Review of Remediation Standards for Clandestine Methamphetamine Laboratories: Risk Assessment recommendations for a New Zealand Standard

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EXECUTIVE SUMMARY

This report provides a proposed standard for methamphetamine (MA) residues in remediated houses previously used as clandestine laboratories, based on a review of published and online literature, international health authority websites, reports, and journal articles relating to health effects and exposures to MA. Risk assessments forming the basis of MA cleanup standards from the Australian Government, the California Environmental Protection Agency, and the Colorado Department of Public Health were reviewed and compared. The California Reference Dose (RfD) of 0.3 µg/kg bw/day is based on a comprehensive review of the toxicological literature, uses human data, and is the preferred comparison value for a safe daily exposure. Exposure scenarios were reviewed that use United States Environmental Protection Agency and New Zealand-specific exposure parameters for a typical case and high, but plausible, exposures to children 1-2 years old, and to an adult woman. A study of a New Zealand epidemiological cohort suggests that foetal exposure to MA during the third trimester via placental transfer of a mother using MA is a critical exposure period that carries potential for long-term neurological effects. However, the MA doses received by both mother and foetus are high in such situations. In contrast, the exposure and risk assessment in this report shows that the estimated dose to a non-MA using woman (and by implication, her unborn baby) in a remediated home scenario, is orders of magnitude lower. The highest calculated exposures to MA are those experienced by children under 2 years of age, due to their frequent contact with household surfaces, their low body weight, and their hand-to-mouth behaviour. However, even these exposures, using conservative exposure assumptions, fall several orders of magnitude below prescribed therapeutic daily MA doses for children as young as 3 years of age. Using conservative assumptions, an MA surface concentration of 2.0 µg/100 cm^2 resulted in an exposure for young children equal to the California RfD. The estimated MA concentration to a woman of child bearing age to reach the RfD was 3.8 µg/100 cm^2. This calculation slightly exceeds the 2010 California MA standard of 1.5 µg/100 cm^2 and it is recommended that the value of 2.0 µg/100 cm^2 be adopted as the standard for maximum MA residue in remediated houses of former MA users in New Zealand. For former clandestine laboratories, the prospect of additional organic chemicals that are either undetected during cleanup operations, or that have uncharacterized toxicity, but possibly add to health risk, leads to a precautionary recommendation that the existing MA standard of 0.5 µg/100 cm^2 be retained as a conservative sentinel value as a cleanup standard.

It is further recommended that, in the case of clandestine laboratories, a survey of heavy metals, particularly mercury and lead, which can be present depending on the type of MA production method employed, should accompany cleanup efforts to ensure elevated concentrations of persistent highly toxic heavy metals are not present resulting from the clandestine laboratory materials. The cleanup standards for MA should not be used as a proxy/substitute for potential heavy metal contaminants.

1. INTRODUCTION

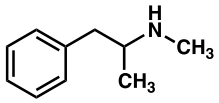
Methamphetamine (MA) is a drug used for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults. At higher doses of MA, a sense of euphoria is experienced, leading to the formation of addiction, with numerous accompanying health effects. MA itself is water soluble and of low volatility. The elimination half-life is about 24–30 hours in humans, but only about 70 minutes in rats (Table 1).

The production of MA in clandestine laboratories (clan labs) involves the use of chemicals and materials that can be acutely or chronically toxic, as well as explosive or corrosive. Clan labs are thus subject to a range of legislation and enforcement strategies designed to take action against the misuse of drugs and to minimise risks to the public. Particular concerns relate to children, who may incidentally contact these chemicals in current or former laboratories, or come into routine contact with chemical residues in homes previously occupied by MA users. (AIC 2007).

The New Zealand Ministry of Health, due to the rise in the number of clan labs between 2000 and 2009, recognised the growing potential risks to those living in a reoccupied house of being inadvertently exposed to chemical residues following remediation of a clan lab. The Ministry of Health published guidance material for cleanup of clan labs to help manage these risks (MoH 2010). Despite the increased prevalence of clan labs, at least one report found that the use of MA appears to have been on the decline since the early 2000's, with 1.4% of the surveyed population aged between 15 and 45 years in 2009 reporting MA use, down from 4.3% in 2006 (Wilkins and Sweetsur 2009).

A similar pattern for declining MA production and use is apparent in much of the United States. Statistics show a 23 percent decrease in clan lab incidents, falling from 12,049 in 2013 to 9,306 in 2014 (USDEA 2015). The number of clan labs across the United States has been steadily falling since 2010, when 15,217 incidents were recorded. An increasing rate of seizures of MA at the Mexican border suggests that as United States production has fallen, production and importation of illicit MA from Mexico has increased (Insight Crime 2016). Thus, while domestic MA production may be declining, illicit MA use remains a significant health problem.

Table 1: Methamphetamine and its properties

Name	Methamphetamine
Synonyms	*MA, meth, crystal meth, desoxyephedrine*
Structure	
CAS No.	537-46-2
Formula	$C_{10}H_{15}N$
Molecular Wt	149.2
Melting point	3 C
Vapor pressure (mm Hg)	0.14
Log K_{ow}*	2.07
Elimination half-life	5 – 30 hours (rodents << humans)

*Log K_{ow} = the logarithm of the octanol:water partition coefficient.

2. EXISTING CLANDESTINE LABORATORY GUIDELINES

2.1 ANALYTICAL VS HEALTH-BASED STANDARDS

In the United States in 2005, there was insufficient scientific evidence to develop a national health-based MA cleanup standard. As a result, many United States states adopted a standard of 0.1 µg/100cm², which was the laboratory detection limit (UDH 2015). This value was considered to be the lowest value that could be measured in a cleanup situation and became the *de facto* standard.

The problem presented by the adoption of an analytical instrument-based standard is that there is an implicit presumption that no measurable exposure is safe, such that exposures must, with increasing analytical precision, approach zero. This is illustrated by the ultra-low values used by the states of Oregon and Arkansas of 0.05 µg/100cm². However, it is worth noting that MA has many years of therapeutic application in children and adults for ADHD and other conditions. Furthermore, animal and human studies have demonstrated that thresholds for both toxicological and therapeutic effects exist with MA, and recent epidemiological studies of pregnant MA drug users/addicts found subtle long lasting neurological effects in their children, but only when exposed to very large doses (Smith et al 2015, Eze et al 2016). The spectrum of doses and effects of MA in these studies requires consideration in relation to the magnitude of exposures experienced by a non-MA user in a remediated house.

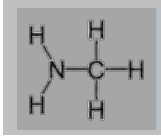
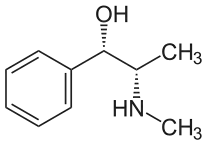
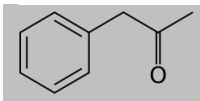
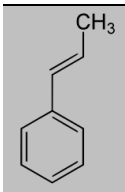
A goal of risk assessment is to define exposures at or below which no adverse effects are anticipated to occur in the vast majority of the population. Several United States (California, Colorado, and Utah) have used a risk assessment approach to develop cleanup standards and criteria for MA residues from clan labs (OEHHA 2009a, CDPHE 2009, UDH 2015). Only California and Colorado have explicitly described their risk assessment processes and assumptions in sufficient detail to enable scientific examination and review. Several differences in approach to such a risk assessment has been described by Kim (Kim 2016).

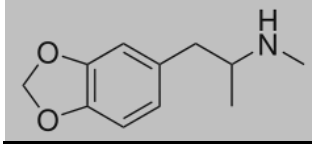
A complication of clan lab remediation assessment is that there are likely to be additional chemicals, either as reaction precursors or contaminants/by-products, that persist on surfaces or end up pooled in places in the house (Table 2). While ideally a detailed analysis and exposure/risk assessment should be carried out with each unique clan lab formulation and remediation, in practice this may not always be feasible. This raises the prospect of using a sentinel marker as a

way to characterise the safety of the house to be reoccupied. MA is an obvious choice of a sentinel marker, due to its prevalence on the household surfaces of clan labs, and its relative persistence on certain types of surfaces.

Table 2: Related chemicals, starting materials, and breakdown products from MA manufacture in clan labs or from MA use.

Chemical	Comments
Starting Materials for MA Production	
Ammonia (NH_4^+) **CAS No. 7664-41-7**	• Birch/Nazi method • Respiratory irritant, rapidly reacted or dissipated/mobilized in the environment.
Benzaldehyde **CAS No. 100-52-7**	• Starting material (P2P (phenyl-2-propanone) method)
Bromide **CAS No. 24959-67-9**	• Starting material – Red P method
Chloroform **CAS No. 67-66-3**	• Potentially all methods • Starting material/solvent
Dichloromethane **CAS No. 75-09-2**	• Potentially all methods • Starting material/solvent
Hydrogen chloride (HCl) **CAS No. 7647-01-0**	• All methods • Corrosive but not acutely toxic in trace amounts • Respiratory irritant • Exposures and health effects expected to be minimal
Iodine (I_2) **CAS No. 7553-56-2**	• Red P method • Stains sometimes seen in former labs • Airborne levels found very low • Exposures and health effects minimal
Lead acetate **CAS No. 301-04-2**	• Catalyst (P2P method)
Lithium **CAS No. 7439-93-2**	• Starting material (Nazi/Birch method)
Mercuric chloride **CAS No. 7487-94-7**	• Catalyst (P2P method)
Methanol **CAS No. 67-56-1**	• Solvent – potentially all methods

Chemical	Comments
Methylamine **CAS No. 74-8 9-5** 	• Starting material (older P2P method) • Volatile – not expected to persist • Low toxicity
Nitroethane **CAS No. 79-24-3**	• Starting material (P2P method)
Phosphorous **CAS No. 7723-14-0**	• Starting material (Red P method)
 **Pseudoephedrine** **CAS No. 90-82-4**	• Red P and Nazi/Birch methods • Starting material for MA production • Therapeutic doses[1] o 2-5 yr = 60 mg/day max o 6-12 yr = 120 mg/day max o 12+ yr = 240 mg/day max
 **P2P (phenyl acetone)** **CAS No. 103-79-7**	• Starting material (older P2P method) • Scarce toxicological information available
Sodium hydroxide **CAS No. 1310-73-2**	• pH adjustment – Red P method
Aromatic hydrocarbons (BTEX) **CAS Nos. 71-43-2, 108-88-3, 100-41-4, 1330-20-7**	• Cheap solvents – potentially found in all labs.
Breakdown Products of MA Use	
 **Trans phenylpropene (TPP)** **CAS No. 873-66-5**	• Break down product of MA when heated • Toxicology unknown • Chemically similar to styrene
By-Products of MA Production	
Phosphine **CAS No. 7803-51-2**	• By-product (Red P method) • There has been no detection of airborne phosphine in former clan labs • Volatile, reactive, and not expected to persist. Not expected to be

Chemical	Comments
	present in homes where MA was smoked. • 0.3 ppm 8 hr TWA – OSHA • 1 ppm 15 min - NIOSH
Related chemicals found in Some Clan Labs	
MDMA (3,4-methylenedioxymethamphetamine) **CAS No. 42542-10-09** 	• "Ecstasy" – a psychoactive hallucinogenic amphetamine derivative, not derived directly from MA. Distinct illicit drug - involves a distinct synthesis pathway.

Because remediated clan labs are not typically subject to a comprehensive analytical screen for metals, aromatics, or semi-volatile organics, this report is not able to present a typical chemical mixture scenario that would allow for a mixtures risk assessment that could be generally applied to remediated sites. Instead, those chemicals that have been reported to be used in MA production are listed in Table 3 and discussed as to their potential contribution to risk in a remediated house. Many of these chemicals have already been listed elsewhere and had their toxicological hazards and properties described in detail (ERS 2009).

2.2 NEW ZEALAND

A guidance document that provides extensive background information on MA clan lab cleanup in New Zealand, together with safety considerations during and post remediation, and roles and responsibilities of government and non-governmental entities was published in 2010 (MoH 2010). The NZ guidance document also describes the occurrence of chemicals with acute or chronic toxicity concerns that have been reported internationally to occur or are theoretically able to occur in clan labs and consequently to be potentially present post-remediation. While the 2010 New Zealand guidance document does not contain a risk assessment, the MA standard of 0.5 μg/100 cm^2, contained in the guidance, is based on a detailed risk assessment report by Environmental Risk Sciences in 2009 (ERS 2009).

New Zealand data indicate that the majority (62%) of clan labs investigated in 2008 were manufacturing MA. Red phosphorus methods were most common followed by clan labs using the Nazi/Birch method. Residential dwellings were most frequently used for clan lab activities, in particular rental properties (Fisher et al 2011, MoH 2010). This is similar to the situation in Australia

(below) for methamphetamine production processes and circumstances (Australian Government 2011).

2.3 AUSTRALIA

The Australian Government Department of the Attorney General published the *Clandestine Drug Laboratory Remediation Guidelines* in 2011 (Australian Government 2011). This document covers the assessment, remediation, validation and management of detected clan labs.

Australia adopted the 0.5 µg/100 cm^2 indoor surface MA residue cleanup standard, based on the risk assessment and review conducted by Environmental Risk Sciences (ERS 2009, Australian Government 2011). The scientific basis for the Australian standard is well described in the Environmental Risk Sciences report, using conservative calculations and assumptions. In addition to the standard for MA, the Environmental Risk Sciences report presented risk assessments for numerous chemicals likely to be found at former clan labs, and included discussion about cancer risk in addition to non-cancer risks (ERS, 2009).

As described in both the New Zealand and Australian guidelines, there is a wide range of chemicals and therefore contaminants associated with clan labs, depending on the illicit drug involved, the production process, and the improvised materials used. Over 100 different chemical recipes may be involved in illicit drug manufacture, resulting in a large number of possible chemical contaminants (ERS 2009, Table 2). Contaminants may include precursor chemicals, process support chemicals, illicit drug products or by-products, and chemical production wastes. The result of this complex landscape is that each remediated laboratory is likely to be somewhat unique. On the other hand, houses where MA was smoked but not produced are likely to have greater homogeneity in the spectrum of different chemical contaminants.

The main illicit drugs made in Australia include amphetamine-type stimulants (ATS), 3,4-methylenedioxymethylamphetamine (MDMA or ecstasy) and pseudoephedrine (PSE)/ ephedrine extraction (for ATS). ATS production primarily consists of methamphetamine, ie, meth, speed or ice, but also covers other drugs such as amphetamine, phenethylamines and MDMA (unless specifically excluded) (enHealth 2013).

2.4 USA

In the United States, national general guidance exists, but is not prescriptive as to the MA cleanup level (USEPA 2013, USDEA 2005). Numerous states have MA remediation standards. However, only two states, California and Colorado, have developed health risk-based MA surface concentrations for cleanup and re-occupation of clan labs (OEHHA 2009a, CDPHE 2005).

Although many other United States also have MA cleanup standards, these are based on analytical detection and reporting limits, and range from 0.05 to 0.5 µg/100 cm^2 (Table 3).

Table 3: Methamphetamine Surface Residue Decontamination Guidelines

Source	Surface Contamination (MA µg/100 cm^2)	Reference
Arkansas **Oregon**	0.05	Hammon and Griffin 2007
Alaska **Arizona**	0.1	Hammon and Griffin 2007
Serrano	0.2	Kate Serrano 2012 (presentation and recommendation)
New Zealand **Australia** **Colorado**	0.5	MoH 2010, Australian Government 2011, ERS 2009; CDPHE 2005
Utah	1.0	UDH 2015
California **Kansas** **Minnesota** **Virginia** **Washington** **Wyoming**	1.5	OEHHA 2009a, Salocks 2016

- AIHA presentation by Kate Serrano 2012. https://www.aiha.org/get-involved/VolunteerGroups/Documents/2012%20AIHce%20RT%20225_Serrano.pdf

2.4.1 California

The California Environmental Protection Agency (EPA) conducted a detailed risk assessment on MA residues and exposures from clan labs, considering two exposure models and using an RfD that was based on human data (OEHHA 2009b). Their risk assessment considered infants' and adults' exposures to MA, but did not consider the possibility of additional chemical precursors or breakdown products as contributors to a potential risk in remediated houses.

In their risk assessment on MA, the California EPA used two exposure models, developed by United States EPA to assess indoor exposure to pesticide residues (OEHHA 2010). The Standard Operating Procedures for Residential Exposure Assessments (SOPs, U.S. EPA 1997, 2001) is a deterministic model composed of three mathematical expressions for calculating estimates of exposure from dermal contact with residues on carpet or hard surfaces, and incidental ingestion resulting from hand-to-mouth transfer. The second approach, used the stochastic human exposure and dose simulation (SHEDS) model for multimedia, multipathway chemicals (SHEDS-Multimedia; U.S. EPA 2007). SHEDS-Multimedia uses probability distributions and Monte Carlo sampling to generate a distribution of exposure estimates for a population. SHEDS-Multimedia provides

estimates of exposure via hand contact with surfaces, body contact with surfaces, and incidental ingestion via hand-to-mouth and object-to-mouth transfer. With both models, dermal exposure and absorption was based on the results of studies conducted at University of California San Francisco showing that the efficiency of dermal absorption of MA is 57 percent.

Results from the two models were evaluated and compared, and the California EPA used the SHEDS-Multimedia as a basis for deriving its risk-based target cleanup standard for MA of 1.5 µg/100 cm^2.

The New Zealand Ministry of Health's guidance document from 2010 discusses several specific concerns about assumptions made in the California exposure/risk assessment:

"The total exposure to methamphetamine with a contaminated structure such as a house (comprising exposure to surface and airborne methamphetamine) may be much higher than that due to surface methamphetamine alone

The duration of exposure for vulnerable population groups such as children living in methamphetamine contaminated properties could be longer than Salocks (2009) suggests.

Children outside the age group range considered by Salocks (2009) as being the most vulnerable (6 – 24 months) could be exposed to problematic levels of methamphetamine "

The validity of these theoretical concerns has been considered. The first, that MA could become volatile if converted chemically to the free-base form, was considered by the Office of Environmental Health Hazard Assessment (OEHHA) to be unlikely, and even if possible, to present a negligible contribution to the overall exposure in comparison to dermal contact.

The second concern, that the duration of exposure may exceed the subchronic exposure duration used in the OEHHA 2010 assessment (and the RfD which is also based on several months exposure), would only apply if the vulnerable group (toddlers) remained constant in their exposure behaviours over a chronic timeframe, if their increasing body weights were not expected to reduce their daily doses, or if the effects of MA were known or suspected to be cumulative. A similar point exists for the third concern: that age groups outside the 6–24 month age group would be inadequately accounted for. The 6–24 month age group is a standard age group for risk assessment due to exploratory behaviour, hand-to-mouth tendencies, and lower body weights. All of these factors decrease in significance with age in their contribution to exposure, making this group the most exposed in a household surface contact/remediation scenario. Regarding the second concern, the observation that MA persists in building materials such that exposure is

prolonged after the surface is cleaned, must be balanced by the observation that, over time, surface residual levels of MA and other organics will slowly reduce, due to cleaning, touching, and volatilising. Thus, exposures decline over time following remediation. The exposure assessments assume, however, that residue levels do not decline, which essentially incorporates an additional margin of safety. This concern is further mitigated by the observation described by Martyny et al (2008), that, once cleaned, residues become less dislodgeable, thereby reducing the transferable quantity.

2.4.2 Colorado

The Colorado Department of Public Health and the Environment (CDPHE) was the first health authority to develop health-based MA cleanup guidelines for clan labs, in 2005 (CDPHE 2005). One goal of the CDPHE standard is to protect the occupants (mainly children) from residual chemicals left from the production of illicit drugs. In their risk assessment, CDPHE estimated exposures and risks for children 1 year old, 6 years old, and adult women of child bearing years (CDPHE 2005). An RfD was derived from a benchmark dose approach on reproductive and developmental toxicity data from mice and rats, of 4 µg/kg bw/day. A deterministic approach was taken, using parameters that were available at the time to support a standard of 0.5 µg/100 cm^2.

The CDPHE report states in its discussion of uncertainties:

"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."

3. CLAN LABS VS NON-LABORATORY REMEDIATED HOUSES

The deposition of MA itself on indoor surfaces, under experimental conditions, has been studied. A study by Serrano (2012) found MA residues on household surfaces to range from 0 to 35 μg/100 cm^2 from a simulated smoke, or from 41 to 101 μg/100 cm^2 from a simulated cook (Serrano 2012). These values, however, do not necessarily represent what would be expected to be present following a thorough cleanup/remediation of a former lab.

As has been discussed in this report and in the 2010 New Zealand Guidelines, clan labs can utilise a range of chemicals in the production of MA. Some of these chemicals are themselves amphetamine derivatives or other organics with pharmacological properties (Table 2). MA may also be smoked in these laboratories, yielding still further chemical breakdown products and forming reservoirs of potential chemical exposure. Shakleya et al (2005) reported trans-phenylpropene (TPP) to be a pyrolytic breakdown product from heated MA, and found TPP in the urine of MA users. Sanga and colleagues reported that TPP is converted by the liver to the oxide form by cytochrome P450 monoxygenase enzymes, with the oxide shown to be cytotoxic *in vitro* to glial cells (Sanga et al 2006). There is very little toxicological information directly relating to TPP that could be quantitatively used in a risk assessment. A structural similarity to styrene would suggest that the toxicity is likely to be low on a dose basis compared with MA itself or related amphetamines.

Other reported pyrolysis products of methamphetamine in tobacco tar were measured and identified as methamphetamine, amphetamine, phenylacetone, dimethylamphetamine, N-formyl-, N-acetyl-, N-propionyl-, and N-cyanomethyl-methamphetamine (Sekine and Nakahara 1987). It is not clear if these same residues are found on the remediated surfaces of houses where MA is smoked. The combusted derivatives of amphetamine may have less potency than MA itself, but there is no research to confirm this possibility.

However, most of these chemicals do not have well defined toxicological thresholds based on a robust data set. This creates an additional layer of uncertainty in the assessment of the safety of any given residence that was formerly used as a lab, when using MA residues alone as a cleanup standard. The presence of precursors, by-products, or contaminants in such situations is expected and can be highly variable in nature, depending on production method, use or production of other drugs and numerous additional factors.

Some of the chemicals encountered are noticeable through smell or visible stains, but may not necessarily be of the greatest concern toxicologically. For example, ammonia and iodine may be encountered from different production methods, but these chemicals, aside from imparting odours and stains, are not of great toxicological concern at doses likely to be encountered post-remediation. On the other hand, there has been at least one report of a significant quantity of mercuric chloride at a clan lab, not detectable through smell, but highly toxic (Megan McKinnel, ESR, 2016, personal communication). The 2010 Guidance document further describes lead acetate as a production chemical in some instances. However, lead has not been found at clan lab sites in New Zealand (Megan McKinnel, ESR, 2016, personal communication). Pseudoephedrine, melamine and phenyl-2-propanone (phenyl-acetone, P2P) are all organic chemicals involved in the production of MA, and may be present in a post-remediation house. Surface concentrations for cleanup from Australia and New Zealand Guidance documents are shown in Table 4.

Table 4: Chemical residues that may be found in former clan labs and New Zealand or Australian guideline surface concentrations for cleanup.

Chemical	New Zealand* Guidance (µg/100 cm^2)	Australia** Guidance (µg/100 cm^2)
Methamphetamine	0.5	0.5
Other amphetamines	--	1.0
MDMA	--	7
Pseudoephedrine	--	600
Trans-phenylpropene (TPP)	--	--
Phenyl-2-propanone (P2P)	--	--
Ammonia	--	--
Bromide	--	2000
Mercury	35	35
Lead	2	10***
Iodine	--	22
Phosphorous	--	0.07
N-Methylformamide	--	10
Methylamine	--	-- (v)
Nitroethane	--	-- (v)
Boron	--	1800
Lithium	--	46
Benzaldehyde	--	1500
Phosphine	--	-- (v)
Safrole	--	16

Chemical	New Zealand* Guidance (µg/100 cm^2)	Australia** Guidance (µg/100 cm^2)
Chloroform	--	-- (v)
Dichloromethane	--	-- (v)
Benzene	--	-- (v)
Toluene	--	-- (v)
Ethylbenzene	--	-- (v)
Xylene	--	-- (v)
pH	6 - 8	

NA = Not available. (v) = volatile

Sources:

* MoH 2010
** Australian Government 2001.
*** NSW 2015

The possible presence of mercury and lead from older production methods presents serious toxicological considerations that would not be adequately accounted for by utilizing an MA standard alone. These and other heavy metals that may be found at a given clan lab scene, should undergo their own separate assessment for safe re-occupation, using airborne (for mercury) and surface wipe samples (for mercury and lead). Mercury salts can persist in contaminated houses and become widespread and bioavailable through volatilization as well as through skin contact (Copan et al 2015). As shown in Table 4, surface standards are reported to exist in New Zealand for these metals, although their basis and review is beyond the scope of the current report.

To analytically capture each and every chemical residue in a given former clan lab and assess the unique combination in terms of a mixtures toxicity risk assessment would be extremely complex, time consuming and fraught with uncertainties. In the absence of such data, one practical alternative approach to addressing the added potential for toxicity of the various chemical residues that may be present in clan labs is to use MA as a sentinel marker, and to then employ a standard stricter than if MA alone were present. The Minnesota Department of Health (MDH 2013) describes the need to consider MA as a surrogate for the variety of other chemicals in a former laboratory setting as described below:

"Other meth lab chemicals are not persistent in the indoor environment and sampling for the purpose of characterizing the extent of contamination would not be productive. For example, volatile organic compounds (VOCs), which are used in most meth labs, dissipate rapidly after the cooking step and under normal ventilation.

Relatively few samples for meth are needed to provide a reasonable estimate of the overall contamination of a structure because meth becomes airborne and disperses throughout the structure in a widespread and contiguous pattern. Some meth lab chemicals, such as reagents (acids, bases, and solvents) used to drive the chemical reactions are not evenly dispersed in a building but are found in small, discrete 'puddles' in several areas of the property and may be easy to miss in cursory sampling."

A sentinel marker approach may, therefore be justified. However, it should be recognized that such an approach essentially amounts to an additional margin of safety due to unknowns and uncertainties. The potential or even likely presence of chemicals listed in Table 4 in a remediated clan lab, invokes a need to consider additional uncertainty and conservative assumptions.

Even though a sentinel marker approach may be justified for practical reasons, it should not replace the need to ensure that highly toxic and persistent materials were not also present in the former clan lab. In particular, because mercury has been found in at least one clan lab in New Zealand, and because other heavy metals may have been used for unknown reasons and not assessed, it is recommended that a heavy metals screen (notably mercury and lead) be conducted in the house (air and/or wipe samples) independently of the MA residues found.

4. RISK ASSESSMENT

4.1 HAZARD ASSESSMENT OF MA

A complete review of the toxicology of MA is not provided in this report. Some brief discussion is provided below with detail added on critical endpoints relevant to the risk assessment. Comprehensive reviews of MA toxicity are available in the OEHHA 2010, CDPHE 2005, ERS 2009 reports.

4.1.1 Acute Toxicity

Characteristic signs and symptoms of MA toxicity in humans include general sympathomimetic effects such as stimulation of the central nervous system (CNS), dyspnea (shortness of breath or laboured breathing), mydriasis (dilation of the pupils), hyperpyrexia (exceptionally high fever), diaphoresis (profuse perspiration) and anorexia (loss of appetite), and cardiovascular effects such as tachycardia (rapid heart rate), palpitations (irregular and/or forceful heart beats), and hypertension. Higher doses and/or repeated exposure can lead to cardiomyopathy, myocardial infarction, rhabdomyolysis (destruction of skeletal muscle cells), intracerebral bleeding and stroke, seizure and coma (NLM 2016). In a report of 18 cases of MA poisoning in pediatric patients the most common presenting symptom was agitation, and the most common presenting signs were tachycardia, inconsolable irritability and crying, and protracted vomiting (Kolecki 1998).

4.1.2 Carcinogenicity/Mutagenicity

MA is not considered by any authority to have mutagenic or carcinogenic properties (OEHHA 2010).

4.1.3 Developmental and Reproductive Toxicity

In 2005, the National Toxicology Program (NTP) [A division of the United States National Institute of Environmental Health Sciences; NIEHS] Center for the Evaluation of Risks to Human Reproduction (CERHR) conducted an evaluation of the potential for amphetamines (including MA) to induce adverse effects on reproduction and development in humans. For MA it was concluded that there was some concern for MA-induced adverse *developmental* effects in therapeutic and non-therapeutic settings for humans. This conclusion was based on evidence from inhalation studies in experimental animals that prenatal and postnatal exposures to methamphetamine could produce neurobehavioral alterations, small litter size, and low birth weight. However, there were no MA developmental toxicity studies in experimental animals completed using the oral route of exposure available for evaluation by the expert panel. This would be the primary route of exposure

for pregnant females in a remediated setting. There was insufficient hazard and or exposure data in laboratory animals to make a conclusion on *reproductive* effects.

Results from studies in humans suggest that MA may cause low birth weight and shortened gestation, but study confounders, such as possible multiple drug usage, have prevented definitive conclusions (NTP 2005). Levels of MA utilized under abusive circumstances are very high (50 – 200 mg/day) and exposure routes are of such a manner (inhalation/smoking, insufflation/snorting, and injection) as to rapidly result in high blood concentrations. The nature of exposure in a remediated setting is vastly different in route (primarily dermal) and the amount and frequency (low and slow) compared to the aforementioned conditions, and as such, the risk to foetuses and neonates in such circumstances are likely quite different. The NTP report concluded that there is insufficient evidence for a conclusion of the effects of MA on reproductive toxicity in humans.

Overall, it was noted that the quality of all the studies in both laboratory animals and humans prevented the NTP from making stronger conclusions about MA's potential to negatively impact reproduction. The United States Food and Drug Administration reproductive category for Desoxyn® (therapeutic MA) is, Category C, which states: "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks." (USFDA 2011).

In the years since the NTP review, a number of publications have emerged examining the effects on foetal neurodevelopment from exposures *in utero* to MA, from drug-using mothers. The Infant Development, Environment, and Lifestyle (IDEAL) study, which includes New Zealand children, examined the outcome of child growth and developmental findings from prenatal exposure to MA through drug-abusing mothers (Smith et al 2015). Control children included those exposed to a range of drugs *in utero* but not MA, and another set of controls included mothers who did not use drugs at all (Chakraborty et al 2015). Among the findings of the IDEAL study were increased neonatal stress correlating with MA metabolites in the meconium, and neurodevelopmental impairments observed at 1 year and beyond, up to 7.5 years of age at the time of this report (Smith et al 2015).

Derauf and colleagues, also using the IDEAL cohort, reported effects on poorer self-control in school age children born from heavy MA user mothers (Derauf et al 2012). Similar effects on early adverse events and aggressive behaviour were also found in prenatally MA-exposed children in a 7.5-year follow up to this study (Eze et al 2016).

Methamphetamine can readily cross the placenta, resulting in intrauterine exposure of foetuses (CDPHE 2005, Williams et al 2003). Studies on methamphetamine use during pregnancy have reported adverse effects including intrauterine growth retardation, prematurity, and perinatal complications (CDPHE 2005, Oro and Dixon 1987). The over-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, and mental retardation (Plessinger 1998). At birth, methamphetamine withdrawal symptoms may include abnormal sleep patterns, tremors, hypertonicity, a high-pitched cry, poor feeding patterns, sneezing, frantic sucking, and tachypnea (Smith et al 2003). In some cases, methamphetamine use during pregnancy has resulted in the death of the developing foetus (CDPHE 2005). Methamphetamine is also readily excreted in breast milk and nursing infants may be exposed as a result of maternal environmental exposure (CDPHE 2005).

Profound neurodevelopmental effects are also found in neonatal rats exposed to human therapeutic doses (McDonnell-Dowling et al 2014, NTP 2005). These relatively new findings indicate that scientists do not yet completely understand the dose-response relationship at low doses of MA to foetuses or early neonates. The database uncertainty factor of 3 employed by the California EPA was incorporated explicitly to acknowledge this data gap, and is completely justified.

Dose levels to the developing foetuses exposed during MA abuse by pregnant women in these clinical and epidemiological investigations are almost certainly substantially higher than any incidental dermal contact by a pregnant woman would cause. However, the lack of a known threshold dose for such effects, and the lasting developmental effects indicate that early exposures to MA, especially *in utero*, may be critically sensitive times for MA to exert toxicity. For this reason we modelled the exposure of both infants and women of child bearing age resident in a house that was either a former clan lab, or a home where MA was routinely smoked.

4.2 REFERENCE DOSE FOR MA

Methamphetamine, although a commonly abused pharmaceutical stimulant, has a history of legitimate medicinal end-uses for which it may be legally prescribed.

The establishment of an exposure or dose level of MA that would be unlikely to induce any detectable physiological effect is needed as a first step in understanding to what degree a former MA clan lab needs to be cleaned during remediation. This dose level is often referred to as a reference dose (RfD) or a health based exposure value (HBEV). Thus, as long as the potential

exposure dose from the remediated clan lab is less than the RfD/HBEV exposure level, the environment should be sufficiently clean and safe for occupancy.

As noted, MA is a drug which has governmental regulatory approval eg, the United States Food and Drug Administration for legitimate medicinal purposes in the treatment of ADHD and for obesity (Trade name: Desoxyn®). For treatment of ADHD it may be prescribed to children age six years and above starting out at 5 mg/day and increasing the dose to achieve the desired effect. This results in doses of 0.25–0.3 mg/kg per day for a six year old female based on the median (50%; 20 kg) to lower 10% (17 kg) percentile of body weight (CDC growth chart 2000, http://www.cdc.gov/growthcharts/data/set1clinical/cj41l022.pdf). Amphetamine, which is pharmacologically similar in its actions to MA (but considered to be less potent) is approved for use in children as young as three years of age.

Three recent comprehensive reviews of the effects of stimulants in children with ADHD have been conducted and were reviewed by OEHHA. While they do not specifically address the adverse effects of MA, these reviews provide detailed, authoritative summaries on the effects of drugs whose pharmacodynamics are similar to those of MA (eg, methylphenidate) or whose pharmacodynamics and chemical structure are similar to that of MA (eg, amphetamine). These reviews include a 1997 study by the American Medical Association's Council on Scientific Affairs that published a report on the diagnosis and treatment of ADHD in children and adolescents (Goldman et al 1997). A 1998 National Institutes of Health (NIH) Consensus Statement on the diagnosis and treatment of ADHD was prepared by a 13-member panel representing the fields of psychology, psychiatry, neurology, pediatrics, epidemiology, biostatistics and education. The panel developed its conclusions based on open forum presentations from 31 experts in the same fields and extensive review of the scientific literature. Two of the predefined questions the panel was tasked with addressing were*, "What are the effective treatments for ADHD?"* and *"What are the risks of the use of stimulant medication and other treatments?"* In addition, in 2001, the American Academy of Pediatrics (AAP 2001) issued a clinical practice guideline for treatment of children between 6 and 12 years of age with ADHD (This study was updated in 2005 by Brown et al). While toxicity endpoints were not the emphasis of their study they concluded that adverse effects, when manifested, are usually mild, of short duration, and controllable with adjustments in dose or the timing of dosing. The most common adverse effects are insomnia, decreased appetite, stomach ache, headache, and jitteriness. The significance of these studies relative to the establishment of an RfD/HBEV is that a physician may utilize such drugs at the therapeutic dose with an *a priori* assumption that the amount being administered is considered safe and without an overt concern for inducing significant toxicity or adverse effects of such a magnitude that the

therapeutic dose may be duly lowered. However, in the case of MA, while a risk/benefit decision may be taken in the context of a prescription medicine, there are no benefits to incidental contact with MA residues.

4.2.1 Reference Dose (RfD)/HBEV

The existing health-based MA surface safe reoccupation numbers were derived using varying approaches, but are derived by applying standard uncertainty or safety factors to the lowest observable dose level at which an undesirable effect occurs. Thus, the RfD is an exposure value at, or below, which it is unlikely that there will be induction of any adverse effect. Currently two such values have been established by United States governmental regulatory agencies (California – Office of Environmental Health Hazard Assessment (OEHHA), and the Colorado Department of Public Health (CDPHE) and are being utilized in the United States as the basis for setting a safe exposure level for remediation of clan labs (Table 5).

Table 5: Comparison of Reference Doses for MA Developed by the States of California and Colorado

Regulatory Agency	California – OEHHA*	Colorado DPHE**
Study Basis	Humans (adult pregnant women)	Laboratory Animals (developmental toxicity studies in rats)
Effects Dose	0.08 mg/kg-day (5 mg/day) • Lowest observed adverse effect level (LOAEL)	1.5 – 20 mg/kg-day • Calculated BMDL10
Effect	Reduced weight gain	Developmental changes in offspring
Uncertainty/Safety Factor	300 10X - Variation in susceptibility among the members of the human population 10X - Uncertainty in extrapolating from a LOAEL to a NOAEL 3X - Uncertainty associated with extrapolation when the database is incomplete	300 10X - Variation in susceptibility among the members of the human population 10X - Uncertainty in extrapolating animal data to humans 3X - Uncertainty associated with extrapolation when the database is incomplete
RfD/HBEV	0.3 µg/kg-day	5 – 70 µg/kg-day

* http://oehha.ca.gov/media/downloads/crnr/methrfdfinal022609.pdf
** CDPHE (2005)

As shown in Table 5, OEHHA utilized studies of the effects of MA in humans as the basis for setting their RfD value. In this context, OEHHA evaluated approximately 160 published research reports in the selection of a key study for establishing the RfD. In general, when data are available, use of human studies is preferred over the use of studies in laboratory animals. Human data remove the need for species extrapolation and use of humans allows for verbalization of minor subjective effects that may go unnoticed in an animal study.

The primary study used by OEHHA for development of an RfD for MA was a sub-chronic study of the drug's efficacy in reducing weight gain in women during pregnancy (Chapman 1961). While this study is old, it was a well-controlled double-blind study. It utilized a total of 84 pregnant women who were administered a sustained-release formulation of d-MA (Desoxyn® Gradumet®). The sustained release formulation best mimics the type of continuous exposure that would be expected to occur in a remediated residence. Patients were seen routinely every two weeks when subtle subjective symptoms of toxicity could be recorded. Each visit included an evaluation of blood pressure, heart rate, body weight, urinalysis, foetal size and uterine size. Blood counts were evaluated each trimester, and blood chemistry was tested at term. Three dose levels were tested over the duration of 15–16 weeks. Sub-chronic dosing with MA produced a dose-related decrease in weight gain over the course of pregnancy that was highly statistically significant upon reanalysis by OEHHA (no statistical analyses were conducted in the original report). Based on the results of this study, the critical effects of methamphetamine were identified as appetite suppression and consequent reduction in body weight gain, and the lowest observed adverse effect level (LOAEL) for methamphetamine was 0.08 mg/kg bw/day. While this physiological effect (weight loss) may not in all instances be considered "adverse", since this was the intended pharmacological outcome, it does demonstrate the onset of measureable biological effects in the pregnant mother, thus presumably also carrying potential for exposure affecting the physiology of the foetus.

The results of the Chapman study were corroborated in a smaller but similar study where pregnant women were given 10 mg/day of Desoxyn® Gradumet® for 15-16 weeks and gained significantly less weight than placebo controls (Bayly 1960).In addition, a study by Young and Turner (1965) assessed the efficacy of MA as an aid in the treatment of enuresis (bed wetting) in children. Most of the children in one treatment group of 110 children were given 5 mg of Methedrine (d-MA) each day just before bedtime. Sleep disturbance was experienced in 8 of the 110 children and the effect disappeared when the dose was reduced to 2.5 mg. These data suggest that the lowest observed adverse effect level (LOAEL) for MA in children was 5 mg (approximately 0.2 mg/kg bw/day), and that the no observed adverse effect level (NOAEL) was 2.5 mg (approximately 0.1 mg/kg bw/day).

This LOAEL dose of 0.2 mg/kg bw/day is similar to, but 2.5-fold higher than, the dose utilized by Chapman.

In assessing the relative sensitivities of adults and children with ADHD to stimulants, Dulcan (1997) suggested that adults are indeed more sensitive to both the therapeutic and side effects of these drugs. To help understand this observation, it is noted that, when normalized to body weight, children had significantly faster clearance rates of MA than adults, with a lower C_{max} (peak blood concentration of the drug) and AUC (area under the curve or the amount of drug absorbed) values than adults (FDA review 2001). Thus, the metabolism of MA is apparently much faster in children than adults. It is unknown if the same holds true regarding human foetal metabolism.

The dataset used by the CDPHE to derive their HBEV was derived from studies conducted in laboratory animals, where the objective was to identify the potential impact of MA on developmental and reproductive toxicity end points. While such data are valuable as this is a sensitive endpoint of concern, ie, developing foetuses, there are several reasons why use of human data may be preferred over that of data obtained using laboratory animals. Foremost among these is the large species-dependent disparity in sensitivity to the drug, with laboratory animals (particularly rats and mice) generally being much less sensitive to MA than humans. For example, in characterizing the cognitive effects of postnatal exposure to MA in mice, Acevedo et al (2007) utilized a daily dose of 5 mg/kg. In an adult human, this would be equivalent to a total dose of 300-350 mg, which would be potentially life-threatening. In addition, the pharmacokinetics of MA in laboratory animals and humans differ substantially. As Cho et al (2003) point out, the elimination half-life of MA is 70 minutes in rats and 12 hours in humans. Thus, these data alone support the use of the 10x safety factor to account for the extrapolation of toxicity data from the results of studies conducted in animals for use in the application to humans.

Uncertainty factors are a means of adding conservativeness to a dose based on various deficiencies in the studies and how they are interpreted. Uncertainty factors ranging from 1 to 10 are typically applied for the following rationale:

- Variation in susceptibility among the members of the human population
- Uncertainty in extrapolating animal data to humans
- Uncertainty in extrapolating from the results of a short-term study to long-term exposure
- Uncertainty in extrapolating from a LOAEL to a NOAEL
- Uncertainty associated with extrapolation when the database is incomplete

In both calculations, the regulatory agencies applied a combined safety factor of 300x to derive their health-based value. Both agencies applied a 10x factor for intraspecies differences, or susceptibility among the members of the human population, and they both also utilized a 3x factor for database insufficiencies. Colorado, however, used a benchmark dose level (BMDL) estimate as their toxicological point of departure. This is an estimated dose level that results from a statistical analysis of all the doses and responses in a study and represents an estimate of a specific response threshold. The BMD approach does not require an additional uncertainty factor adjustment to estimate a NOAEL. Accordingly, the CDPHE used an additional uncertainty factor of 10 to account for the use of laboratory animals *in lieu* of human data. While the RfD from OEHHA was based on human data, an extra safety factor of 10 was employed to approximate a NOAEL as the Chapman study only provided a LOAEL.

The State of Utah considered the above approaches from Colorado and California and chose to use a different (intermediate) RfD value of 1 µg/kg bw/day (Utah Department of Health 2016). The scientific basis for this value was not presented on the Utah website and is not further discussed in this report.

4.2.2 RfD Summary and Conclusions

Two different approaches were utilized in establishing a dose of MA that would be considered to represent the highest amount of material that could be ingested on a daily basis without significant concern that such an exposure would induce an adverse effect. Both methodologies utilized conservative assumptions to derive their values. The combined results lead to a range of RfD/HBEV values from 0.3 to 70 µg/kg-day. This 233-fold difference in RfDs is indicative of the level of uncertainty and variability using the available data, in this case, for risk assessment. While, on face value, any dose estimate within this range could be deemed to be safe, given the overall preference for using human data particularly when humans are known to be the more sensitive species, it is recommended that the value developed by the California OEHHA be adopted and used as the RfD (0.3 µg/kg bw/day).

This is the most conservative of the published RfD values and it was derived from data using the most sensitive species (adult humans), using a study that was conducted over a relatively long period of time (4 months). The MA formulated product in the key study by Chapman was a slow-releasing material that would also be better reflective of a continuous exposure in a remediated home. This value would also allow for the protection of developing human foetuses, as it is 16-fold lower than the lowest dose derived by the CDPHE (4–70 µg/kg/day), which was based on an oral

developmental toxicity data in laboratory rats. The California RfD was also used by Australia in their risk assessment (ERS 2009).

4.3 EXPOSURE ASSESSMENT

We assessed MA exposure to two groups in this risk assessment: adult women of child bearing age, and young children age 1–2 years. This is a similar approach to that used in previous MA risk assessments (ERS 2009; OEHHA 2010; CDPHE 2005). The different assumptions used by these various assessments were compared (see Appendix). Where possible we used published New Zealand-specific exposure parameters in place of default parameters from international sources (Cressey and Horn 2016). Due to the low volatility of MA, and absence of evidence of airborne MA in remediated houses, our assessment did not include inhalation as a significant route of exposure. This same assumption was also explored and used by the existing risk assessments by California, Colorado, and Australia reviewed in this report. Exposures from mouthed objects were considered to represent a negligible route of exposure in either remediated house scenario, as in the previously existing assessments. Details of exposure calculations and assumptions in this report are provided in the Appendix.

Scenarios representing the 1-2 year old toddler resulted in the highest estimates of exposure to MA, with the vast majority (85%) of exposure coming from direct dermal contact and absorption. We assumed no exposure from soft surfaces since carpeting is likely to be removed during remediation as described in the Appendix. Oral exposures from hand-to-mouth intake contributed 15% to exposure. For the adult woman scenario, dermal exposures were assumed to be 100% of the exposure route. At a modelled surface MA concentration of 0.1 μg/100 cm^2, the estimated total dose for a 1-2 year toddler was 0.021 μg/kg bw/day, while the estimated dose for the adult woman was 0.014 μg/kg bw/day.

Despite widely varying starting points for exposure and RfD from Colorado, Australia, and California, all estimates were within an order of magnitude. The present assessment aligned most closely with that of California, using current 2012 standard operating procedures (SOP) exposure values and parameters from Environmental Science and Research (Cressey and Horn 2016). The surface concentrations corresponding to the California RfD are 2.0 μg/100 cm^2 and 3.8 μg/100 cm^2 for 1-2 year olds and adult women, respectively. This calculated value is sufficiently different from the OEHHA recommended standard of 1.5 μg/100 cm^2 to justify departing from the California standard in this case.

The exposure assessments all assume that exposures will remain constant post-remediation, even though in the real situation, surface dislodgeable residue levels will almost certainly decrease with time.

5. PROPOSED MA STANDARD

5.1 REMEDIATED CLAN LABS

Based on our review of the hazards, exposures, and uncertainties inherent with remediated clan labs, the recommended New Zealand MA cleanup standard remains:

Methamphetamine standard (former labs): 0.5 µg/100 cm^2.

While the risk assessment of MA itself would support a 2.0 µg/100 cm^2, it is acknowledged that a former clan lab is likely to contain a wide variety of persistent toxicants that may be inadequately accounted for without a complete and costly analytical measurement and risk assessment of the remediated house. Thus a lower MA residue standard is proposed as a sentinel value for added precaution in such settings.

We recommend that mercury (Hg) and lead (Pb) be separately determined and remediated in former clan labs, as necessary, independent of this proposed standard.

5.2 REMEDIATED (NON-LAB) HOUSES OF MA USE

Based on the exposure and risk assessment of MA, including conservative assumptions on both hazard and exposure parameters, the proposed standard for MA, if carpeting is removed, is:

Methamphetamine standard (non-lab houses, without carpet): 2.0 µg/100 cm^2.

In case the carpeting is not removed in non-lab houses, the proposed standard for MA is:

Methamphetamine standard (non-lab houses, with carpet): 1.5 µg/100 cm^2.

6. DISCUSSION

We present an analysis of existing MA guidelines and standards internationally, with an examination of health-based MA cleanup standards from the California EPA (OEHHA 2010), the Colorado Department of Public Health and the Environment (CDPHE 2005), and an assessment from Australian researchers (ERS 2009). The risk assessment approaches from all three sources differ both in terms of determining an RfD and in the parameters and assumptions used in calculating exposures. We propose the adoption of the OEHHA 2010 RfD of 0.3 µg/kg bw/day as the dose against which exposure calculations are assessed. Our calculations, using conservative deterministic values and exposure parameters from New Zealand, show that dermal contact and absorption with MA in remediated houses for infants/toddlers is the most likely route of exposure, accounting for about 85% of estimated exposure, and support an MA standard of 2.0 µg/100 cm^2. This standard would apply to houses where MA was used, but not produced. The range of possible scenarios presented by a remediated clan lab further support a reduction in MA to serve as a sentinel for the potential for additional chemical exposures that may contribute to an additive exposure and effect. For former labs, we propose that the existing standard of 0.5 µg/100 cm^2 is retained.

It should be noted that these standards should be taken to be conservative guideline values, and not as definitive thresholds above which toxicological effects will definitely occur.

A recent publication by Van Dyke and colleagues (Van Dyke et al 2014) examined experimental and modelled dermal exposures to MA and concluded that 1.5 µg/100 cm^2 may not provide adequate protection against the California RfD in all instances. This group used cotton gloves to measure dermal transfer efficiencies, which they acknowledge are likely to overestimate the transfer of surface residues as compared with human skin. Furthermore, the direct application of their data (particularly transfer efficiency) in regard to their conclusion that a “clean” value of 1.5 µg /100 cm^2 can still lead to excessive exposure, ie, an exceedence of the RfD, is likely exaggerated. This is because transfer efficiency from a surface cleaned to 1.5 µg/100 cm^2 is likely to be less than estimated by Van Dyke. For example, it is noted by Martyny (2008) that once a surface has been cleaned with a solvent such as “simple green” (a common household cleaner) very little material remains readily dislodgeable. These authors noted that additional washings were not particularly effective in removing more material. Thus, once cleaned, the efficiency of transfer from surface-to-dermis is going to be significantly less than assessed by Van Dyke, who measured transfer efficiency using cotton gloves on a freshly contaminated surface. It is our view

that the study by Van Dyke does not provide sufficient cause for concern about the health protective nature of the California guidance value, but does illustrate the widely varying results one can generate using artificial experimental exposures and modelling assumptions.

OEHHA, using a highly complex probabilistic exposure model, determined that a surface concentration of 1.5 µg/100 cm^2 resulted in a 95th percentile estimate of total exposure at 0.278 µg/kg/day, just under the 0.3 µg/kg/day RfD. The dermal route of exposure to the body accounted for 80% of the total dose, whereas incidental ingestion via hand-to-mouth and dermal exposure via the hands accounted for about 10% each, respectively. Our exposure assessment (see Appendix) found similar results for the 1–2 year old age group, using conservative exposure parameters that approximate the 95th percentile. For adult women, a surface concentration of 3.8 µg/100 cm^2 results in an exposure at the OEHHA RfD.

For some perspective on the magnitude of the doses discussed in this report with doses resulting in known health effects, Table 6 below presents doses ranging from RfD to lethality.

Table 6: Calculated or reported doses of MA and relevant health effects

Exposure scenario	MA doses (µg/kg/day)	Effect
This report (6 mo – 2 yr)	0.3	Neurodevelopment
California (6 mo – 2 yr)	0.3	Neurodevelopment
ERS report (1-2 yr)	0.3	Neurodevelopment
Utah	1	Neurodevelopment
Colorado (6 mo – 2 yr)	4-70	Neurodevelopment
Chapman 1961 (pregnant women)	80	Weight loss
Therapeutic dose range	(~250 – 1000)	ADHD therapy
Drug abuse doses range	(~1400 – 16,700)	Abuse/Addiction
Lethal dose (humans)	3000	Sribanditmongkol 2000
Lethal dose (mice)	70,000	HSDB 2016

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APPENDIX

Evaluation of Post-Remediation Residential Methamphetamine Exposure for Purposes of Calculating Risk-Based Cleanup Levels

A.1 Introduction

Calculation of risk-based cleanup levels for residual methamphetamine in residences formerly used for clandestine drug synthesis requires (1) a reliable method for exposure concentration measurement (typically wipe samples reported drug mass per unit area), (2) robust estimates of dose for receptors of concern (young children and foetuses – ie, pregnant women), preferably generated in a well-documented and easy-to-use spreadsheet format, and (3) absorbed-dose toxicity criteria relevant to the exposure routes and receptor populations of interest.

The purpose of this document is to briefly review and evaluate these published approaches, and recommend an exposure methodology concordant with current regulation and knowledge. The deterministic method for methamphetamine exposure assessment suggested here is based on elements of the approaches taken by the United States states of California and Colorado, with reference to New Zealand exposure data and more recent literature as relevant.

A.2 Overview of California and Colorado methamphetamine exposure models

California's Office of Environmental Health Hazard Assessment (OEHHA) evaluated both the United States Environmental Protection Agency's (USEPA's) Standard Operating Procedures (SOP) for Residential Exposure Assessment (referred to herein as the 2001 SOP) (EPA 1997, 2001) (a deterministic model) and the Stochastic Human Exposure and Dose Simulation for multimedia (SHEDS-Multimedia version 3) (a probabilistic model) for estimating exposure (absorbed dose) of children aged 6 to 24 months to methamphetamine in remediated residences (OEHHA 2009a). Both models incorporate surface loading of methamphetamine, dermal transfer efficiency, dermal absorption, and exposure factors for frequency of contact with contaminated surfaces (including hand-to-mouth behaviours). Exposure via inhalation is considered to be negligible. Gastrointestinal (oral) absorption was assumed to be 100% in both models. Dermal absorption was assumed to be 100% in the 2001 SOP model, vs. a value of 57% (Salocks et al 2012, 2014) used in the SHEDS model. Hand-to-mouth contact frequency was set at 19.6 per hour in the SHEDS model

based on a metaanalysis of children's hand-to-mouth frequency data (Xue et al 2007). This study also forms the basis for the USEPA's recommended indoor hand-to-mouth frequency for children aged 1 to ≤ 2 years (USEPA 2011), which has been recommended for use by the Institute of Environmental Science and Research in New Zealand (Cressey and Horn 2016). OEHHA ran the 2001 SOP model with both the default hand-to-mouth contact frequency of 1.56 per hour and 19 per hour.

Methamphetamine exposures calculated by OEHHA using the two models for children aged 1 to ≤ 2 years in a residence with a methamphetamine surface concentration of 0.1 µg/100 cm^2 differed by two orders of magnitude (approximately 0.00002 mg/kg-d [95th percentile total absorbed dose] for SHEDS vs. 0.007 mg/kg-d for the 2001 SOP with the higher hand-to-mouth contact frequency). Further, the proportion of exposure contributed by the oral route was about three times higher in the 2001 SOP model. OEHHA noted that the SOP was labelled "DRAFT – DO NOT CITE OR QUOTE," and determined that the critical dermal exposure parameter dermal transfer coefficient for young children (6,000 cm^2/hr) was overestimated. A study to develop transfer coefficients for young children engaged in routine activities reported values ranging from 10 to 6,000 cm^2/hour (Cohen Hubal et al 2006). In view of these results, OEHHA (2009a) concluded that while "[t]he algorithms and default parameter values prescribed by the SOP appear to be appropriate for obtaining very conservative, screening level estimates of exposure," the SHEDS model provided a better exposure estimation tool. The SHEDS model was therefore run to calculate deposited residue concentration that yielded an absorbed dose equal to the OEHHA reference dose (RfD) of 0.0003 mg/kg-d. The deposited residue concentration of 1.5 µg/100 cm^2, which fell between the 95th and 99th percentile estimates of absorbed dose, was selected as the OEHHA cleanup standard.

The Colorado Department of Public Health and Environment (CDPHE) used 2001 SOP (EPA 1997, 2001) to calculate exposures to children and women associated with three technology-based methamphetamine cleanup levels used in the United States: 0.05 µg/100 cm^2, 0.1 µg/100 cm^2 and 0.5 µg/100 cm^2. Receptor groups were infants, young children, and women of childbearing age. Only hard surfaces were considered as potential exposure sources, as carpeting was assumed to have been removed and replaced during remediation. Gastrointestinal absorption was assumed to be 100%, and dermal absorption was estimated at 10% based on USEPA defaults for other compounds (USEPA 2004). Because all calculated exposures were below the range of selected toxicity criteria (0.005 to 0.07 mg/kg-d), the highest cleanup level was selected as it is more practical to implement

(Hammon and Griffin 2007). The calculated dose for 1 to ≤ 2-year old children presented by Hammon and Griffin (2007) assuming a surface methamphetamine concentration of 0.1 µg/100 cm^2 was around 0.00004 mg/kg-d. Exposure via dermal absorption was similar to that calculated with the SHEDS model, while oral exposure was an order of magnitude higher. Despite the significant differences in approach, it is noteworthy that CDPHE's overall results were within an order of magnitude (higher) of OHHEA's 95th percentile SHED output (Figure A1).

Major characteristics of the OEHHA and CDPHE methamphetamine exposure models are compared in Table A1

Table A1: Comparison of OEHHA and CDPHE approaches to calculating risk-based cleanup levels for methamphetamine

Characteristic	OEHHA	CDPHE
Model	SHEDS-Multimedia v 3	2001 SOP
Receptor ages	1 to ≤ 2 years	1 year 6 years Woman of child-bearing age
Exposure source	Hard floor Carpet	Hard floor (carpet assumed to have been removed in remediation)
Exposure route	• Ingestion due to hand-to-mouth activities • Ingestion due to object mouthing • Dermal contact (body) • Dermal contact (hands)	• Ingestion due to hand-to-mouth activities • Dermal contact
Oral absorption fraction	1	1
Dermal absorption fraction	0.57	0.1
Hand-to-mouth frequency (h^{-1})	19.6	9.5
Total dose (mg/kg-d) to infant at surface concentration of 0.1 µg/100 cm^2	0.00002	0.00004
Surface concentration corresponding to OEHHA RfD (0.0003 mg/kg-d) (µg/100 cm^2)	1.5	0.8

A.3 Suggested approach to characterizing post-remediation methamphetamine exposure in New Zealand

The flexible and powerful SHEDS-Multimedia model permits users to specify chemical- and scenario-specific parameter values and distributions as inputs, yielding a distribution of

potential exposures to receptors of concern. However, it requires SAS software and considerable expertise to run. For purposes of developing conservative (health-protective) cleanup criteria, the USEPA and other authorities typically rely on much simpler deterministic models such as the SOP that provide upper-bound but not unrealistic exposure estimates. While calculated exposures may represent only the higher percentiles of the exposed population, the models are straightforward to use (and modify), and provide confidence that exposure is not underestimated. Values for critical exposure parameters such as surface-to-skin transfer efficiency and dermal absorption fraction can be readily updated as scenario- and chemical-specific research data become available.

The overall methodology/algorithms in USEPA's Residential SOP were substantially revised and updated in 2012 to include the most reliable scientific data available. Data analyses were performed with more complete or appropriate statistical procedures, including distributional analyses to evaluate a more complete range of potential exposure parameter values. Use of the 2012 SOP results in lower dermal and oral exposure estimates than the 2001 version due to incorporation of a modified version of the algorithm utilized in the SHEDS model. This reflects a more realistic removal/replenishment mechanism between hand/object mouthing events, and establishes a maximum dermal hand loading. Of note is the fact that key parameters observed by OEHHA to be overestimated in the 2001 SOP available to them, dermal absorption and dermal transfer coefficient, have also been better defined.

A.3.1 Receptors and exposure pathways

To support calculation of a scientifically defensible risk-based surface cleanup criterion for methamphetamine, the 2012 SOP post-application indoor exposure scenario had been adapted to represent post-remediation conditions in residences formerly used as clan labs. Methamphetamine residues may be present on carpeted and hard surfaces, and exposure duration is expected to be chronic (greater than six months) (USEPA 2012). However, because current New Zealand Ministry of Health removal and remediation guidelines specify that carpeting and all other absorbent materials should be removed (MoH 2010), only hard surfaces are considered exposure sources. Receptors of concern are (1) young children aged 1 to ≤ 2 years (expected to be maximally exposed due to primarily indoor presence and high degree of hand-to-mouth contact) (USEPA 2005), and (2) women of child-bearing age (13 through 49 years) whose foetuses could be at risk.

Neither OEHHA nor CDPHE considered inhalation to be a significant exposure route for methamphetamine in remediated houses. Both adults and children may be exposed via

dermal contact and absorption. Young children may also receive oral exposures via mouthing of their hands and objects, but this exposure route is considered insignificant for adults and hence omitted from the model (USEPA 2012). Because potential exposure via object mouthing appears to be relatively small, and was not considered by CDPHE (Hammon and Griffin 2007) or discussed in detail by OEHHA (OEHHA 2009a), it is not included here.

A.3.2 Exposure equations

An electronic spreadsheet for calculating indoor exposures according to the 2012 SOP is available online.[1] The general equation used in this spreadsheet for exposure via dermal contact and absorption (assuming the same residue concentration on hard and soft surfaces) is:

$$\text{Dose}\left[\frac{\text{mg}}{\text{kg-day}}\right] = \frac{ABS_d \times TC \times 10^{-3}\frac{\text{mg}}{\mu\text{g}} \times DR \times FTSS_h \times ET_h}{BW} \quad \{1\}$$

where:

ABS_d	Dermal absorption fraction (unitless)
BW	Body weight (kg)
DR	Deposited residue (µg/cm^2)
ET_h	Time spent on hard surface (hr/day)
$FTSS_h$	Fraction transferred from hard surface to skin (unitless)
TC	Transfer coefficient (cm^2/hr)

The equation for exposure via ingestion due to hand-to-mouth contact is:

$$\text{Dose}\left[\frac{\text{mg}}{\text{kg-day}}\right] = \frac{ABS_o \times TC \times FH \times F_m \times SA_{hand} \times 10^{-3}\frac{\text{mg}}{\mu\text{g}} \times DR \times \left(1-\left(1-SE\right)^{\frac{Fr_{h-m}}{NR}}\right) \times FTSS_h \times ET \times NR_h}{SA_{hand} \times 2 \times BW} \quad \{2\}$$

where:

ABS_o	Oral absorption fraction (unitless)
BW	Body weight (kg)
DR	Deposited residue (µg/cm^2)
ET	Time spent on hard surface (hr)
ET_h	Time spent on hard surface (hr/day)
FH	Fraction on hands compared to entire body (unitless)
F_m	Fraction of hand surface area mouthed/event (unitless)
Fr_{h-m}	Frequency of hand-to-mouth contacts (events/hr)
$FTSS_h$	Fraction transferred from hard surface to skin (unitless)
NR	Number of replenishments per hour

[1] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

	NR_h	Number of replenishments on hard surface per day (ET_h x NR)
	SA_{hand}	Surface area of hand (cm^2)
	SE	Saliva extraction factor (unitless)
	TC	Transfer coefficient (cm^2/hr)

A.3.3 Exposure parameter values

Suggested parameter values were drawn from the 2012 SOP (USEPA 2012), the New Zealand Ministry of Health (Cressey and Horn 2016), OEHHA (2009a), and the scientific literature. As discussed previously, both OEHHA and CDPHE assumed 100% absorption of ingested methamphetamine. Studies with human volunteers have indicated oral bioavailability (absorption fraction) for methamphetamine hydrochloride of around 67% (Cook et al 1993). However, given the low concentrations of compound expected on remediated residential surfaces and the small proportion of total dose contributed by the oral route, the assumption of 100% oral bioavailability is retained here (Table A2).

Table A2: Exposure parameter values

Parameter (units)	Abbreviation	Value	Source
Body weight (kg)	BW	11 (child)[a] 69 (woman)[b]	Cressey and Horn 2016 USEPA 2012
Dermal absorption fraction (unitless)	ABS_d	0.57	OEHHA 2009a
Oral absorption fraction (unitless)	ABS_o	1	OEHHA 2009a
Fraction of hand surface area mouthed/event (unitless)	F_m	0.13	USEPA 2012
Fraction on hands compared to entire body (unitless)	FH	0.15	USEPA 2012
Fraction transferred from hard surface to skin (unitless)	$FTSS_h$	0.07	OEHHA 2009a
Frequency of hand-to-mouth contacts (events/hr)	Fr_{h-m}	20	Cressey and Horn 2016
Number of replenishments on hard surface per day (ET_h x NR)	NR_h	8	Calculated
Number of replenishments per hour	NR	4	USEPA 2012
Saliva extraction factor (unitless)	SE	0.48	USEPA 2012
Surface area of one hand (cm^2)	SA_{hand}	150	Cressey and Horn 2016
Time spent on hard surface (hr)	ET	2	USEPA 2012
Time spent on hard surface (hr/day)	ET_h	2	USEPA 2012
Transfer coefficient (cm^2/hr)	TC	1,800 (child) 6,800 (woman)	USEPA 2012

[a]Child age: 1 to ≤ 2 years
[b] Woman age: 13 to ≤ 49 years

Residue-to-skin transfer efficiency is dependent on the properties of the residue, the material with which it is associated, and the receptors' skin. USEPA (2012) uses a generic default value of 0.08 for fraction transferred from hard surfaces to skin ($FTSS_h$). The similar

value (0.07) chosen by OEHHA (2009a) for methamphetamine (based on limited available data with other chemicals) is considered more appropriate for use here. Van Dyke et al (2014) compared uptake of methamphetamine from drywall and linoleum by dry cotton gloves and gloves moistened with simulated saliva. Dry gloves picked up a geometric mean of 12%, while wet gloves picked up geometric means of 19% (drywall) to 27% (linoleum). These values are two to four times higher than OEHHA's recommendation. However, because cotton gloves overestimate dermal transfer by 2.5- to 5-fold (Davis et al 1983; Fenske et al 1999), this work supports the appropriate conservatism of a value of 0.07 for this parameter.

The output of these equations was compared with previous results by assuming a deposited residue concentration of 0.1 µg/100 cm^2. The total absorbed dose for children is 1.3E-05 mg/kg-d (dermal) + 1.7E-06 mg/kg-d (oral) = 1.5E-05 mg/kg-d – slightly lower than the 95th percentile calculated by OEHHA using the SHEDS model (which included carpet exposure), and almost three times lower than the total dose calculated by Hammon and Griffin (2007) using the 2001 SOP (Figure A1). For women, the absorbed dose is 8E-06 mg/kg-d (dermal route only, as adult hand-to-mouth activity is considered negligible [USEPA 2012]). As shown in Figure A2, this dose is slightly higher than that calculated by CDPHE, probably due to the higher dermal absorption fraction assumed.

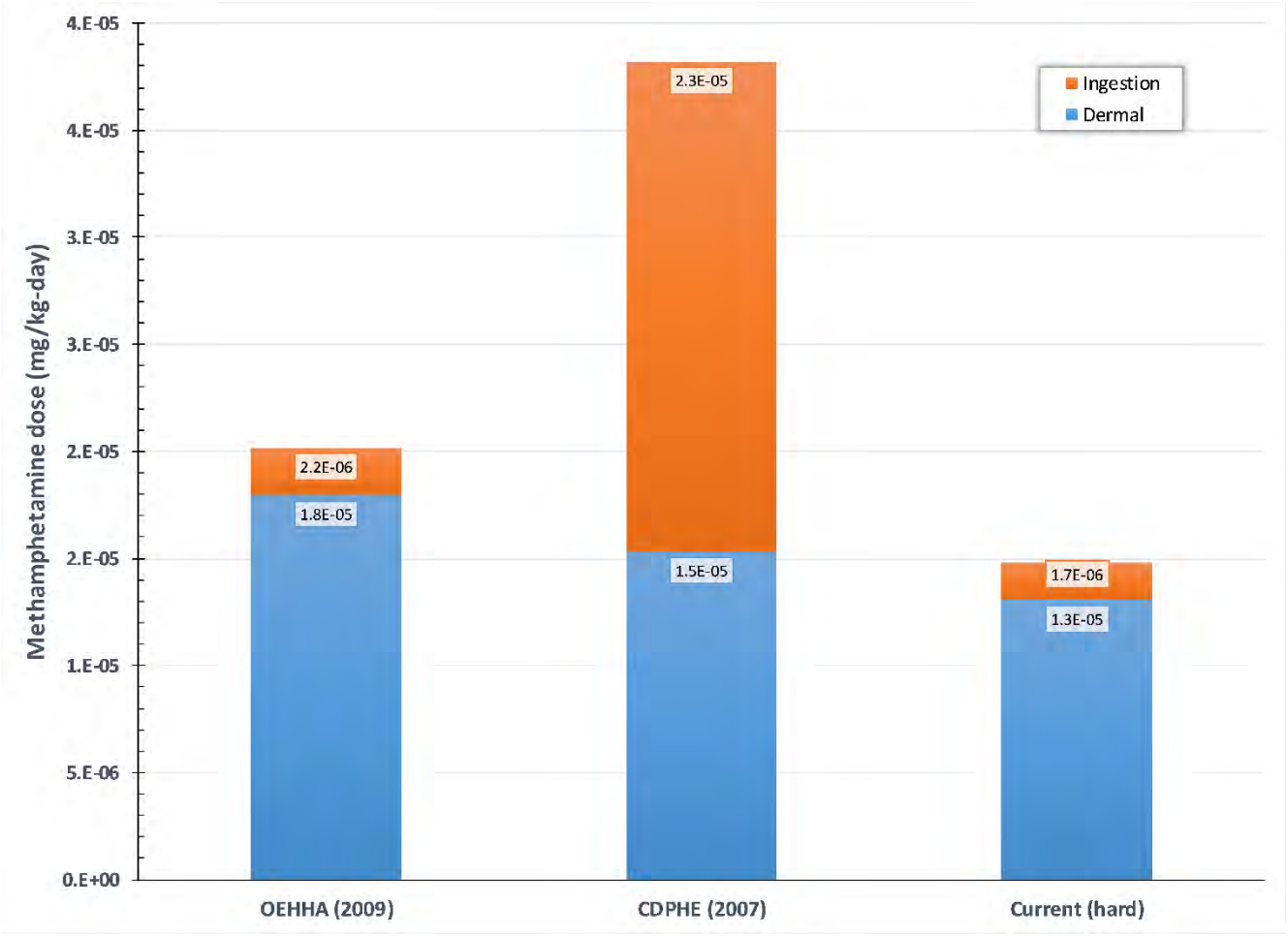

Figure A1. Comparison of methamphetamine doses calculated for 1 to ≤ 2-year old children assuming deposited residue = 0.1 µg/100 cm^2

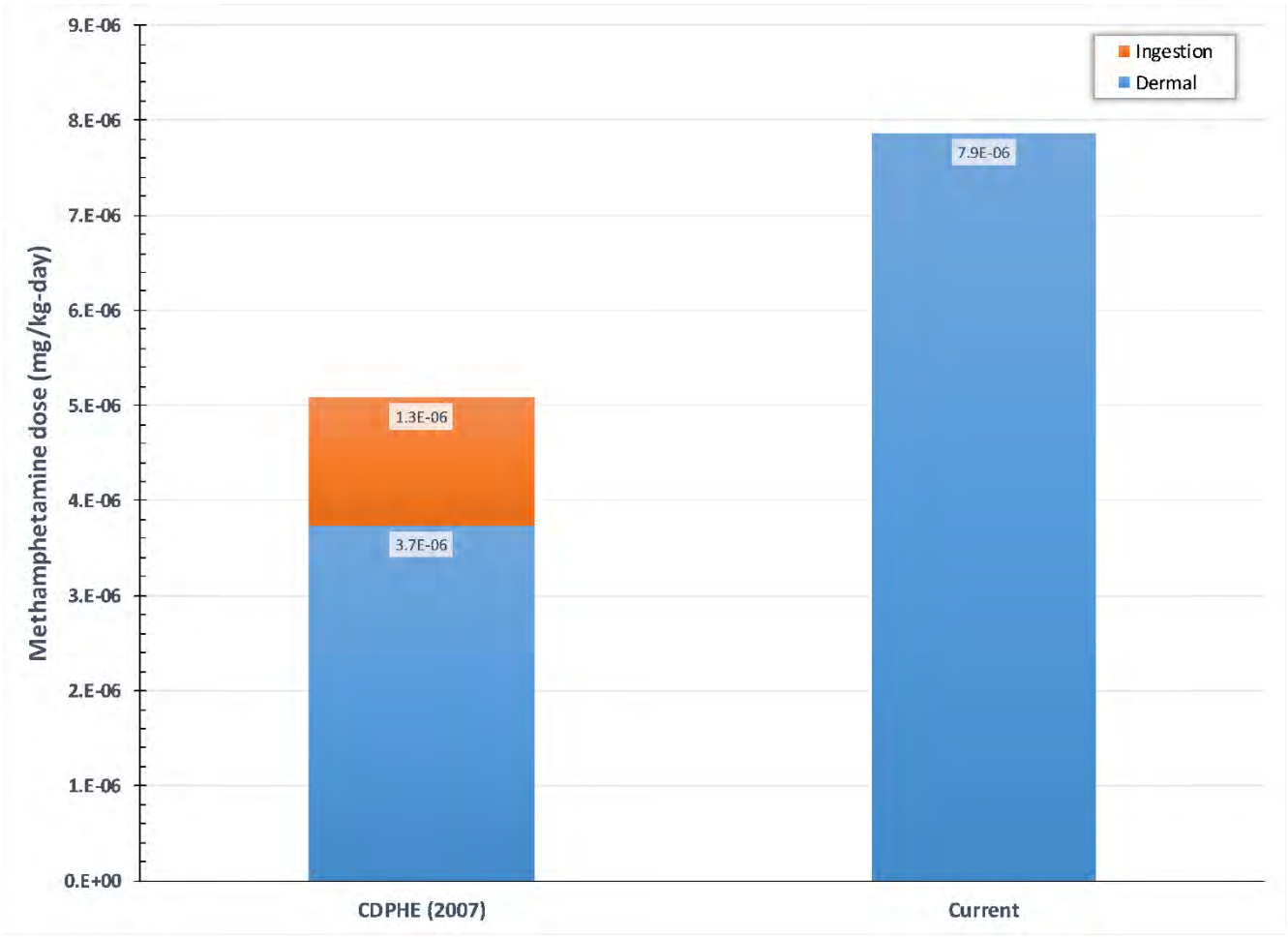

Figure A2. Comparison of methamphetamine doses calculated for women assuming deposited residue = 0.1 µg/100 cm^2. Calculation of risk-based methamphetamine surface cleanup levels

As mentioned previously, the oral bioavailability of methamphetamine hydrochloride has been reported to be around 67% (Cook et al 1993). It is not considered appropriate to adjust the RfD for methamphetamine developed by OEHHA (OEHHA 2009b) and used in this analysis (0.0003 mg/kg-d) with this factor, because it does not apply to the sustained release form of the drug (Desoxyn Gradumet) administered in the critical study (Chapman 1961). For purposes of this analysis, the administered RfD is assumed to be an absorbed RfD.

Setting dose equal to the RfD, surface cleanup levels can be calculated by rearranging equations {1} and {2} to solve for DR. For the dermal route,

$$\text{Cleanup}_{\text{dermal}}\left[\frac{\mu g}{cm^2}\right] = \frac{RfD \times BW}{ABS_d \times TC \times 10^{-3}\frac{mg}{\mu g} \times FTSS_h \times ET_h} \quad \{3\}$$

For ingestion,

$$Cleanup_{oral}\left[\frac{\mu g}{cm^2}\right] = \frac{RfD \times SA_{hand} \times 2 \times BW}{ABS_o \times TC \times FH \times F_m \times SA_{hand} \times 10^{-3}\frac{mg}{\mu g} \times \left(1-\left(1-SE\right)^{\frac{Fr_{h-m}}{NR}}\right) \times FTSS_h \times ET \times NR_h} \quad \{4\}$$

To calculate a cleanup level accounting for both exposure routes simultaneously,

$$Cleanup_{all}\left[\frac{\mu g}{cm^2}\right] = \frac{1}{\frac{1}{Cleanup_{dermal}} + \frac{1}{Cleanup_{oral}}} \quad \{5\}$$

Cleanup levels for children and women calculated according to these equations with the OEHHA RfD are presented in Table A3 in units of µg/100 cm^2. The cleanup level for children, 2 µg/100 cm^2, is marginally greater than the current OEHHA cleanup standard.

Table A3: Calculated cleanup levels for deposited methamphetamine residues based on OEHHA RfD (0.0003 mg/kg-d)

Exposure route	Cleanup level (µg/100 cm^2)	
	Child	**Woman**
Dermal	2.3	3.8
Oral	17.5	--
Both	2	3.8
-- = not calculated		

A.4 Conclusion

The SHEDS-Multimedia model is clearly a powerful tool for complete characterization of exposure distributions (dependent upon quality of inputs). However, it is neither readily accessible nor easy to manipulate. Indeed, it was not possible to run the current version of the SHEDS model within the timeframe of this project.

Use of current SOP equations with appropriate parameter values provides conservative but reasonable exposure levels, and can be readily modified by users to reflect different exposure conditions, assumptions, and parameter values. The fact that application of the simple methamphetamine exposure model described in this document results in exposure estimates similar to upper-bound (95th percentile) estimates derived using SHEDS demonstrates its conservatism and appropriateness for the purpose. A study of New Zealand (Auckland area) residences used as clandestine laboratories showed little change in surface methamphetamine concentrations before and after remediation. The fact that

most concentrations remained above the current New Zealand standard of 0.5 µg/100 cm^2 (McKenzie 2014) indicates the practical difficulty of achieving such a low level. The revised cleanup standard calculated in this document, 2 µg/100 cm^2, is around twice the median level of methamphetamine measured in the houses post-remediation (McKenzie 2014), suggesting that while health-protective, it may be more practicable. Both standards are compared with the range of post-remediation concentrations in Figure A3.

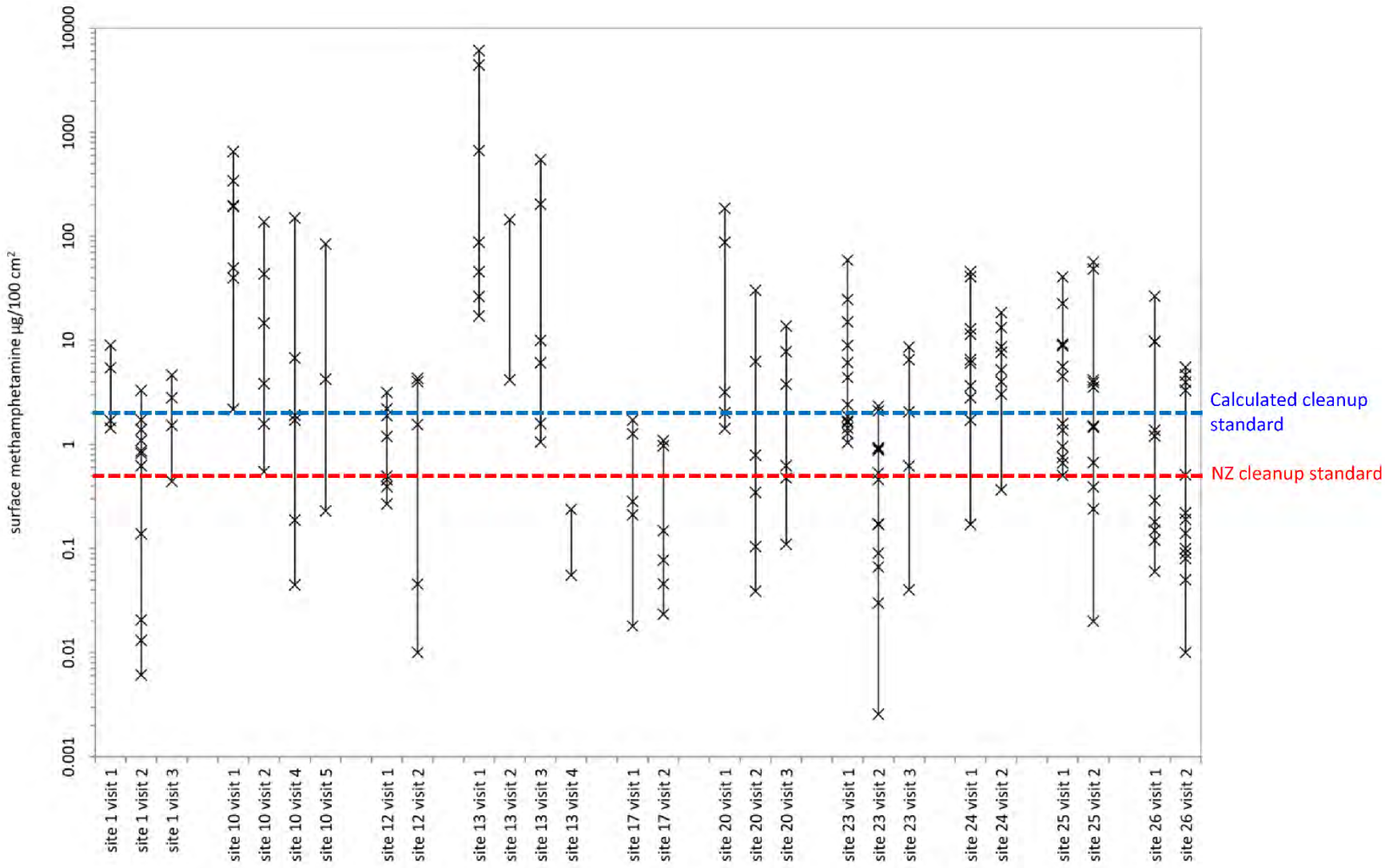

Figure A3. Comparison of surface wipe concentrations in remediated clandestine methamphetamine laboratories with the New Zealand cleanup standard and the cleanup level calculated in this document (base figure from McKenzie 2014)

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