
PDR = \left[ (CSL_{hard} \times FTSS_{hard} \times TC \times ET_{hard} \times ABSD) + (CSL_{soft} \times FTSS_{soft} \times TC \times ET_{soft} \times ABSD) \right] / BW
\]

The inputs used for the equation parameters are discussed below and summarized in Table 2.

2.1.1. Contaminant surface load (CSL)

This is the amount of contaminant per surface area. In this model, the concentration of the chemical on a hard surface was set according to each of three scenarios; 0.5 μg/100 cm², 0.1 μg/100 cm², or 0.05 μg/100 cm². These three scenarios are representative of the various state-specific cleanup levels for methamphetamine that are currently in use nationwide. For carpeted surfaces, the contaminant surface load concentration was set to zero. This is due to the removal of impacted carpets from a property during remediation. Any new replacement carpet is not expected to have measurable levels of methamphetamine. The units shown in Table 2 were converted from μg/100 cm² to mg/cm² because the equations required this as an input.

2.1.2. Fraction transferred from surface to skin (FTSS)

This parameter represents the fraction of residue on a surface that can be transferred to the skin. The SOP guidance recommends a default value of 5% of application rate for carpets and 10% for hard surfaces. These default assumptions were based on wet hand and wet palm (from human saliva) transfer efficiencies from carpet and vinyl flooring for the pesticides chlorpyrifos, pyrethrin I, and piperonyl butoxide.

2.1.3. Transfer coefficient (TC)

This parameter represents the rate of skin contact with the indoor surface. Our assessment was based on infants (age 1), children (age 6) and adult females.

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.

\[
SA = \frac{(4W + 7)}{(W + 90)}
\]

where SA is the surface area (m²); constants are 4, 7, and 90; W is the body 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
total surface area of 0.511 m². However, it is not assumed that the entire surface area of the infant will be exposed. For a 1 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 transfer coefficient used for the 1-year-old infant is 0.429 m²/h (4290 cm²/h).

2.1.4. Exposure time (ET)

This parameter represents the amount of time spent indoors where a person could come into contact with the contaminated surfaces. The SOP guidance recommends defaults of 8 h/day for carpeted surfaces and 4 h/day for hard surfaces. The 8 h value is based on the mean total time spent indoors for a young child (1–4 years of age) and subtracting the amount of time spent sleeping, eating, and bathing (approximately 13 h). The 4 h value for hard surfaces is based on the 90th percentile value for time spent in the kitchen and bathroom for all age groups.

2.1.5. Dermal absorption fraction (ABSD)

This parameter represents the amount of contaminant on the skin surface area which is absorbed. The SOP guidance does not provide a default value for this parameter. However, a methodology for evaluating dermal absorption of soil-borne contaminants and default recommendations for compounds/classes of contaminants can be found in USEPA (2004). Dermal absorption fractions for TCDD, DDT and Lindane ranged from 0.001 to 0.04, while dermal absorption fractions for PCBs and semivolatile organic compounds were 0.14 and 0.1, respectively. The value selected for use in these equations was 0.1 (10%).

2.1.6. Body weight (BW)

Our assessment was based on infants (age 1), children (age 6) and adult females.

Infant: A 1-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 (USEPA, 2002a).

Child: A 6-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 (USEPA, 2002a). [Note: The EPA recommended default of 15 kg for a child’s body weight was not used as this may underestimate the body weight of a 6 year old, as it is intended to represent the weight for all children ranging up to age six.]

Adult female: An adult female of childbearing age was assumed to have a body weight of 61 kg. This is based on the average of the 50th percentile body weights of females 18–24, 25–34 and 35–44 years of age. (USEPA, 1997b).

2.2. Estimation of oral dose

The following equation from the SOP guidance was used to estimate incidental non-dietary ingestion of residues and contaminated dust on indoor surfaces.

\[
PDR = \frac{(ISR \times SA \times FQ \times SE \times ET \times ABSD)}{BW}
\]

where PDR is the potential dose rate (mg/kg/day), ISR is the indoor surface transferable residue (mg/cm²), SA is the sur-
face area (cm^2/event). FQ is the frequency of hand to mouth events (events/h), SE is the saliva extraction factor (unitless), ET is the exposure time (h/day), ABSO is the oral absorption fraction (unitless), BW is the body weight (kg).

As discussed previously for dermal exposure, the ISR is calculated by multiplying the contaminant surface load (CSL) by the fraction transferred from surface to skin (FTSS). By making this substitution and rearranging the equation to allow varying exposure times to carpeted and hard surfaces, the equation is rewritten as follows:

\[
\text{PDR} = \left[\left(\frac{\text{CSL}}{\text{FTSS}}\right) \cdot \left(\frac{\text{ET}}{\text{SA}}\right)\right] \cdot \text{BW} \cdot \text{CSL} \cdot \text{FTSS} \cdot \text{ET} \cdot \text{SA} \cdot \text{FQ} \cdot \text{SE} \cdot \text{ABSO}/\text{BW}
\]

The inputs for the equation parameters are discussed below and summarized in Table 2.

### 2.2.1. Contaminant surface load (mg/cm^2)
See discussion above for dermal exposure.

### 2.2.2. Fraction transferred from surface to skin (FTSS)
See discussion above for dermal exposure.

### 2.2.3. Exposure time (ET)
See discussion above for dermal exposure.

### 2.2.4. Surface area (SA)
This parameter represents the skin area contacted during the mouthing event. Our assessment was based on infants (age 1), children (age 6) and adult females.

**Infant:** Assuming that an infant’s hands comprise approximately 5.3% of the total body surface area as calculated above (5110 cm^2), a value of 270 cm^2 for total hand area (both hands) can be derived. 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. Therefore, in the exposure model the exposed area (palm side) of an infant’s hands was determined to be 135 cm^2.

**Child:** The average total body surface area for a 6-year-old child is 8200 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).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 &lt; 6</td>
<td>7930 cm^2</td>
<td>7790 cm^2</td>
<td>7860 cm^2</td>
</tr>
<tr>
<td>6 &lt; 7</td>
<td>8660 cm^2</td>
<td>8430 cm^2</td>
<td>8550 cm^2</td>
</tr>
</tbody>
</table>

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, USEPA, 1997a,b), the exposed hand surface area for the adult female is 410 cm^2.

### 2.2.5. Frequency of hand to mouth events (events/h)
A default value of 9.5 events/h for children 1–6 years of age is recommended by the SOP guidance. This is based on reported hourly frequencies of hand-to-mouth events in pre-school children using video tape observations. This hand to mouth frequency is expected to decline with age. We used 9.5 events/h for the 1- and 6-year-old child and 1 event/h for the adult female.

### 2.2.6. Saliva extraction factor (SE)
This represents the fraction of contaminant transferred from the skin to the mouth. The SOP guidance recommends a default value of 0.5 (50%) based on studies using surgical sponges wetted with human saliva to remove residues from the hands of volunteers. We used this value for all ages.

### 2.2.7. 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). An oral absorption fraction of 1 was used based on the assumption that oral absorption of residues would be the same as the degree of absorption in the toxicity studies used to assess adverse health effects.

### 2.2.8. Body weight (BW)
See discussion above for dermal exposure.

### 2.3. Dose estimates
Using the above equations and input parameters, the following estimated daily doses (mg/kg-day) of methamphetamine were calculated. As seen, the infant is predicted to receive the highest daily dose of methamphetamine on a body weight basis.

<table>
<thead>
<tr>
<th>Methamphetamine cleanup standard</th>
<th>Target population</th>
<th>Oral dose (mg/kg-day)</th>
<th>Dermal dose (mg/kg-day)</th>
<th>Total dose (mg/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 µg/100 cm²</td>
<td>Infant</td>
<td>1.1E–04</td>
<td>7.7E–05</td>
<td>1.9E–04</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>8.4E–05</td>
<td>2.6E–05</td>
<td>1.1E–04</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>6.7E–06</td>
<td>1.9E–05</td>
<td>2.5E–05</td>
</tr>
<tr>
<td>0.1 µg/100 cm²</td>
<td>Infant</td>
<td>2.3E–05</td>
<td>1.5E–05</td>
<td>3.8E–05</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>1.7E–05</td>
<td>5.1E–06</td>
<td>2.2E–05</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>1.3E–06</td>
<td>3.7E–06</td>
<td>5.1E–06</td>
</tr>
<tr>
<td>0.05 µg/100 cm²</td>
<td>Infant</td>
<td>1.1E–05</td>
<td>7.7E–06</td>
<td>1.9E–05</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>8.4E–06</td>
<td>2.6E–06</td>
<td>1.1E–05</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>6.7E–07</td>
<td>1.9E–06</td>
<td>2.5E–06</td>
</tr>
</tbody>
</table>

### 3. Health effects of methamphetamine
The estimated intakes from the range of proposed cleanup standards can be compared to what is known about health
effects associated with methamphetamine exposure. The majority of the human toxicity information comes from illicit users and therapeutic approved uses. Both therapeutic effects and effects of illicit drug use can be viewed as adverse health effects for unintentional exposures and are therefore reviewed in the following sections. There are also a number of experimental animal studies that examine adverse health effects associated with administered doses. The intent of this section is not to provide an exhaustive review of the toxicity literature for methamphetamine. The intent is to highlight the adverse effects that occur at the lowest dose levels in some of the more sensitive species.

3.1. Therapeutic use in humans

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 obesity. An initial dose of 5 mg DESOXYN once or twice a day is recommended for children 6 years or older with attention deficit disorder with hyperactivity. 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 20–25 mg daily (Abbott, 1995). For obesity, one 5 mg tablet prior to each meal is recommended. 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. Even as prescribed, there are numerous documented side effects associated with therapeutic doses of methamphetamine such anxiety, difficulty falling asleep, and reduced appetite among others.

3.2. Illicit use in humans

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 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).

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).

The average amount of methamphetamine taken during an illicit use event is estimated at 20-40 mg (Madden et al., 2004), which for a 70 kg female is equivalent to a dose of 0.29–.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 5 mg (0.07 mg/kg) (Acuff-Smith et al., 1996). Although it is unclear as to exactly how much methamphetamine is consumed by drug abusers, it has been reported that a typical daily dose for a novice user may range from 60 to 100 mg/day (0.86–1.4 mg/kg-day). Individuals who have developed a tolerance to methamphetamine based on extended drug abuse may have daily doses ranging from 5000 to 15,000 mg/day (71–214 mg/kg-day) (Acuff-Smith et al., 1996). Other reports suggest that substance dependent users may consume 700–1000 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.

3.3. Age-dependent susceptibility

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, 2006). 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.

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 10–12.5 mg have had peak blood levels of 20–30 ng/mL (INFOTEXT, 2004). Additionally, according to at least one website, a 10-fold difference in the estimated lethal dose of methamphetamine is identified (100 mg in children and 1 g (1000 mg) in adults) (SDRL, 2004).

3.4. Adverse health effects in experimental animals

Neurological, developmental and reproductive effects have been identified as the most sensitive endpoints from methamphetamine exposure (NIDA, 2002).

3.4.1. Neurotoxicity

It is thought that chronic exposure to methamphetamines may lead to irreversible damage of brain dopamine neurons. Repeated subcutaneous administration of methamphetamine to rats resulted in long-term depletions of both dopamine and serotonin in the rat brain (Ricaurte et al., 1980; Ricaurte et al., 1984). In Ricaurte et al. (1980), Sprague-Dawley rats were administered methamphetamine HCl subcutaneously at 0 (n = 13), 25 (n = 9), and 100 (n = 13) mg/kg-day. The brains were dissected into regions and analyzed for dopamine and serotonin levels. Statistically significant decreases in dopamine and serotonin were observed at 100 and 25 mg/kg-day, respectively. In Ricaurte et al. (1984), methamphetamine was administered continuously via the subcutaneous route to Sprague-Dawley rats by implanted osmotic mini-pumps. Dose levels were 0, 4, 8 and 16 mg/kg-day with six rats per group. The brains were dissected into regions, analyzed for dopamine and serotonin levels, and examined histologically for nerve fiber degeneration. Dopamine levels were significantly depleted in striatal region samples and histological studies indicated that this depletion is associated with striatal nerve fiber degeneration (Ricaurte et al., 1984). Reductions in brain dopamine and serotonin following administration of methamphetamine have also been observed in rhesus monkeys (Woolverton et al., 1989) and baboons (Villemagne et al., 1998). The effects observed in these studies and the dose levels at which they occurred are shown in Table 3. The Woolverton et al. (1989) study is not included in Table 3 because the dosing regimen was increased by 4–8 mg/kg/day every other day and it is not possible to determine the Lowest Observable Adverse Effect Level (LOAEL).

Methamphetamine exposure also has effects on brain development and behavior when exposure occurs postnatally. In Vorhees et al. (1994), Sprague-Dawley rats were injected subcutaneously with 30 mg/kg-day methamphetamine early in postnatal development (days 1–10), later (postnatal days 11–20), or with water during both of these periods. Because the brain matures on a different time scale in rats than in humans, in order to model human third-trimester drug exposure, treatment corresponding to the same events in the rat has to be administered during the neonatal period (Bayer et al., 1993). Dose groups ranged from 20 to 30 animals/group. Rats were tested for locomotor activity, spontaneous alternation, passive avoidance, and acoustic startle. Both early and later methamphetamine exposed rats exhibited significantly reduced locomotor activity from that of the controls. In a more recent study, Vorhees et al. (2000) injected rats subcutaneously with 40 mg/kg-day methamphetamine on postnatal days 11–20 and tested the rats for impairments of spatial learning and memory. Each treatment group, including the saline controls, consisted of fifteen litters with four males and four females per litter. Statistically significant spatial learning impairments, as evidenced by performance in the Morris water maze, and reduced memory performance on probe trials were observed in the treatment groups when compared to the controls. Williams et al. (2003) observed similar deficits in spatial learning and hypoactivity with rats injected subcutaneously with 20 mg/kg-day on postnatal days 11–20. Other systemic effects associated with methamphetamine exposure include decreases in body weight, retinal hemorrhage, and mortality (Gomes-DA-Silva et al., 1998; Ricaurte et al., 1980; Vorhees et al., 2000; Williams et al., 2003).

3.4.2. Developmental toxicity

Several developmental studies have been conducted with experimental animals exposed to methamphetamine. These studies are briefly summarized below and are listed in Table 3. Kasirsky and Tansy (1971) dosed 50 mice/group, intravenous, with 0, 5 or 10 mg/kg body weight/day with methamphetamine HCl for 3,4 or 7 days during gestational days 9–15. Maternal and fetal body weights were recorded and fetal mice were observed for gross anomalies. Maternal and fetal weights of the experimental animals were significantly lower than those of the controls for all dose groups. Significant increases in malformations (exencephaly, cleft palate, microphthalmia, anophthalmia, and cyclopia) occurred in fetuses from both the 5 and 10 mg/kg-day treatment groups on gestational days 9–15. 9–11, 9–12 and 12–15. In the Yamamoto et al. (1992) study, ICR mice were administered a single intraperitoneal dose at multiple dose levels on gestational day 8. The doses administered were 0 (n = 13), 11 (n = 10), 13 (n = 11), 14 (n = 10), 15 (n = 16), 17 (n = 19), 19 (n = 17) and 21 (n = 26) mg/kg/day. The fetuses were examined for
external malformations and evaluated for skeletal abnormalities. Skeletal malformations were observed as low as 14 mg/kg/day and external malformations were observed at 19 mg/kg/day. Martin (1975) administered 0, 1, 3, and 5 mg/kg of methamphetamine HCl twice per day (for a daily dose of 0, 2, 6, and 10 mg/kg-day) to Sprague–Dawley rats (6 per dose group) via subcutaneous injection on gestational days 1–21. Maternal measures included number of deliveries, weight gain, and gestation length. Offspring were evaluated for litter size, weight gain, developmental measures (e.g., eye opening) and behavioral measures (e.g., conditional avoidance response). Decreased litter size and delayed eye opening were observed as a function of dose with 2 mg/kg-day as the lowest observable effect level.

In the Cho et al. (1991) study, methamphetamine HCl was administered subcutaneously to Wistar rats (13–14 rats per dose group) at 0, 1, 2, 3, and 4.5 mg/kg for 14 days from days 7 to 20 of gestation. The dams were examined for health, mortality, and weight gain. The offspring were evaluated for weight gain, external anomalies, development of physical characteristics (e.g., incisor eruption, eye opening, and testicular descent) and functional reflexes (e.g., conditional avoidance response, spontaneous motor activity, and surface righting reflex). Statistically significant reductions in rate of offspring body weight gain and delayed testicular descent and incisor eruption were observed at 3 and 4.5 mg/kg-day. One study demonstrated that increases in stillbirths and postnatal mortality are greater with late (gestational days 13–18) versus mid- (gestational days 7–12) gestational exposures (Acuff-Smith et al., 1996). In this study, Sprague–Dawley rats (14–16 litters per dose group) were administered 0, 5, 10, 15, or 20 mg/kg methamphetamine by subcutaneous injection twice daily on either days 7–12 or days 13–18 of gestation. Daily doses would be 0, 10, 20, or 30 mg/kg-day. Assessment endpoints included ocular development, regional brain determinations of dopamine and serotonin, and tests of function including activity, reactivity, learning/memory, and activity with pharmacological challenges. Offspring treated early in gestation showed more alterations in behavior such as delayed development of early locomotion and memory impairment, whereas the late exposed group showed higher mortality, decreased litter sizes and reduced body weights. The observed LOAEL was 10 mg/kg-day.

### 3.4.3. Male reproductive toxicity

No adequate female reproductive toxicity studies were found, however, several male reproductive toxicity studies were conducted in rats, mice and rabbits (Saito et al., 1991; Yamamoto et al., 1999; Kasirsky and Tansy, 1971).
These studies are briefly summarized below and listed in Table 3. Saito et al. (1991) dosed male Wistar–Imamichi rats (six rats per group) with a single intraperitoneal dose of 0, 1, 2, or 4 mg/kg methamphetamine and tested copulatory behavior with a sexually receptive female. At 4 mg/kg–day, the number of mounts, intromissions, and ejaculations over a 90 minute period were significantly reduced compared to the control group. Yamamoto et al. (1999) administered a single ip dose of methamphetamine to 8-week-old male ICR mice as follows: 0 (n = 30), 3.75 (n = 20), 7.5 (n = 20) or 15 (n = 60) mg/kg-day. Twenty-four hours after the injection, the male mice were paired 1:1 with untreated female mice until a plug was detected or for 14 days. Assessment endpoints included litter size, weight gain of pups, external malformations, testicular and epididymal weights and histology, serum testosterone levels, and sperm motility and morphology. The number of vaginal plugs and births was significantly reduced in the females paired with male mice dosed at 15 mg/kg/day methamphetamine. Decreased sperm motility at 24 and 48 h after treatment was also observed at 15 mg/kg/day. Both Saito et al. (1991) and Yamamoto et al. (1999) were based on single intraperitoneal doses. Because of the limited duration of exposure, the full spectrum of reproductive effects may not have been exhibited.

Kasirsky and Tansy (1971) evaluated the offspring of six male New Zealand White rabbits injected intravenously with 0, 1.5, 3.0 and 5.0 mg/kg body weight/day methamphetamine for three months prior to mating. The males were then mated 1:1 with untreated females. The females were killed on gestational day 30 for examination of the fetuses. There were no significant effects on whole litter resorptions, offspring survival, malformations, or fetal weight at the dose levels tested.

### 3.5. Development of a reference value for methamphetamine

The intent of this effort is to compare the intakes expected from the range of proposed cleanup standards to a health-based reference value to determine if the proposed cleanup standards are adequately protective for children and adults. The studies described in the previous sections highlight the neurological, developmental and reproductive effects that are considered the most sensitive endpoints from methamphetamine exposure (NIDA, 2002). These studies, however, were conducted in laboratory animals using single or short term exposures. Using the NOAEL or LOAEL values from these studies as a reference value may not be protective of humans exposed in a home contaminated with methamphetamine residue. For this reason, we are using a process similar to the U.S. Environmental Protection Agency’s (USEPA) Reference Dose process to develop a health-based reference value for methamphetamine. It should be noted that this is not a Reference Dose for methamphetamine and should not be construed as such. The intent of this paper is to determine if the technology-based cleanup standards are above levels associated with the potential for adverse health effects.

The USEPA Reference Dose process is described in detail in IRIS (1993). 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.

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-than-life-time 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 toxicity studies summarized in Table 3 are shown graphically in Fig. 1. The lowest doses at which neurological, developmental, and reproductive effects occur are around 2–5 mg/kg/day (Villemagne et al., 1998; Martin, 1975; Cho et al., 1991; Kasirsky and Tansy, 1971; Saito et al., 1991). Each study has inherent strengths and limitations in study design, reporting results, etc. For example, several of the developmental studies (Martin, 1975; Yamamoto et al., 1992) administered methamphetamine by intraperitoneal or subcutaneous injection which is not considered a relevant route of exposure for humans. Humans typically administer methamphetamine via the oral or intravenous route with substance abuse. In cases where an individual occupies a property formally used to manufacture methamphetamine the primary routes of exposure are assumed to be oral and dermal. Methamphetamine is metabolized in the liver by aromatic hydroxylation, N-dealkylation and deamination (Caldwell et al., 1972). Generally speaking, toxicants administered by the intraperitoneal route are absorbed primarily through the portal circulation and must pass through the liver before reaching the systemic circulation (Casaret and Doull, 1993). Toxicants administered via the oral route also undergo a first-pass effect before reaching the systemic circulation. Based on this, it would be expected that methamphetamine administered via the intraperitoneal or oral routes would be less toxic than when injected via the intravenous or subcutaneous routes. There did not appear to be marked differences between the LOAELs discussed in Section 3.3 and shown in Table 3 by route of administration for the reproductive and developmental studies. It is unclear why this is, although studies have shown that metabolism of methamphetamine by hydroxylation produces the active metabolites norephedrine and 4-hydroxy-
norephedrine which have been implicated as false neurotransmitters and may account for some of the drug effects seen in chronic users (Caldwell et al., 1972). Therefore, rather than choose a single study we chose multiple studies as our critical/supporting studies based on the conclusions of the National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) Expert Panel Report on the Reproductive and Developmental Toxicity of Amphetamine and Methamphetamine (2005).

The NTP-CERHR report concluded that the data are insufficient to evaluate the reproductive toxicity of methamphetamine in animals; however, there was “sufficient evidence that methamphetamine produces developmental toxicity in animals” and “the experimental animal data are assumed relevant to humans”. The developmental toxicity studies described in Section 3.4 and listed in Table 3 were chosen as the critical and supporting studies. The LOAELs of these studies ranged from 2–14 mg/kg/day. The NTP-CERHR Expert Panel Report also developed BMDLs for several of these developmental studies. These BMDLs were calculated per EPA’s Reference Dose methodology and are described in NTP-CERHR report (2005). Table 4 shows the calculated BMD_{10} (the benchmark dose associated with a 10% effect) and the BMDL (the dose associated with the 95% confidence interval around the BMD_{10}) for the lowest observable effect level in each of the studies. The BMDLs ranged from 1.5 mg/kg-day for decreased fetal weight in the Kasirsky and Tansy study (1971) to 20 mg/kg-day for decreased litter size in the Acuff-Smith et al study (1996). Using these BMDLs ranging from 1.5 to 20 mg/kg-day we applied an uncertainty factor of 300. A factor of 10 was applied for interspecies variability because the critical studies are in experimental animals. A factor of 10 was applied for variations in susceptibility within the human population (interspecies variability). An additional factor of 3 was applied for database deficiencies, due to the lack of chronic studies and the uncertainty regarding adverse effects from long term exposures. Although this factor of three may not have been necessary based on the logic that the critical studies based on reproductive and development effects have identified the most sensitive endpoints in the most sensitive populations, the authors included this factor to account for the fact that an exhaustive literature search was not performed. No factors were applied for sub-chronic to chronic because the effects were observed in reproductive and developmental studies. No factor was applied for LOAEL to NOAEL because benchmark dose levels were calculated. Application of the UF’s to the BMDL’s results in a calculated reference value range of 0.005–0.07 mg/kg-day.

4. Comparison of exposures to health-based reference values

As discussed previously, the infant was determined to have the highest predicted exposure to residual methamphetamine on a body weight basis. Although the reference values were based on some endpoints that are not necessarily relevant to an infant, for simplicity the calculated daily intakes to this maximally exposed receptor from each of the proposed methamphetamine cleanup standards (0.05, 0.1, and 0.5 μg/100 cm²) are shown in Table 5 in comparison to the reference value range derived in the proceeding section. Each of the calculated intakes for the infant are well below the toxicity reference values, suggesting that all of the proposed cleanup standards would be protective of human health exposure. By analogy, the proposed
cleanup standards are also protective of the 6-year-old child and female of childbearing age.

A common criticism of extrapolating from animal studies to human exposures is that the doses used in the experimental animal studies are often unrealistic of those typically received by humans. The following calculations illustrate how untrue that criticism is for exposure to methamphetamine contaminated homes and how important remediation of these properties is. Martyny et al. (2003) reported surface methamphetamine concentrations up to 16,000 \( \mu g/sample \) at former drug laboratories. Based on a total of 97 samples collected at these locations, the average concentration was determined to be 499 \( \mu g/sample \). Whenever possible, the authors attempted to collect samples from areas of 100 cm\(^2\). When estimates of 499 \( \mu g/100 \text{ cm}^2 \) for average surface concentrations and 16,000 \( \mu g/100 \text{ cm}^2 \) for maximum surface concentrations at an unremediated property are entered into the exposure model developed above, the resulting dose to an infant is 0.38 and 12.2 mg/kg-day, respectively. By comparison, central nervous stimulation may occur at doses as low as 0.07 mg/kg, doses to a novice drug user have been reported to range from 0.86 to 1.4 mg/kg-day, and the LOAEls observed in the animal developmental studies ranged from 2 to 14 mg/kg-day. These numbers highlight the importance of remediation at former methamphetamine laboratories as the predicted exposures to an infant are well within the range where adverse health effects are observed in humans and laboratory animals.

### 5. Discussion and conclusions

The intent of this effort was to evaluate whether the proposed technology based cleanup standards of 0.5, 0.1, and 0.05 \( \mu g/100 \text{ cm}^2 \) for methamphetamine, would be protective of children and adults living in residences which were former drug laboratories. To date, no one has attempted to evaluate the potential health risks associated with the implementation of these standards. Using a model developed to assess the exposure dose correlated with a known wipe sample concentration, it was predicted that a 1-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 0.00002 to 0.0002 mg/kg-day depending on which cleanup standard was input to the exposure model.

A range of toxicity reference values were developed using developmental endpoints from the available literature and applying uncertainty factors to the lowest adverse effect levels observed in these studies. The resulting toxicity reference values ranged from 0.0005 to 0.07 mg/kg-day. These reference values were much larger than the calculated exposure doses for each of the proposed cleanup standards, suggesting that all of these standards would be protective of children and adults. On the basis of risk alone, any of the proposed cleanup standards would be adequate.

A second major factor in the selection of a methamphetamine cleanup standard for the state of Colorado was the cost and practicability of obtaining each of the technology-based levels. We spoke with several industrial hygienists and remediation contractors who had experience in cleaning up former methamphetamine labs. A dividing line between the proposed standards was clearly apparent. When cleaning
down to a level of 0.5 μg/100 cm², the contractor would remove all personal belongings, appliances, computers, stereo, upholstery, and carpets from the residences. As a general rule, it costs more to sample and clean these items than they are worth. These items are generally disposed of in a landfill because they are considered solid waste, not hazardous waste. The ceilings, walls, floor, and fixtures are cleaned with a water-soluble detergent. The air heating vents are cleaned with a HEPA vacuum system and water systems are flushed. Often times, the walls are painted or encapsulated to seal in residual contamination. Because methamphetamine labs are found in residences ranging from hotel rooms to single family homes, it is difficult to predict how much a typical remediation effort will cost. Estimates for a three bedroom home range from $10,000 to $15,000 for the cleanup effort alone, when the cleanup standard is 0.5 μg/100 cm². This does not include sampling costs or replacement costs of disposed items.

Cleanup standards of 0.01 and 0.05 μg/100 cm² are much more difficult to attain. The experts we spoke with felt that a detergent cleanup of the walls, floors, etc. and encapsulation with paint were not sufficient to meet these lower standards. Typically, building walls and building structures, such as kitchen cabinets and kitchen counters, would have to be demolished and then replaced. In some cases, it is more cost effective to demolish the entire residence, rather than demolish and rebuild the walls. Again, it is difficult to predict costs associated with attaining the 0.01 and 0.05 μg/100 cm² cleanup standards, but estimates for a three bedroom single family home ranged from $15,000–$20,000 up to $40,000–$60,000.

Whereas each of the proposed cleanup levels would have been protective of children and adults living in a former methamphetamine lab residence, the costs and difficulty associated with cleaning down to a 0.01 or 0.05 μg/100 cm² standard was significantly greater. In their final regulation (6 CCR 1014-3), the state of Colorado selected 0.5 μg/100 cm² as their final cleanup standard for methamphetamine residues.

References


USEPA/New York City Department of Health and Mental Hygiene, 2003. World Trade Center Indoor Environment Assessment: Selecting Contaminants of Potential Concern and Setting Health-based


