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METHAMPHETAMINE CONTAMINATION IN RESIDENTIAL ENVIRONMENTS: ANALYSIS OF EVIDENCE RELATED TO HUMAN HEALTH EFFECTS

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ACRONYMS AND ABBREVIATIONS

AF	Assessment factor
ADHD	Attention deficit hyperactivity disorder
BDNF	Brain-derived neurotrophic factor
$BMDL_{10}$	Lower 95th percentile confidence limit for a benchmark dose equated to a 10% increase in response, over baseline
bw	Body weight
CalEPA	California Environmental Protection Agency
CHAD	Consolidated human activity database
CNS	Central nervous system
ECHA	European Chemicals Agency
ELISA	Enzyme-linked immunosorbent assay
GC-MS	Gas chromatography-mass spectrometry
HBGV	Health-based guidance value
HSEES	United States Hazardous Substances Emergency Events Surveillance
HUD	Ministry of Housing and Urban Development
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOAEL	Lowest observed adverse effect level
NMDA	N-methyl-D-aspartic acid
NOAEL	No observed adverse effect level
PMCSA	Prime Minister's Chief Science Advisor
POD	Point of departure
PPE	Personal protective equipment
RfD	Reference dose
ROS	Reactive oxygen species
SOP	Standard operating procedure
USEPA	United States Environmental Protection Agency

EXECUTIVE SUMMARY

Residential environments may become contaminated by the illicit drug, methamphetamine, due to the use of the premises for the synthesis of methamphetamine (clandestine laboratories) or due to the use of methamphetamine by occupants of the premises. Residues of methamphetamine, precursor chemicals and processing chemicals may persist and constitute a health hazard to subsequent residents of the premises.

The Ministry of Housing and Urban Development (HUD) have legal obligations in relation to the built residential environment. HUD is developing regulations under section 138C of the Residential Tenancies Act 1986, with a primary objective of minimising the health impacts of methamphetamine contamination and requested advice from ESR in relation to potential adverse human health effects from third-hand[1] exposure to methamphetamine.

HUD's request for advice from ESR was captured in a series of questions. The following text addresses these questions in the context of the analysis and review provided in the current report.

Can ESR provide brief evidence to the effect that methamphetamine residue may be harmful to health, in the context of residential accommodation?

While the study of Wright et al. (2020) has many shortcomings, it is likely to be the best evidence of adverse effects due to third-hand methamphetamine exposure that can be ethically obtained. The symptoms reported by residents of methamphetamine-contaminated premises are reasonably consistent with symptoms reported by responders exposed in clandestine laboratories. The symptoms are also reasonably consistent with methamphetamine's known mechanism of action.

Reported symptoms are mainly related to local effects on the skin, eyes or respiratory tract or systemic neurological effects (i.e. effects mediated by the central nervous system). All effects appear to be reversible.

Does ESR recommend that HUD prescribe maximum acceptable levels of contamination, or a means of calculating maximum acceptable levels?

While the study of Wright et al. (2020) did not identify a clear biological gradient for adverse effects associated with methamphetamine exposure, principles of toxicology require such a gradient. A biological gradient means that with increasing exposure, either the probability and/or the severity of adverse health effects will increase. This further suggests that there will be a level of methamphetamine contamination that results in unacceptable risks of adverse effects and some mechanism is required to protect residents of methamphetamine-contaminated premises from unacceptable levels of risk.

What does ESR recommend that those maximum acceptable levels, or means of calculating those levels, should be? (noting that "levels" includes the potential for setting ranges of methamphetamine contamination)

[1] Third-hand exposure is defined as unintended exposure to residues remaining from the manufacture or use of methamphetamine

Section 2 of this report discusses the derivation of the reference dose (RfD) that was used as the basis for the original ESR risk assessment (Fowles *et al.*, 2016) and a less conservative revised RfD, based on a reconsideration of the uncertainty factors used in the RfD derivation. The revised RfD is 10-fold higher than the California Environmental Protection Agency RfD and would support a 10-fold higher limit for methamphetamine surface contamination. The higher surface contamination limit is co-incidentally the same as the value proposed in the Prime Minister's Chief Science Advisor report (Bardsley and Low, 2018).

As an in-detail assessment of the exposure model used for the ESR risk assessment suggests that the model is neither overly or insufficiently conservative, a maximum mean surface contamination concentration below 15 μg/100 cm^2 will be associated with a very low probability of harm, although such residues should still be viewed as undesirable. Given the relatively mild and reversible nature of the adverse health effects described by Wright et al. (2020) and in the pivotal toxicological studies used as a basis for RfD derivation, ESR considers that a mean surface contamination concentration of 15 μg/100 cm^2 should be viewed as a guideline level. Analytical results above this level should be considered along with information on the possible use of the premise for methamphetamine production, the presence of sensitive individuals (pregnant women, infants) in the household and reports of adverse health effects amongst residents of the premises.

What are the options for presentation of maximum acceptable levels, or means of calculating those levels, taking into account the potential for new scientific evidence on health risks?

Any health-based guidance value (exposure limit), or concentration limit based on a health-based guidance value should be qualified as being derived on the basis of currently available information. If significant new information becomes available, it should be considered and weighted as to its relevance for revision of the existing limits.

What is international best practice in setting exposure limits?

Procedures for deriving exposure limits are not uniform across organisations and it is not unusual for different organisations to derive different exposure limits from the same toxicological data. These differences are usually due to the application of more or less conservative uncertainty factors.

Does ESR recommend a "bright line" approach to a maximum inhabitable level, or a different approach?

What does ESR recommend as a maximum inhabitable level, above which a tenancy should be terminated due to the health risk?

How does ESR recommend that a maximum inhabitable level should be applied in practice, particularly where that level is present in only part of the premises?

ESR does not consider that there is sufficient evidence to define a maximum inhabitable level for methamphetamine. No evidence is available of severe health effects associated with third-hand methamphetamine exposure.

1. INTRODUCTION

Residential environments may become contaminated by the illicit drug, methamphetamine, due to the use of the premises for the synthesis of methamphetamine (clandestine laboratories) or due to the use of methamphetamine by occupants of the premises. Residues of methamphetamine, precursor chemicals and processing chemicals may persist and constitute a health hazard to subsequent residents of the premises. This is termed third-hand exposure; unintended exposure to residues remaining from the manufacture or use of methamphetamine.

People may be exposed to a range of chemical hazards in the residential environment, including residues from tobacco smoking, metabolites of moulds, residues from building and decorating materials (asbestos and lead) and household chemicals. It is not currently possible to say what the public health risks of exposure to methamphetamine are, relative to exposure to other chemicals.

1.1 BACKGROUND

In 2017, Standards New Zealand published *NZS 8510:2017 Testing and decontamination of methamphetamine-contaminated properties*. Section 2.1.2 of the Standard specifies that:

> "Individual high-use areas of a property that have been tested according to methods in this standard and shown to have methamphetamine present at levels exceeding 1.5 μg/cm^2 shall be regarded as contaminated. These areas shall be decontaminated by cleaning or removing contaminated materials, or both, and tested to verify that decontamination has been effective."

Under this interpretation, the limit (1.5 μg/cm^2) is viewed as a 'trigger' for remediation, with any concentration above the limit requiring remediation.

The limit value for methamphetamine contamination of 1.5 μg/cm^2 was informed by a risk assessment commissioned by the Ministry of Health (Fowles *et al.*, 2016). The risk assessment proposed a slightly higher limit (2.0 μg/cm^2) and stated that the limit represented "a proposed standard for methamphetamine (MA) residues in remediated houses", that is, a level of contamination for remediation to achieve, rather than a level of contamination above which remediation should be initiated.

In 2018, the Office of the Prime Minister's Chief Science Advisor (PMCSA) published a report, *Methamphetamine contamination in residential properties: Exposure, risk levels, and interpretation of standards* (Bardsley and Low, 2018). The report concluded that:

> "….methamphetamine levels that exceed the NZS 8510:2017 clean-up standard of 1.5 μg/100 cm^2 should not be regarded as signalling a health risk. Indeed, exposure to methamphetamine levels below 15 μg/100 cm^2 would be highly unlikely to give rise to any adverse effects."

Based on this report, some have interpreted the higher figure (15 μg/100 cm^2) as a trigger for remediation of methamphetamine-contaminated residential environments.

1.2 RISK ASSESSMENT APPROACH

The risk assessment approach adopted by Fowles *et al.* (2016) and others includes three main components:

- A proposed level of surface contamination in a methamphetamine-affected environment;
- An exposure model, to represent physical characteristics and human activities, to translate a surface contamination concentration into an exposure dose; and
- A health-based guidance value (HBGV); an exposure dose below which there is a very low probability of adverse health effects.

Both the exposure model and the HBGV include aspects of expert judgement and assumptions in their derivation.

1.3 THE CURRENT PROJECT

The Ministry of Housing and Urban Development (HUD) have legal obligations in relation to the built residential environment, including under section 138C of the Residential Tenancies Act 1986:

138C Regulations in respect of contaminants and contaminated premises

(1) The Governor-General may, by Order in Council made on the recommendation of the Minister, make regulations prescribing substances, or classes of substances, as contaminants for the purposes of this Act.
(2) Before making a recommendation for the purposes of subsection (1), the Minister must be satisfied that the substance may be harmful to the health of persons.
(3) The Governor-General may, by Order in Council, make regulations for all or any of the following purposes:
(a) prescribing maximum acceptable levels, or a means of calculating maximum acceptable levels, of contaminants for premises for the purposes of the definition of contaminated:
(b) prescribing maximum inhabitable levels of contaminants for premises for the purpose of section 59B.

HUD is developing regulations under section 138C of the Residential Tenancies Act 1986, with a primary objective of minimising the health impacts of methamphetamine contamination. The regulations also seek to:

- provide certainty to tenants and landlords about their rights and responsibilities around methamphetamine contamination
- provide clear rules and processes for testing for methamphetamine contamination, and decontamination
- support professional behaviours and standards in the testing and decontamination industry
- ensure that the costs of testing and decontamination are well managed.

The current project is intended to provide evidence to support these activities and specifically:

- Assess the exposure model and the basis for the HBGV used in the New Zealand risk assessment, to determine if the degree of conservatism included is commensurate with the risks due to methamphetamine contamination; and
- Review literature that has been published since the 2016 risk assessment was carried out to determine if there is any novel information that can further inform the risks from methamphetamine exposure.

2. METHAMPHETAMINE REFERENCE DOSE (RFD) CONSIDERATIONS

The ESR 2016 methamphetamine report uses a published and peer-reviewed RfD developed by the California Environmental Protection Agency (CalEPA) for methamphetamine of 0.3 μg/kg bw/day (Fowles *et al.*, 2016; Salocks, 2009). Alternative RfDs, derived by the state of Colorado, based on neurological development in rodents, were in the range 5-70 μg/kg/day (Fowles *et al.*, 2016; Hammon and Griffin, 2007) (Table 1). The highly disparate bases of the two RfDs were discussed in the ESR report, and further considered in light of the standard default 300-fold cumulative uncertainty factors used in their derivations (Bardsley and Low, 2018; Kuhn *et al.*, 2019).

A critical issue in deriving reference doses for methamphetamine is the well documented vast differences in metabolism kinetics between humans and rodents. The drug is much more rapidly cleared by rodents and humans are more susceptible to effects of low, daily, additive chronic doses. Doses administered to rodents in experimental studies often approach equivalent lethal doses in humans, on a body weight basis.

Ordinarily, such differences in metabolism are taken into consideration as toxicokinetic (metabolism, distribution, and clearance) and toxicodynamic (the differential impact at target organ sites, due to differences in physiology and biochemistry) factors. When deriving human health-protective guidance or regulatory exposure limits from animal study data, it is normal to assume that, in absence of empirical data on both species, rodents are less sensitive to toxic effects than humans and an inter-species extrapolation factor (10x) is applied. However, for methamphetamine, this difference extends beyond the default 10x factor and toxicokinetics alone, based on empirical data, accounts for the full 10x factor, leaving any potential toxicodynamic differences unaccounted for.

For this reason, ESR concluded that the CalEPA RfD was more appropriate for methamphetamine risk assessment, than the Colorado RfD (Table 1).

Table 1. Methamphetamine reference dose parameters

Regulatory Agency	CalEPA[a]	Colorado DPHE[b]
Study Basis	Humans (adult pregnant women)	Laboratory Animals (developmental toxicity studies in rats)
Effects Dose	0.08 mg/kg bw/day (5 mg/day) • Lowest observed adverse effect level (LOAEL)	1.5 – 20 mg/kg bw/day • Calculated $BMDL_{10}$
Effect	Reduced weight gain	Developmental changes in offspring
Uncertainty/Safety Factor	300 10X - Variation in susceptibility among the members of the human population	300 10X - Variation in susceptibility among the members of the human population

Regulatory Agency	CalEPA[a]	Colorado DPHE[b]
	10X - Uncertainty in extrapolating from a LOAEL to a NOAEL 3X - Uncertainty associated with extrapolation when the database is incomplete	10X - Uncertainty in extrapolating animal data to humans 3X - Uncertainty associated with extrapolation when the database is incomplete
RfD/HBEV	0.3 µg/kg bw/day	5 – 70 µg/kg bw/day

BMDL: Benchmark dose level (10% response), LOAEL: Lowest observed adverse effect level, NOAEL: No observed adverse effect level

[a] Salocks (2009)
[b] Hammon and Griffin (2007)

2.1 KEY STUDIES USED BY CALEPA FOR THE METHAMPHETAMINE RFD

The primary study used by CalEPA for development of an RfD for methamphetamine was a subchronic study of the drug's efficacy in reducing weight gain during pregnancy (Chapman, 1961; Salocks, 2009). The study involved a total of 84 women who were administered a sustained-release formulation of d-methamphetamine. Three doses of methamphetamine were tested, and the study was conducted under placebo-controlled, double blind conditions. The duration of treatment was 15-16 weeks. Participant diets were not standardised and it is unknown what impact differences in food intake may have had on the results observed.

Sub-chronic dosing with methamphetamine produced a dose-related decrease in weight gain over the course of pregnancy (Table 2). This effect was highly statistically significant. Based on the results of this study, the critical effects of methamphetamine were identified as appetite suppression and consequent reduction in body weight gain in women receiving 5 mg/day of methamphetamine. As weight loss was observed at all dose levels, no NOAEL could be determined and the LOAEL for methamphetamine was 0.08 mg/kg bw/day, based on the average body weight of the studied women.

Table 2. Methamphetamine effects reported in Chapman (1961)

Group	No. affected (%) Control (n=25)	No. affected (%) 5 mg/kg (n=17)	No. affected (%) 10 mg/kg (n=43)	No. affected (%) 15 mg/kg (n=20)
"Controlled" weight gain	7 (28%)	6 (35%)	23 (53%)	5 (20%)
Weight loss	0	4 (24%)	12 (28%)	11 (55%)
Controlled weight gain or loss	7 (28%)	10 (59%)	35 (81%)	16 (80%)
Intolerance	2 (8%)	5 (25%)	8 (19%)	1 (5%)
Nervousness + intolerance	7 (28%)	5 (29%)	9 (21%)	4 (20%)

A somewhat larger study of the efficacy of methamphetamine as an aid in the treatment of enuresis (bed wetting) in children was evaluated by CalEPA as a potential basis for

development of their RfD (Young and Turner, 1965). This study involved 299 children 4-15 years of age. Most of the children in one treatment group of 110 children were given 5 mg of Methedrine (d-methamphetamine) each day just before bedtime. There were 105 children in the control (non-drug) group. Sleep disturbance was experienced in eight of the 110 children who received Methedrine. This effect disappeared when the dose of the drug was reduced to 2.5 mg. These results were consistent with the frequently reported observation that a critical effect of MA is disturbance of sleep. The results suggest that the LOAEL for methamphetamine-related sleep disturbance in children was 5 mg (0.2 mg/kg bw/day, based on a mean 25.1 kg body weight for a 7 year-old child), and the NOAEL was 2.5 mg (0.1 mg/kg bw/day, based on a mean 25.1 kg body weight for a 7 year-old child).

Comparing the experimentally determined NOAEL from the Young and Turner study (0.1 mg/kg bw/day) with the estimated NOAEL from the Chapman study (0.008 mg/kg/day), it was concluded that the choice of Chapman (1961) as the primary basis for development of a methamphetamine RfD effectively adds an additional 12.5-fold uncertainty factor (Salocks, 2009) (Table 3).

The LOAELs reported by Chapman (1961) and Young and Turner (1965) were 0.08 mg/kg/day and 0.2 mg/kg/day, respectively, suggesting that adults may be more sensitive to methamphetamine than children. The fact that the critical effects were weight loss in the adult study and sleep disturbance in the childhood study may account in part for this disparity, but it is unknown which of these effects is the more sensitive endpoint in humans. Within the Chapman study, Table 2 indicates that measures of nervousness and intolerance were not dose-dependently associated with methamphetamine in the pregnant women, while weight changes were related to methamphetamine dose.

Another significant difference between the two studies was the drug formulation. A slow release formulation, which produces more constant blood levels over a longer duration, was used in the adult study, but not in the childhood study. It was suggested that the kinetics of this release form may have rendered the adults apparently more sensitive to the daily dose of methamphetamine, although this has not been confirmed.

The decision by CalEPA to adopt the results of Chapman (1961) as a basis for derivation of the RfD for methamphetamine was based on the following considerations:

1. Use of a sustained release formulation of methamphetamine, which reduces the rate of drug absorption and produces more constant blood levels over a longer duration. This more closely mimics the long term, low-level exposure that is anticipated to occur as a result of living in a methamphetamine-contaminated home.
2. The NOAEL reported by Young and Turner was based on interviews with the parents of the children who participated in the study, not on direct observation by the researchers themselves. This endpoint is subjective and was observed in just eight of the 110 treated children.
3. As noted in several authoritative reviews (discussed by CalEPA), children may develop tolerance to the common side effects of stimulants. Therefore, the children in the Young and Turner study who initially experienced disturbance of sleep may have simply developed tolerance to this effect. If this were the case, sleep disturbance may have disappeared even if the dose of methamphetamine had not been reduced by half.

Further supporting information is available from a study in rhesus macaque monkeys (Table 3) (Madden *et al.*, 2005).

Table 3. Summary of key and supporting studies to CalEPA methamphetamine RfD calculations

Reference	NOAEL (N)/LOAEL (L)	Critical effect	Comments
Chapman (1961)	0.08 mg/kg/day (L)	Appetite suppression and weight loss in 17 pregnant women	160 published studies reviewed. Chapman 1961 study selected as POD, with supporting studies
Young and Turner (1965)	0.2 mg/kg/day (L) 0.1 mg/kg/day (N)	Sleep disturbance in 8/110 children	Supporting study
Madden *et al.* (2005)	0.75 mg/kg/day (L)	Decreased food intake, increased cortisol in rhesus macaque monkeys.	Chronic daily injections of methamphetamine. Supporting study

2.2 METHAMPHETAMINE DEVELOPMENTAL NEUROTOXICITY

Methamphetamine has been widely studied for impacts on neurodevelopment, due to its abuse as a recreational and addictive drug. Rodent models for critical brain development endpoints and outcomes are often used, although the experiments are usually aimed at mechanistic investigations, and are not typically designed to be of use in finding threshold dose LOAELs and NOAELs for the dose-response purposes of risk assessment (Table 4).

According to Jablonski and colleagues, a number of potential neuromolecular and endocrine targets may explain the developmental neurotoxicity resulting from maternal exposure to high doses of methamphetamine:

"The most reliable effects found so far from certain critical periods of neonatal development in rodents are impaired allo- and egocentric learning and memory, reduced open-field activity, increased acoustic startle response, increased locomotor sensitivity to challenge with a D1 agonist or an NMDA antagonist, transient changes in striatal dopamine and 5-HT content, reductions in D2 receptor binding and PKC activity, and induction of ACTH and corticosterone production, with the latter not associated with long-term memory or learning deficits.

…At present, the leading candidates for how prenatal and neonatal methamphetamine induces long-term effects on the CNS are through generation of ROS, or actions on specific neurotransmitter receptors, with the most evidence pointing toward dopamine D1, glutaminergic NMDA, histaminergic H1 receptors. It should be noted, however, that little attention has been given to other neurotransmitters or receptors, neurotrophic factors other than BDNF, and almost no attention to transcription factor regulation or epigenetic modulation." (Jablonski et al., 2016)

Efforts have been made to assess the long-term developmental consequences of prenatal methamphetamine exposure. Chakraborty and colleagues followed 145 New Zealand children as part of the longitudinal IDEAL study on developmental outcomes from recreational drug exposure *in utero*, and found no effect of mother's methamphetamine use on global motion perception in 4.5 year old children, a critical developmental neurological measure for key brain developmental periods (Chakraborty *et al.*, 2015)(Table 4).

Table 4. Summary of recent methamphetamine studies on neurobehaviour or development

Reference	NOAEL (N)/LOAEL (L)	Effect(s)	Comments
Chakraborty *et al.* (2015)	NA (yes/no for MA exposure)	No effect of prenatal MA exposure on visual motion perception in 4.5 year olds	Part of the IDEAL study of 145 children (NZ)
Alburges *et al.* (2015)	0.25 mg/kg (N/L) 1.0 mg/kg (L)	Increase in neurotensin release in rats at low MA dose, but decrease at higher dose	Authors conclude that the inverse effects MA at lower dose, are relevant for therapeutic effects vs dependence forming effects of MA. Effect at 0.25 mg/kg not clearly adverse
Rau *et al.* (2016)	0.5 mg/kg (N), iv 24 hr	Improved recovery from stroke, no sign of induced pathology in rats	Short term study. No adverse effects of low dose MA found.
Lloyd *et al.* (2017)	5 mg/kg/day, 10 days (L)	Altered microglial activity in hypothalamus in mice	Suggested to indicate implications for low dose effects on neuroinflammation and endocrine homeostasis
Jacobskind *et al.* (2018)	5 mg/kg/day, 10 days (L)	Histological changes in brain regions in hypothalamus in mice	Sex-dependent findings indicating stronger effects in females
Taslimi *et al.* (2018)	0.25 mg/kg (N), 0.5 mg/kg (L), sc 8 days	Neurobehavioral response to restraint stress (CPP) rats	Behavioural study
Boyette-Davis *et al.* (2018)	1 mg/kg/day, 3 days (N)	No impact on anxiety in female rats	Behavioural study
Shahidi *et al.* (2019)	1 mg/kg (N), 5 mg/kg (L), ip 7 days	Synaptic plasticity in rats	
Taslimi *et al.* (2019)	0.125 mg/kg (L), single dose sc	Increased electrophysiological activity in restrained (stressed) male rats	No effect was seen in unrestrained rats at this dose. Unclear if this is an adverse effect

MA: methamphetamine, NA: not applicable, iv: intravenous, sc: sub-cutaneous, ip: intra-peritoneal

2.3 UNCERTAINTY FACTOR CONSIDERATIONS

2.3.1 Individual variability uncertainty factor (intra-species)

The risk-based New Zealand cleanup Standard (NZS 8510:2017) for methamphetamine is based on an exposure scenario involving 1-2 year olds as the most exposed population. Children in the 1-2 year age bracket are also widely regarded as being more sensitive to the adverse effects of neurotoxicants than adults. However, there is no research on the effects of methamphetamine in 1-2 year olds. Three studies of the use of methamphetamine to treat enuresis in children were reviewed in the CalEPA report, but none of those studies involved children younger than 4 years of age (Salocks, 2009). For example, in an investigation conducted by Young and Turner (1965), children whose average age was 7 years were administered methamphetamine at 0.2 mg/kg bw/day for an average duration of 2 months (Salocks, 2009). In this study, 8 out of the 110 participating children had sleep disturbances, and the dose was dropped to 0.1 mg/kg bw/day, after which the sleep disturbances ceased. On the other hand, as previously discussed, clinical studies in adults and children indicate that children require similar or greater doses of methamphetamine to elicit pharmacological effects. This may be due to faster metabolism and clearance of the drug, but the reasons for this observation are not known and cannot be ethically studied.

According to European Chemicals Agency, conditions under which lower assessment factors (AFs)[2] can be justified include (ECHA, 2008):

"Use of AFs lower than the standard assessment factors is appropriate when it can be shown that some of the factors that cause the intraspecies variation in the target population, such as gender, age, nutritional status, health, susceptibility and genetic polymorphism have been covered in the study population. When this is the case, a value lower than the standard assessment factor should be selected and justified based on expert judgment.

In some cases, substance specific information might be available that can be used to justify special assessment factors. This information could be from toxicokinetic and/or toxicodynamic studies where variation in the human population has been measured. For example, when measurements in sufficient number of humans have shown that toxicokinetic and toxicodynamic factors, taken together, can be accounted by an AF between 2 and 5/10, that value can be used instead of "standard" or "lower" AFs. It should be acknowledged that the number of substances for which this information is currently available seems limited. It is also noteworthy that when substance specific information is obtained from studies where the sample size (number of people) is small (10-30), it is not justified to set a low AF, since the effects of human variability cannot be fully observed in a study with a relatively small sample size. In principle, the intraspecies variability for workers can be addressed in a smaller study sample, in comparison with a study that aims to cover the human variability in the general population. Guidance for the use of substance specific data and some examples are provided in the IPCS document 'Chemical-specific adjustment factors for interspecies differences and human variability".

The CalEPA rationale was to retain a default 10x uncertainty/assessment factor for intra-species variability, despite describing similar or lower sensitivity of children as compared with adults (Salocks, 2009):

[2] Assessment factors are the same as uncertainty factors

"Clinical studies of the use of stimulants for treatment of ADHD indicate that children are not more sensitive than adults to this class of medications and may in fact be less sensitive to them."

"The fact that LOAELs in the Chapman (1961) study and the Young and Turner (1965) study are similar also indicates that children and adults have similar sensitivities to methamphetamine. "

"Variation in human sensitivity to stimulants is well-characterized. Reports on the use of stimulants (amphetamine and methylphenidate) in children and adults with ADHD emphasize the need to individually titrate the dose of the drug."

CalEPA Conclusion: 10-fold uncertainty factor to account for variation in individual sensitivity to methamphetamine.

Suggested alternative conclusion: 3.16-fold[3] uncertainty factor for intra-species variability, since the pivotal study is already based on sensitive human subjects (pregnant women), and children are not known to be more sensitive from a toxicokinetic or toxicodynamic standpoint than adults.

2.3.2 LOAEL to NOAEL uncertainty factor

The Chapman study provides a LOAEL for a slight effect on weight gain in pregnant women at a dose level of 5 mg/day (0.08 mg/kg bw/day). A slightly higher NOAEL of 0.1 mg/kg/day in 110 five-year-old children with sleep disturbance was reported in the Young and Turner supporting study. Considering that many of the children tolerated methamphetamine at dose up to 40-fold above the NOAEL, without adverse effects, suggests that a NOAEL for this effect in 1-2 year olds could arguably be less than an order of magnitude below the LOAEL.

According to ECHA Guidance:

"…*some of the uncertainties associated with the reliability/accuracy of the dose-response relationship of a substance, such as dose/exposure spacing, group sizes and statistical methods, cannot be dealt with using formalised assessment factors. These uncertainties have to be addressed qualitatively. In cases where the uncertainties are major, the study should not be used for derivation of the DNEL[4]…The only major uncertainty in the dose-response relationship that is traditionally addressed with the application of assessment factors is the extrapolation of the LOAEL to the NOAEL when only a LOAEL is available.*

It is proposed that when the starting point for the DNEL calculation is a LOAEL, an assessment factor ranging from 3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases) is applied. An AF of 3 may be more appropriate for instance in situations, where the effects at the LOAEL are mild, or the LOAEL represents the lower boundary of the exposure range in which the effect is observed. Higher numerical values should be considered in situations where the effects at the LOAEL are severe and

[3] The standard 10-fold uncertainty factor is considered to be the product of individual factors for toxicokinetics and toxicodynamics, each of approximately 3.16

[4] DNEL: derived no-effect level

irreversible, or the shape of the dose-response curve is shallow or the quality of the study (e.g. group sizes, statistical methods, study design, exposure data) gives rise to uncertainties about the reliability of the identified LOAEL. It is especially important to apply a high assessment factor to a shallow dose-response curve, when dealing with incidence data."

The proximity of this LOAEL to a NOAEL, considering the low proportion of affected women and children, and the reversible/threshold nature of reported neurological effects (i.e. sleep disturbances) in children would suggest that an uncertainty factor of 3 may be more appropriate as an alternative to the default 10x factor for extrapolation from an LOAEL to a NOAEL.

CalEPA Conclusion: 10-fold uncertainty factor to account for estimation of a NOAEL from the LOAEL of the Chapman 1961 study.

Suggested alternative conclusion: 3.16-fold uncertainty factor for estimation of a NOAEL since the endpoint (reduced weight gain/loss changes) is not clearly adverse (weight change can be considered a mild effect) and reversible threshold effects (sleep disturbances) were seen in 4-15 year-old children.

2.3.3 Incomplete database uncertainty factor

Methamphetamine is very widely studied in terms of neurophysiological actions in rodents and humans. Most of the studies examine doses relevant to pharmacological or recreational drug use and do not explore lower subclinical doses and effects. However, there are some studies that have considered the effect of doses less than 1 mg/kg bw/day in animals (Taslimi *et al.*, 2019). Most of these studies (Table 4) operate with the implicit understanding that methamphetamine pharmacology involves a threshold dose, above which a measurable effect may occur. Some of the low dose studies found beneficial effects of methamphetamine in rats (Rau et al., 2016, Table 4). Some of these studies suggest that repeated doses below those normally employed for mechanistic studies, can still have an effect under certain conditions, such as with added stress. The fact that neurological findings have been reported at doses as low as 0.125 mg/kg bw/day in rats, under conditions of stress, and knowing that rats are less susceptible to the effects of methamphetamine than humans, due to toxicokinetic differences, indicates that uncertainties still exist with regard to low dose effects of methamphetamine in humans.

2.3.4 Uncertainty factors conclusions

The default uncertainty factors used by CalEPA are maximal values used to derived health-based guidance values for compounds with much less available human and animal data than are available for methamphetamine. The point of departure (POD) basis of a LOAEL for weight changes in pregnant women, with supporting study in young children would suggest the uncertainty factors for intra-species variability and extrapolation from LOAEL to NOAEL could each be 3x, each, rather than 10x. Retaining the uncertainty factor of 3 for database uncertainties, results in a cumulative (rounded) uncertainty factor of 30 for the RfD for methamphetamine (Table 5).

Table 5. Proposed RfD for methamphetamine

RfD parameters	CalEPA	Proposed RfD
Study Basis	Primary: Humans (adult pregnant women) Supporting: Children 4-15 years old	Primary: Humans (adult pregnant women) Supporting: Children 4-15 years old
Effects Dose	0.08mg/kg-day (5 mg/day) (LOAEL) 0.1 mg/kg-day (NOAEL)	0.08 mg/kg-day (5 mg/day) (LOAEL) 0.1 mg/kg-day (NOAEL)
Effect	Reduced weight gain Sleep deprivation in 8/110 children	Reduced weight gain Sleep deprivation in 8/110 children
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	30 (rounding up from 27) **3x** - Variation in susceptibility among the members of the human population **3x** - Uncertainty in extrapolating from a LOAEL to a NOAEL **3x** - Uncertainty associated with extrapolation when the database is incomplete
RfD	0.3 µg/kg/day	3.0 µg/kg/day

2.4 CONCLUSIONS

The RfD used in the ESR 2016 report was 0.3 µg/kg bw/day, the same value as used by the CalEPA (Salocks, 2009). This RfD uses a POD of a LOAEL of 0.08 mg/kg bw/day (80 µg/kg bw/day) from weight gain/loss measurements in pregnant women and a cumulative uncertainty factor of 300. The supporting NOAEL for this RfD was a 0.1 mg/kg bw/day (100 µg/kg bw/day) NOAEL in children reporting sleep disorders. Numerous research papers using experimental animals have been published since 2016, none of which directly provide a dose-response basis for a new POD and a newly derived RfD. While the CalEPA RfD value is based on clear assumptions and calculations, there is an argument, based on European assessment factor guidance, that the uncertainty factors applied are unnecessarily conservative. This review of the evidential basis for this RfD, and current guidance on assessment factors in Europe, leads to the conclusion that there is justification that the current cumulative uncertainty factor of 300 could be reduced to 30. This would be accomplished by reducing the intra-species variability and LOAEL to NOAEL extrapolation default uncertainty factors from 10x to 3x, each, and retaining the existing database deficiency factor of 3. The resulting proposed RfD for methamphetamine is 3.0 µg/kg bw/day.

During peer review of the current report it was suggested that “data supporting the LOAEL to NOAEL uncertainty factor of 10x is most conservative, but a case could be made that there is very limited data on continuous, all-route exposures to low-concentration methamphetamine” and “Because there is such a data gap, a 10x uncertainty factor may be

more protective".[5] The reviewer's suggestion would result in an intermediate RfD of 1 μg/kg bw/day. While ESR agree that a 10x factor would be more protective, given that the derivation of the RfD includes a further 3x factor for database uncertainties, ESR considers that a 3x factor is sufficiently protective.

Given that the current New Zealand standard, *NZS 8510:2017 Testing and decontamination of methamphetamine-contaminated properties* and the associated limit (1.5 μg/100 cm^2) are based on achieving an estimated exposure for a 1-2 year old child of less than the CalEPA RfD of 0.3 μg/kg bw/day, the revised RfD proposed in the current report would equate to a mean surface contamination level of 15 μg/100 cm^2.

[5] Peer review by Dr John Snawder of the US Centers for Disease Control and Prevention – National Institute for Occupational Safety and Health (CDC-NIOSH)

3. METHAMPHETAMINE EXPOSURE MODELLING

The exposure model used for risk assessment of methamphetamine in residential dwellings includes several exposure factors, such as the rate of absorption of methamphetamine following dermal or oral contact. Some of these factors may be conservative. In the context of risk assessment, the term conservative means erring on the side of caution. Conservatism is included in risk assessments to ensure that the results of the assessment are protective of virtually all potentially exposed individuals.

The exposure models used in the 2016 methamphetamine assessment are deterministic. That is, each factor is represented by a single point value. The current study examined the basis for each of these factors and the degree of conservatism in the values used. This assessment focuses on the young child assessment, as this results in the greatest estimated exposure and is, consequently, the determining factor on the assessment of any remediation level for methamphetamine.

3.1 YOUNG CHILD EXPOSURE

Both adults and children may be exposed to methamphetamine in the residential environment through dermal contact with contaminated surfaces and absorption of methamphetamine through the dermis. 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 was omitted from the model. The young child exposure model was based on a child aged 1-<2 years (expected to be maximally exposed due to primarily indoor presence and high degree of hand-to-mouth contact).

The adverse effects of concern due to methamphetamine exposure occur after repeated exposure (sub-chronic or chronic). Additionally, there are several behavioural factors that contribute to exposure. Consequently, the most appropriate measure of exposure will be the mean or a similar measure of central tendency. The rationale for this is that it is unlikely that an individual will be above (or below) average for all contributing exposure factors and individual exposures, over time, are likely to tend towards the population mean.

3.1.1 Dermal exposure

Exposure through dermal contact with contaminated surfaces is calculated by the following equation:

$$E = \frac{ABS_d \times TC \times DR \times FTSS_h \times ET_h}{BW} \qquad \text{(Equation 1)}$$

Where:

E	dermal exposure dose (μg/kg bw/day)
ABS_d	dermal absorbed fraction (unitless)
TC	transfer coefficient (cm^2/hour)
DR	deposited residue (μg/cm^2)
$FTSS_h$	fraction of residue transferred from hard surfaces to skin (unitless)
ET_h	time spent on hard surface (hours/day)
BW	body weight (kg)

ABS_d

The exposure model used a value of 0.57 for the proportion of methamphetamine dermally absorbed (Fowles *et al.*, 2016). This value was determined from laboratory studies employing ^{14}C-radiolabelled methamphetamine and cadaver skin. The absorption value was reported in the CalEPA risk assessment, but although the assessment stated that the laboratory study had been appended, this does not appear to be the case (Salocks, 2009). However, results of the laboratory study have subsequently been published (Salocks *et al.*, 2014). The study found that, irrespective of the contact time between the contaminated surface and skin, maximal absorption occurred approximately 12 hours after contact. Radiolabelled methamphetamine was applied to either vinyl or fabric discs and placed in contact with skin for periods from 15 seconds to 24 hours. At 24 hours post-topical application radioactivity was determined in:

- Methamphetamine disk
- Skin surface washings (non-absorbed dose)
- Tape-stripped skin (1-2 strippings) (surface removable dose)
- Tape-stripped skin (3-10 strippings) (dose retained in stratum corneum)
- Excised skin, separated into epidermal and dermal layers (skin-absorbed dose)
- Surrounding skin (diffused dose)
- Receptor fluid (absorbed dose)

Percutaneous absorption was defined as the sum of the percentages of total radioactivity determined in the stratum corneum, epidermal and dermal layers, surrounding skin and receptor fluid.

These experiments examined two separate processes; the transfer efficiency of methamphetamine from a material (vinyl, dry or damp material, to the skin surface ($FTSS_h$) and subsequent absorption of transferred methamphetamine into and through the skin (ABD_d). These two components are separate in Equation 1 above but are not separately quantified by Salocks *et al*. (2014). For the current exercise, the data of Salocks *et al.* (2014) were reanalysed, with ABS_d calculated as:

$$ABS_d = \frac{dose\ absorbed\ into\ or\ through\ skin}{dose\ not\ evaporated\ and\ not\ remaining\ on\ vinyl/material} \qquad \text{(Equation 2)}$$

It is reasonable to assume that dermal absorption will be independent of the media transferring the substance to the skin surface. However, dermal absorption may be dependent on the length of time the contaminated material is in contact with the skin, as this will allow for ongoing renewal of the transferred dose.

The data included in the paper of Salocks *et al.* (2014) allows calculation of 12 separate estimates of ABS.[6] The estimates range from 0.35 to 0.83, with a mean 0.61.

Commentary on the CalEPA risk assessment noted that surface loadings of methamphetamine used in these laboratory experiments were high compared with those likely to be experienced in a residential situation (Salocks, 2009). It was further noted that the proportion of a dermal dose absorbed was generally higher at lower surface loadings. The commentator suggested that a dermal absorption figure of 100% may be more

[6] The data for absorption of methamphetamine from vinyl, with a four-hour contact, appears to contain errors, as the sum of the various components give a very different value to the stated sum. Data from this experiment have been excluded.

appropriate for the low surface loadings likely in a residential situation. This suggests that the figure of 57% may be an under-estimate.

TC

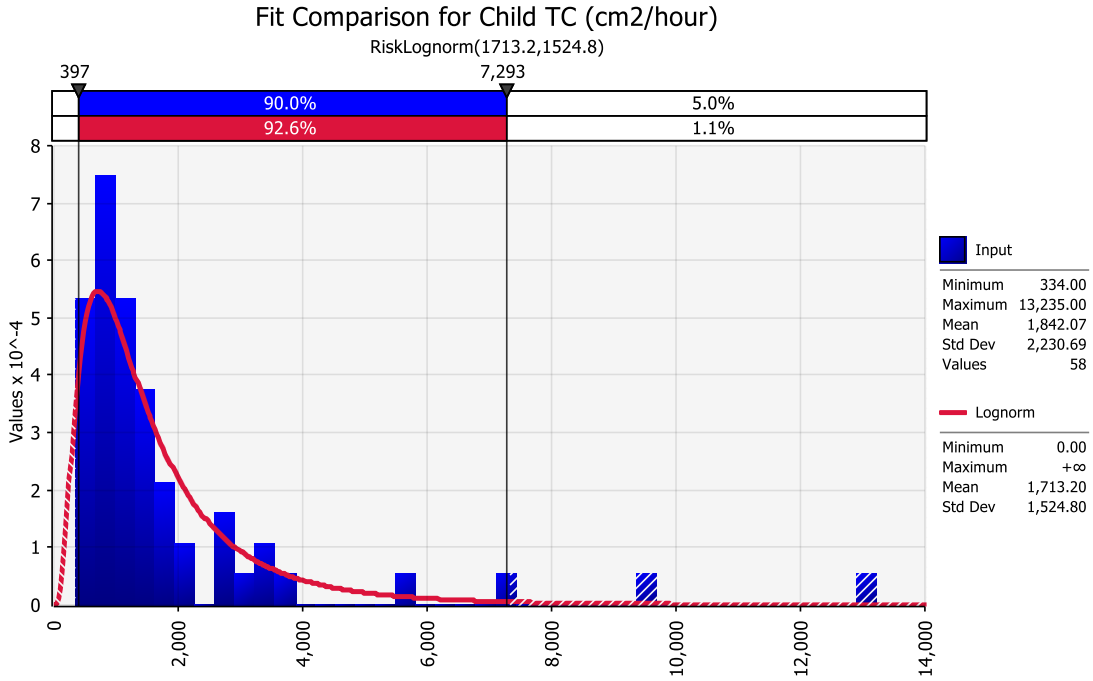
The exposure model used a value of TC of 1800 cm^2/hour (Fowles *et al.*, 2016). The value is taken from the USEPA publication *Standard Operating Procedures for Residential Pesticide Exposure Assessment* (USEPA, 2012). The value is the arithmetic mean of transfer coefficients derived from two studies (Krieger *et al.*, 2000; Selim, 2004). In these studies, an exercise routine was performed to achieve maximum contact of the entire body with a surface using low impact aerobic movements. All body surfaces (dorsal, ventral, and lateral) contacted the treated surface. The potential dermal exposure was measured by using whole-body dosimetry. The dosimeters were expected to normalise differences in surface contact and to increase the total sample area relative to patches. The assumption is that the dosimeter represents the skin and that the dose retained by the dosimeter is equivalent to dermal exposure. In the Krieger study, adult males performed two 20-minute exercise routines, which yielded a transfer coefficient of 50,953 cm^2/0.67 hours for chlorpyrifos. In the Selim study, adult males performed one 20-minute exercise routine, which yielded transfer coefficients of 18,736 cm^2/0.33 hours for pyrethrin, 20,354 cm^2/0.33 hours for piperonyl butoxide and 21,572 cm^2/0.33 hours for MGK-264.

The individual data are reproduced in the USEPA document (Appendix D.7.3). TCs were determined for adults and were converted to equivalents for a 1-<2-year child by scaling by mean body surface areas. The scaling factor is approximately 0.272. The mean adult body surface area for New Zealanders 21 years and over (males and females combined) has been estimated to be 1.95 m^2 (Cressey and Horn, 2016), while the USEPA *Exposure Factors Handbook* gives a mean body surface area for a 1-<2-year child (males and females combined) of 0.53 m^2 (USEPA, 2011). These figures equate to a scaling factor of 0.272.

The individual TC data were examined and were able to be represented by a range of right-skewed[7] continuous distributions (e.g. loglogistic, lognormal, gamma, Weibull). Figure 1 shows the fit of these data to a lognormal distribution, determined used the Excel add-in @Risk (Palisades Corporation).

[7] Right skewed statistical distributions are asymmetric and characterised by a long right-hand 'tail'

Figure 1. Fitting of USEPA transfer coefficient data for children to a lognormal distribution



The lognormal distribution is considered to be 'biologically plausible' for representing right-skewed human-associated factors and the TC value used in the methamphetamine exposure assessment is similar to the mean of the fitted distribution. This analysis suggests that the TC value used in the exposure model is not overly conservative.

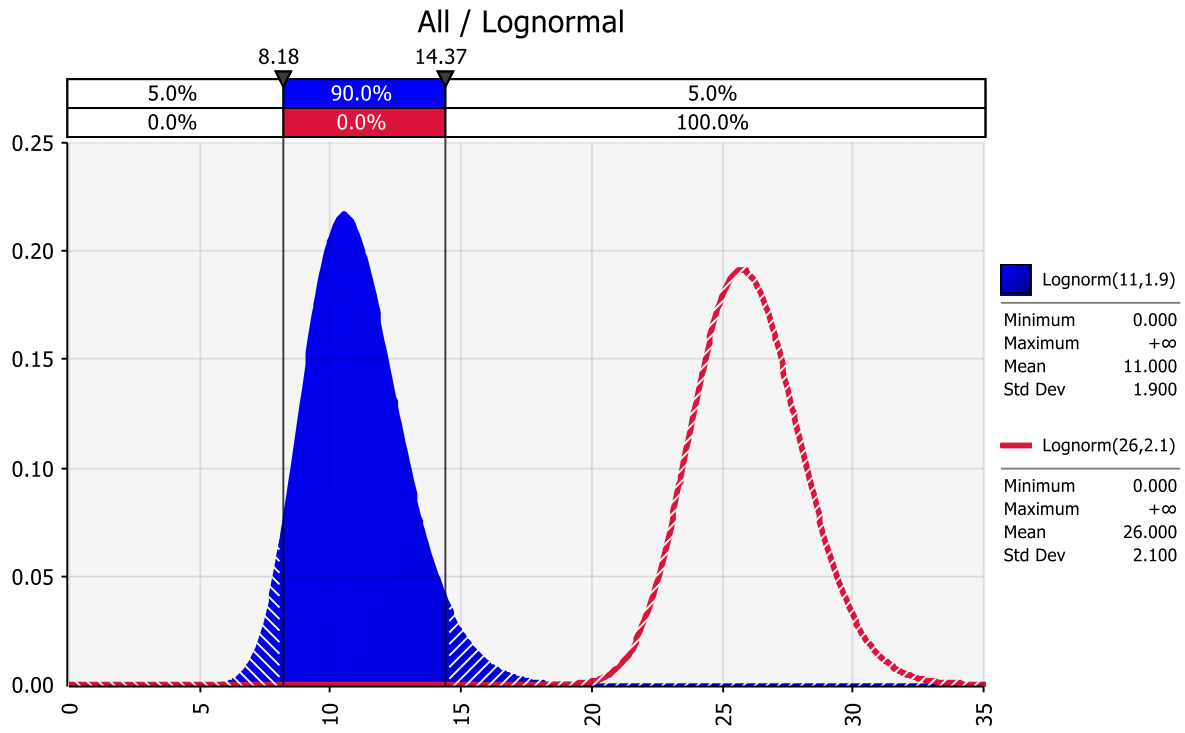
FTSS$_h$

The exposure model used a value of FTSS$_h$ of 0.07 (7%) (Fowles *et al.*, 2016). This value was based on the CalEPA assessment of child exposure to methamphetamine, which used a beta distribution with shape factors 0.6 and 8.4 for the transfer efficiency (Salocks, 2009). This distribution has a mean of 0.07. It should be noted that the transfer efficiency data represented by this distribution relate to three pesticides (chlorpyrifos, pyrethrin and piperonyl butoxide), rather than for methamphetamine.

The USEPA pesticide assessment SOP uses a generic transfer factor from hard surfaces to skin of 0.08 (USEPA, 2012). However, it is noted that this is a screening value to be used in the absence of chemical-specific data.

Van Dyke *et al*. (2014) determined transfer efficiencies for methamphetamine for three surface types (carpet, drywall and linoleum). Transfer was determined to cotton gloves, as these had previously been shown to have similar transfer characteristics to human skin. Transfer efficiencies were also determined for dry gloves and for gloves moistened with simulated saliva. Single event transfers from all surfaces to dry gloves were similar; 8, 12 and 12% for carpet, drywall and linoleum, respectively). Transfer efficiencies were higher and more variable for saliva-moistened gloves; 37, 20 and 27% of carpet, drywall and linoleum, respectively). The authors of this study noted that the distribution of transfer efficiencies was approximately lognormal and used combined transfer efficiencies for dry and moistened hands to re-examine methamphetamine exposures. The respective lognormal distributions are shown in Figure 2.

Figure 2. Transfer efficiencies for transfer of methamphetamine from surfaces (carpet, drywall and linoleum combined) to dry or wet hands



Blue: dry hands red: moist hands

The study of Van Dyke *et al.* (2014) did not consider the impact of surface contamination level on transfer efficiency and the concentrations of methamphetamine removable from surfaces by a methanol wipe (mean 27, 6.6 and 15 μg/100 cm^2 for carpet, drywall and linoleum, respectively) were markedly higher than the surface contamination levels examined in their exposure assessments (0.1, 0.2, 0.5 and 1.5 μg/cm^2). It is uncertain whether the transfer efficiencies would be dependent on the surface contamination level.

Transfer efficiencies were calculated relative to the surface loading determined by methanol wipe. As methanol (or isopropanol) wipes are used for determining methamphetamine contamination in New Zealand, determination of transfer efficiencies on this basis appears appropriate to the exposure assessment. Analysis of the residual bulk surface material demonstrated that, for carpet and drywall, a greater surface loading remained in the bulk surface material (mean 140 and 13 μg/cm^2 for carpet and drywall respectively) than was removed by the methanol wipe. For linoleum, the methanol wipe removed the majority of the methamphetamine contamination, with only 2.4 μg/cm^2 remaining in the bulk material.

The study of Van Dyke *et al*. (2014) suggests that the value for $FTSS_h$ used in the exposure model (7%) may underestimate the transfer of methamphetamine from hard surfaces, with a figure of 12% (dry wall or linoleum) appearing to be more appropriate.

ET_h

The methamphetamine exposure model used a value of 2 hours for the time spent on hard surfaces (Fowles *et al.*, 2016). The value is taken from the USEPA publication *Standard Operating Procedures for Residential Pesticide Exposure Assessment* (USEPA, 2012). The document notes that:

"A study which provides information specific to time spent on different types of surfaces indoors is not available.

The *Exposure Factors Handbook 2011 Edition* (USEPA, 2011) provides information on total time spent in a residence and time spent in various rooms within a residence. In order to develop inputs for exposure time on carpets and hard surfaces, two assumptions were made: (1) kitchens and bathrooms would represent time spent on hard surfaces and (2) time spent in a residence, less time spent sleeping and napping, would represent time spent on carpets."

The base data are included in the USEPA *Exposure Factors Handbook 2011* (USEPA, 2011). The data identifies the proportion of respondents who spent time in each of six rooms (kitchen, living room/family room/den, dining room, bathroom, bedroom and garage) and percentiles of the distribution of time spent in each room. Based on the USEPA assumption that time spent in the bathroom and kitchen represents the time spent on hard surfaces, the relevant data for 1-<2-year olds are summarised in Table 6.

Table 6. USEPA data on time spent in kitchen and bathroom, 1-<2-year olds

Total participants	Number in room type	Time in room (occupants only), mean or percentile (minutes/day)				
		Mean	**5**	**50**	**75**	**95**
Kitchen						
118	76 (64%)	87	19	70	110	214
Bathroom						
118	77 (65%)	39	10	30	30	60

The distribution of time spent in a particular room is right skewed. The 5th, 50th and 95th percentiles can be used to define a lognormal distribution describing the amount of time a population of 1-<2 year olds may spend in these rooms. Table 7 gives the percentiles for the resulting lognormal distributions and the empirical percentiles from the USEPA publication.

Table 7. Comparison on percentiles of fitted lognormal distributions to empirical percentiles for time spent in kitchen and bathroom by 1-<2-year olds

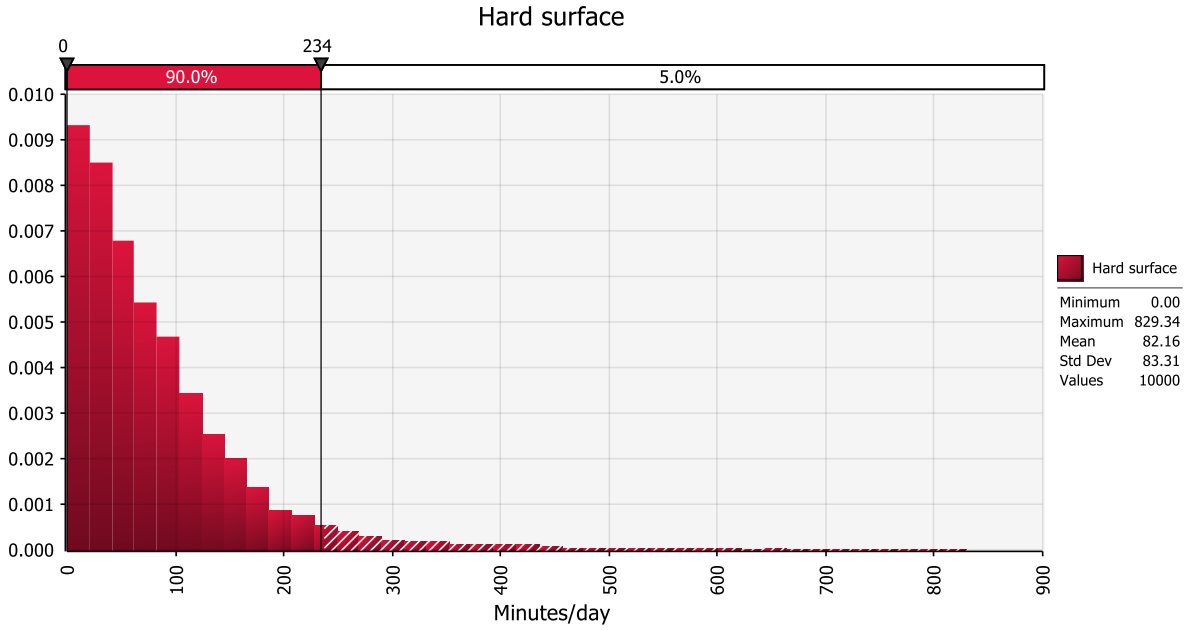
Percentile	Kitchen (minutes/day)		Bathroom (minutes/day)		
	Lognormal	**Empirical**	**Lognormal**	**Piecewise**	**Empirical**
1	9.2	10	3.8	4.4	6
5	19.0	19	10.0	9.9	10
10	26.2	30	13.7	13.2	15
25	42.6	45	20.8	20.3	15
50	70.0	70	30.0	30.1	30
75	112	110	40.9	40.6	30
90	168	173	52.3	52.6	45
95	214	214	60.0	69.5	60
99	334	281	76.5	359	349

The lognormal distribution provides a good representation of the empirical data, except at the high extremes (99th percentile). In particular, the distribution of time spent in the bathroom is characterised by a small population (probably two or three participants) who spend extremely long periods of time in the bathroom. The maximum reported time of 600

minutes (10 hours/day) seems extraordinary. To accommodate this phenomenon, the distribution of time spent in the bathroom was represented by a piecewise distribution with the lognormal distribution, representing 95% of instances, truncated at 60 minutes/day and a triangular distribution with minimum and maximum of 60 and 600 minutes/day and most likely of 60 minutes/day, representing 5% of instances. This distribution results in a satisfactory representation of the empirical data.

To represent the time spent on hard surfaces, these two distributions were combined with beta-binomial distributions representing the likelihood than any individual would spend time in these rooms on any given day. Assuming that time spent in each room is independent for an individual, the time spent on hard surfaces was taken as the sum of time spent in the kitchen and time spent in the bathroom. Figure 3 shows the output of the resulting simulation of time spent on hard surfaces for a 1-<2-year-old child. The resulting distribution has a mean value of 82 minutes/day spent on hard surfaces.

Figure 3. Simulation of time spent on hard surfaces (minutes/day), 1-<2 years child



This analysis suggests that the value of 2 hours/day (120 minutes/day) spent on hard surfaces is quite conservative and exceeds the mean estimated time spent on hard surfaces by about 50%.

BW

The exposure model used a body weight for a 1-<2 years child of 11 kg (Fowles *et al.*, 2016).

No New Zealand specific information is available on the body weight of children 1-<2 years (Cressey and Horn, 2016). Percentiles of body weight for this age group have been published by USEPA (USEPA, 2011; 2012). The 5th, 50th and 95th percentile body weights for the age group are 8.9, 11.3 and 14 kg, respectively.

The value for body weight used in the exposure model appears appropriate.

Dermal exposure – summary

The value for the fraction of surface contamination transferred from a hard surface to skin ($FTSS_h$) used in the estimation of dermal exposure to methamphetamine by a young child in the New Zealand risk assessment appears to be insufficiently conservative, although derived from a suitable source. Conversely, the value for the amount of time spent on a hard surface appears likely to be an over-estimate. Overall, the values selected to estimate dermal exposure do not appear likely to have significantly overestimated dermal exposure, based on current knowledge.

It should be noted that the exposure model does not, and probably cannot, account for the depletion of methamphetamine residues on surfaces due to normal household cleaning and the transfer of residues to occupants of the dwelling.

Laboratory studies indicate that, following a drug broadcast event such as smoking, recovery of methamphetamine residues from common residential surface types (silicon, plastic, laminate, artificial leather) decreased rapidly over the first seven days, but then remained reasonably constant up to the experiment conclusion at four weeks (Bitter, 2017). The decreases appeared to be, at least partly, due to decomposition of methamphetamine.

In contrast, no obvious degradation of methamphetamine residues was found on surfaces in a domestic dwelling, up to five years after its use for producing methamphetamine (Wright *et al.*, 2019).

3.1.2 Oral exposure

Oral exposure to methamphetamine in contaminated residential environments is considered to occur mainly through hand-to-mouth activities. Exposure from this route is estimated from the equation:

$$E = \frac{ABS_o \times TC \times FH \times F_m \times SA_{hand} \times DR \times \left(1-(1-SE)^{\frac{Fr_{h-m}}{NR}}\right) \times FTSS_h \times ET_h \times NR_h}{SA_{hand} \times 2 \times BW} \quad \text{(Equation 3)}$$

E	oral exposure dose (μg/kg bw/day)
ABS_o	oral absorbed fraction (unitless)
TC	transfer coefficient (cm^2/hour)
FH	fraction on hands compared to entire body (unitless)
F_m	fraction of hand mouthed/event (unitless)
SA_{hand}	surface area of the hand (cm^2)
DR	deposited residue (μg/cm^2)
SE	saliva extraction factor (unitless)
Fr_{h-m}	frequency of hand-to-mouth contacts (events/hour)
NR	Number of replenishments per hour
$FTSS_h$	fraction of residue transferred from hard surfaces to skin (unitless)
ET_h	time spent on hard surface (hours/day)
NR_h	number of replenishments on hard surface per day (ET_h x NR)
BW	body weight (kg)

ABS_o

The methamphetamine exposure model used a value of 1 for the oral absorbed fraction (Fowles *et al.*, 2016). The California methamphetamine risk assessment used the same value, but identified it as a conservative assumption (Salocks, 2009).

Methamphetamine has been reported to be 67% bioavailable by the oral route of exposure, compared to 100% bioavailable by intravenous administration (Cruickshank and Dyer, 2009). There is potential that the assumption made in the exposure model will overestimate oral absorption of methamphetamine.

TC

The oral exposure dose for methamphetamine in the exposure model is preceded by dermal exposure. Consequently, the transfer coefficient (TC) is as discussed previously and appears appropriate.

FH

The methamphetamine exposure model used a value of 0.15 for the fraction of active ingredient on hands (Fowles *et al.*, 2016). This value was taken from the USEPA SOP (USEPA, 2012). The value is reported to be a mean based on two source studies (Krieger *et al.*, 2000; Selim, 2004). Unfortunately, the Selim (2004) study is not generally available. The study of Krieger *et al.* (2000) was carried out using the pesticide chlorpyrifos. The amount of chlorpyrifos on cotton gloves, socks and a 'union' suit following a structured exercise routine was determined. Data from the Krieger *et al.* (2000) study and associated estimates of FH are shown in Table 8.

Table 8. Residues of chlorpyrifos transferred to hands, feet and body

Subject	Chlorpyrifos transferred to body areas (μg)				FH[a]
	Gloves	**Socks**	**Union suit**	**Total**	
1	154	440	1930	2524	0.06
2	305	262	899	1466	0.21
3	3880	5700	19400	28980	0.13
4	244	1950	1100	3294	0.07
5	4100	8510	39980	52590	0.08
6	4320	4840	13790	22950	0.19
7	324	557	1200	2081	0.16
8	2500	4400	7830	14730	0.17
9	481	1950	2110	4541	0.11
10	352	1050	3610	5012	0.07
11	137	377	814	1328	0.10
12	115	304	1160	1579	0.07
13	4040	12700	21030	37770	0.11
Mean	**1611**	**3311**	**8835**	**13757**	**0.118**

Source: Krieger *et al*. (2000)

[a] FH: chlorpyrifos transferred to hands, as a proportion of total chlorpyrifos transferred

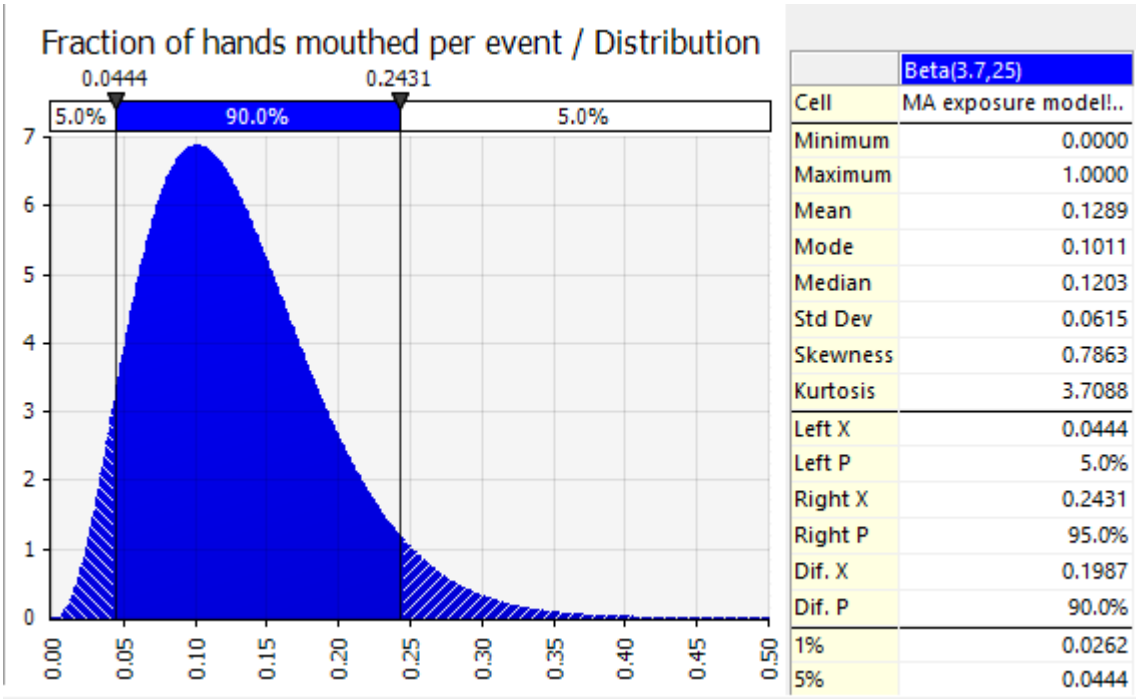
The mean proportion of the transferred residues that end up on the hands from the Krieger *et al*. (2000) study (0.12) is slightly lower than the value in the USEPA SOP (0.15). However, as the other study drawn on by USEPA was not available for review, that study must have contained similar, but slightly higher results.

Based on available evidence, the value of FH used in the exposure model appears appropriate.

F_m

The exposure model employed a figure of 0.13 for the fraction of the hand surface mouthed in each hand-to-mouth event (Fowles et al., 2016). The USEPA SOP discusses the derivation of this figure from two unpublished studies (USEPA, 2012). USEPA also stated that the data set could be best represented by a beta distribution, with parameters α = 3.7 and β = 25. This distribution is shown in Figure 4 and has a mean value of 0.13.

Figure 4. Best-fitting beta distribution for the proportion of the hand that is mouthed in child hand-to-mouth events



	Beta(3.7,25)
Cell	MA exposure model!..
Minimum	0.0000
Maximum	1.0000
Mean	0.1289
Mode	0.1011
Median	0.1203
Std Dev	0.0615
Skewness	0.7863
Kurtosis	3.7088
Left X	0.0444
Left P	5.0%
Right X	0.2431
Right P	95.0%
Dif. X	0.1987
Dif. P	90.0%
1%	0.0262
5%	0.0444

The value of F_m used in the exposure model appears appropriate.

SA_{hand}

The exposure model used a value of 150 cm^2 for the area of a child's hand (Fowles et al., 2016). This is based on a mean body surface area for a 1-<2-year child of 0.53 m^2 and a figure for the hands as a proportion of the total body surface area of 5.7% for this age group (Cressey and Horn, 2016; USEPA, 2011). The resulting figure is halved to give the surface area of one hand.

The proportional value of 5.7% for the surface area of the hands as a proportion of the body surface area came from an USEPA publication (USEPA, 1985). However, reference to this source document does not make it clear where these values originated. For a 1-<2-year child, the area of the hands as a proportion of the total body surface area is given as 5.68%, with a range from 5.57 to 5.78%. However, this appears to have been based on analysis of two subjects; one male and one female.

Based on available information, the value used in the exposure model appears appropriate.

SE

The exposure model used a value for the fraction of a chemical extracted from hands during a hand-to-mouth event of 0.48 (Fowles *et al.*, 2016). This value was adopted from the USEPA SOP (USEPA, 2012) and was based on the study of Camann *et al.* (1996). This study determined the removal efficiencies from hands of three pesticides (chlorpyrifos, pyrethrin and piperonyl butoxide) with gauze moistened with artificial and human saliva. The saliva removal efficiency across the three pesticides was in the range 22.0 to 71.3%, with an arithmetic mean of 47.9% (0.48).

No specific information on removal of methamphetamine from hands by saliva was found.

While the factor used in the exposure model is not specific to methamphetamine, it is the best available information.

$Fr_{h\text{-}m}$

The exposure model used a value for the frequency of hand-to-mouth contacts of 20 events/hour (Fowles *et al.*, 2016). This is also the point estimate proposed in the USEPA SOP (USEPA, 2012). The data underlying the USEPA values were derived from a meta-analysis of five individual studies (Xue *et al.*, 2007). The raw data are included in an appendix to the USEPA SOP. USEPA suggested the data could be represented by a Weibull distribution with scale factor = 18.79 and shape factor = 0.91. Using the Best-fit function of @Risk an exponential function with mean = 19.65 was also found to provide a good representation of the base data.

While there was considerable variability in the observational data (range 0-113 hand to mouth events/hour), the mean value of 19.7, rounded to 20, appears most appropriate for the exposure model.

$FTSS_h$

As noted under dermal exposure, there is evidence from the study of Van Dyke *et al*. (2014) to suggest that the value for $FTSS_h$ used in the exposure model may be an under-estimate.

ET_h

As noted under dermal exposure, there is evidence to suggest that the value for ET_h used in the exposure model may be an over-estimate.

NR

The number of replenishments per hour refers to the frequency with which the chemical loading on the hands will be replenished, by contact with contaminated surfaces. The exposure model used a value of 4 (replenishments/hour) (Fowles *et al.*, 2016), in line with the USEPA SOP (USEPA, 2012). The basis for this factor is not explicitly stated. It is stated that this figure is “a conservative assumption based on the use of 30 minutes in the SHEDS model to coincide with the Consolidated Human Activity Database (CHAD) diaries”. The CHAD database was investigated, and it is unclear how the replenishment rate was derived from this database.

There is insufficient information available to comment on the appropriateness of the value used for the replenishment rate.

Oral exposure – summary

As for the dermal exposure model, the oral exposure model includes a mixture of factors that are mostly appropriate, but in some cases may be under- or over-estimates, or not assessable as to their appropriateness. The overall impression is that the oral exposure model is probably appropriate, based on currently available information, and certainly does not represent a major over-estimation of the likely exposure.

4. RECENT SCIENTIFIC EVIDENCE

This section focuses particularly on scientific publications that were published after the PMCSA report and that inform the subject of residential exposure to methamphetamine. The most significant publications appear to be those published by Jackie Wright and co-workers.

4.1 ADVERSE HEALTH EFFECTS FROM METHAMPHETAMINE EXPOSURE

4.1.1 Wright et al. (2020)

In this publication information is reported from 25 'opportunistic' case studies (Wright *et al.*, 2020a). Five of the case studies were also reported, in greater detail in the lead author's doctoral thesis (Wright, 2016), while one of the case studies has also been published in more detail elsewhere (Wright *et al.*, 2017). The study authors interviewed individuals who had lived in 25 properties known to have been contaminated with methamphetamine. The case studies included a mixture of premises where manufacture was known or suspected to have occurred and premises where there was no evidence that manufacture had occurred. Information collected included:

- The amount of time the individuals and their families had been resident in the contaminated dwelling
- Health or behavioural symptoms that had appeared or increased in severity during the period of residence in the methamphetamine-contaminated dwelling. Where possible the symptoms and their timeframe were verified by medical or school records
- The results of surface wipe analyses from the dwelling for methamphetamine
- Any information to indicate whether the dwelling had been contaminated during methamphetamine manufacture or as a result of methamphetamine use

In addition, hair samples were obtained from some individuals and analysed for methamphetamine.

Due to the opportunistic nature of the case studies, there were several weaknesses in this study:

- The study was not 'blinded'. That is, the reporting individuals knew that they had been living in methamphetamine contaminated environments and it is uncertain how much the associated stress and anxiety may have contributed to the adverse effects reported.
- The study was not 'controlled'. No reference cohort of non-exposed individuals was examined, to determine the prevalence of the adverse effects reported in the general population.
- No attempt was made to account for confounding exposures. It is possible that other aspects of the individuals' living environment may have contributed to the adverse effects reported, but this was not investigated.
- Adverse effects were mainly subjective and self-reported. While some behavioural assessment testing was carried out on children, many of the symptoms reported (headaches, moodiness, anxiety, vagueness, etc.) are not amenable to objective verification.

It should be noted that these shortcomings are inevitable, and this study is currently the best available assessment of adverse health effects in a cohort experiencing third-hand exposure to methamphetamine.

The key question in relation to this study is whether the adverse health effects reported are causally related to the methamphetamine contamination of the dwellings. The available evidence was considered in terms of the so called Hill 'criteria' (Hill, 1965). This is a list of characteristics of the relationship that should be considered when attempting to determine if an association is actually a causal relationship. The criteria are; strength of the association, consistency, specificity, temporality, biological gradient, plausibility and coherence.

Strength of the association

No particular measure of the strength of the association is available, other than that adverse effects ascribed to the methamphetamine contamination were reported in all case studies.

Consistency

The symptoms reported, in most cases, fall within a range that could be considered consistent. For more detail, see under 'Plausibility'.

Specificity

The reported symptoms are uniformly non-specific and could have been due to a range of environmental exposures.

Temporality

Temporality refers to the fact that for an exposure to be causal of adverse effects, the exposure must occur before the appearance of the adverse effects. In the study of Wright et al., respondents reported that symptoms appeared after they took up residency in the methamphetamine-contaminated dwelling and, in many cases resolved or lessened when they left the dwelling.

Biological gradient

A biological gradient may also be known as a dose-response relationship and refers to the expected increase in the frequency and/or severity of adverse effects with increasing exposure. The study of Wright et al. provides no information on a biological gradient associated with methamphetamine exposure. Similarly, there is no evidence of an exposure threshold, as symptoms were reported by individuals whose dwelling showed only very low levels of methamphetamine contamination.

Plausibility

Effects reported by participants in the Wright et al. study included:

- Dermal effects (rashes, irritation)
- Ocular effects (sore or watering eyes)
- Respiratory effects (persistent cough or asthma-like symptoms)
- Immune effects (persistent infections)
- Neurological or neuro-behavioural effects (headaches, difficulty sleeping, unusual dreams, fatigue or tiredness, increased aggression or irritability, moodiness, depression, anxiety, vagueness, memory issues)
- Exacerbation of pre-existing conditions

While little other information is available on individuals living in methamphetamine-contaminated environments, there is information available on adverse effects reported by enforcement personnel investigating clandestine drug laboratories. This is particularly true of the period before widespread use of personal protective equipment (PPE).

Burgess et al. (1996) reported on adverse effects reported by 59 enforcement officials who had been involved in more than 2800 investigations, the majority (81-97%) of the investigations were of methamphetamine laboratories. The main symptoms reported were headaches, issues of the respiratory tract or mucous membranes, and skin irritation.

A standardised, self-administered survey was distributed to 258 law enforcement personnel taking part in national/regional training during 2004-2005 (Witter *et al.*, 2007). A response rate of 93% was achieved. Respondents reported symptoms experienced while investigating clandestine methamphetamine laboratories, with more than 70% of respondents reported headaches, CNS symptoms, respiratory symptoms, sore throat and other symptoms. The symptoms were usually transitory, although in some cases individuals had sought medical attention due to the persistence of symptoms.

Case reports from the US Hazardous Substances Emergency Events Surveillance (HSEES) system were investigated and injuries reported by first responders to clandestine methamphetamine laboratories were reported (Cooper *et al.*, 2000). During 1996-1999, 112 methamphetamine-associated events were reported and included 155 injured individuals. Injuries were predominantly respiratory and eye irritations.

A study of Utah policemen (n = 69) with persistent symptoms due to exposure to methamphetamine laboratories evaluated symptoms prior to treatment (Ross and Sternquist, 2012). Participants were 69 consecutive entries to the Utah Meth Cop Project. The Medical Director of the project included participants according to their comprehensive history and physical examination, electrocardiogram, and blood analysis. Further tests were done, including testosterone levels, when direct questioning revealed problems that warranted evaluation. Common symptoms included fatigue, insomnia, headaches, heartburn, personality changes, numbness in hands or feet, memory loss, allergic history, poor concentration, back pain, joint pain, shortness of breath, skin irritation, anxiety/depression, abdominal gas/pain, sinusitis/congestion and sore throat.

Case reports to the Washington State Poison Control Center were examined for the period 1999 to 2004 (Thrasher *et al.*, 2009). Reported exposures mainly related to residence in or investigation of current or former clandestine laboratory sites. The most frequently reported symptoms were headaches, nausea/vomiting, respiratory (cough, throat irritation, breathing difficulties) and eye irritation.

While this summary of studies is not comprehensive, it suggests that the symptoms reported by participants of the opportunistic case studies could plausibly by related to methamphetamine exposure or to exposure to other chemicals associated with methamphetamine manufacture.

Coherence

A causal relationship between methamphetamine exposure and the reported adverse health effects would be coherent with available knowledge concerning adverse effects due to incidental exposure to a methamphetamine-contaminated environment.

Conclusions

The information presented in the paper of Wright et al. is suggestive of a causal relationship between methamphetamine contamination of the identified dwellings and the adverse health effects reported by occupants. The reported symptoms are reasonably consistent, plausible

and coherent with other available knowledge. However, the lack of specificity of the symptoms and the lack of any evidence of a biological gradient mean that no stronger statements can be made in relation to the causality of the observed associations.

It should be noted that the adverse effects reported in this study are generally transitory and reversible. Indeed, in many instances, cases reported improvement or resolution of symptoms while they were absent from the premises for relative short periods of time. This suggests that the effects should be viewed as acute toxicological responses, which is consistent with the adverse effects being mainly mediated through the CNS.

4.2 SUITABILITY OF CURRENT RISK ASSESSMENT PRACTICES

At present, the level of methamphetamine contamination in a dwelling is usually assessed by a series of wipe tests. A methanol or isopropanol dampened wipe is used to wipe a defined area of a dwelling surface. This procedure is repeated for several locations. Wipes are transferred to a laboratory and analysed for methamphetamine, by techniques such as enzyme-linked immunosorbent assay (ELISA), gas chromatography with mass spectrometric detection (GC-MS) or liquid chromatography with tandem mass spectrometric detection (LC-MS/MS).

In carrying out risk assessments it is assumed that:

- Methamphetamine residues detected by wipe testing are similar to residues on surfaces contacted by residents. For example, for a crawling infant, most contact will be with the floor. Floors are not commonly examined during wipe testing.
- The residue levels on contact surface will remain constant. That is, the residues will be replenished to replace residues removed through human contact.
- Residues removed by human contact will be a subset of residues determine by wipe testing. Wipe testing is generally not 100% efficient for removal of residues present on surfaces.

4.2.1 Wright et al. (2019)

This study analysed for methamphetamine in both wipe samples and bulk samples of household features and items brought into the dwelling post-contamination (Wright *et al.*, 2019). No decrease in the results of surface wipe samples was seen between samples approximately 2.5 years apart and, on average, concentrations appear to increase.

Possessions brought into the dwelling post-contamination were consistently contaminated with methamphetamine, suggesting migration of residues or continued deposition.

Analysis of ‘gyprock’ plasterboard from several locations within the dwelling showed that although the outer paper surface usually had the highest concentrations of methamphetamine, contamination could also be detected from the internal gyprock and the inner water surface.

While this publication raises questions over the ability of wipe testing to fully represent the burden of methamphetamine contamination in a dwelling, it did not provide information that is directly applicable to risk assessment. Indeed, the observation that surface concentrations of methamphetamine may be replenished supports the current risk assessment approach of assuming that methamphetamine concentrations on surface may remain constant over time.

4.2.2 Wright et al. (2020)

The exposure assessment component of risk assessments carried out for exposure to methamphetamine from dwelling contamination considers dermal exposure from contact with contaminated surfaces and oral exposure from hand to mouth or object to mouth

transmission route (children only) (Fowles *et al.*, 2016; Hammon and Griffin, 2007). Exposure by the inhalation route is considered to be negligible.

Air samples were taken from various locations in a dwelling known to be contaminated with methamphetamine approximately nine years previously and had not undergone remediation (Wright *et al.*, 2020b). Methamphetamine concentrations in the range 0.5 to 8.3 $\mu g/m^3$ were determined. The authors carried out an assessment of methamphetamine exposure by dermal, oral and inhalation route for young children and adults for the assessed dwelling. It was concluded that inhalation exposure could account for 10-20% of total exposure. It appears that this estimate assumed residence in the dwelling for 24 hours/day and 100% absorption of methamphetamine by the inhalation route of exposure. These are conservative assumptions.

Exposure assessment has been used to assess residual risk following remediation and it is uncertain what the implications of this study are for remediated properties. Particularly, it is uncertain whether there will be a constant relationship between surface contamination and air concentrations over a range of surface contamination levels.

5. CONCLUSIONS

HUD's request for advice from ESR was captured in a series of questions. The following text addresses these questions in the context of the analysis and review provided in the current report.

Can ESR provide brief evidence to the effect that methamphetamine residue may be harmful to health, in the context of residential accommodation?

While the study of Wright et al. (2020) has many shortcomings, it is likely to be the best evidence of adverse effects due to third-hand methamphetamine exposure that can be ethically obtained. The symptoms reported by residents of methamphetamine-contaminated premises are reasonably consistent with symptoms reported by responders exposed in clandestine laboratories. The symptoms are also reasonably consistent with methamphetamine's known mechanism of action.

Reported symptoms are mainly related to local effects on the skin, eyes or respiratory tract or systemic neurological effects (i.e. effects mediated by the central nervous system). All effects appear to be reversible.

Does ESR recommend that HUD prescribe maximum acceptable levels of contamination, or a means of calculating maximum acceptable levels?

While the study of Wright et al. (2020) did not identify a clear biological gradient for adverse effects associated with methamphetamine exposure, principles of toxicology require such a gradient. A biological gradient means that with increasing exposure, either the probability and/or the severity of adverse health effects will increase. This further suggests that there will be a level of methamphetamine contamination that results in unacceptable risks of adverse effects and some mechanism is required to protect residents of methamphetamine-contaminated premises from unacceptable levels of risk.

What does ESR recommend that those maximum acceptable levels, or means of calculating those levels, should be? (noting that "levels" includes the potential for setting ranges of methamphetamine contamination)

Section 2 of this report discusses the derivation of the reference dose (RfD) that was used as the basis for the original ESR risk assessment (Fowles *et al.*, 2016) and a less conservative revised reference dose (RfD), based on a reconsideration of the uncertainty factors used in the RfD derivation. The revised RfD is 10-fold higher than the California Environmental Protection Agency RfD and would support a 10-fold higher limit for methamphetamine surface contamination. The higher surface contamination limit is co-incidentally the same as the value proposed in the Prime Minister's Chief Science Advisor report (Bardsley and Low, 2018).

As an in-detail assessment of the exposure model used for the ESR risk assessment suggests that the model is neither overly or insufficiently conservative, a maximum mean surface contamination concentration below 15 μg/100 cm^2 will be associated with a very low probability of harm, although such residues should still be viewed as undesirable. Given the relatively mild and reversible nature of the adverse health effects described by Wright et al. (2020) and in the pivotal toxicological studies used as a basis for RfD derivation, ESR considers that a mean surface contamination concentration of 15 μg/100 cm^2 should be viewed as a guideline level. Analytical results above this level should be considered along

with information on the possible use of the premise for methamphetamine production, the presence of sensitive individuals (pregnant women, infants) in the household and reports of adverse health effects amongst residents of the premises.

What are the options for presentation of maximum acceptable levels, or means of calculating those levels, taking into account the potential for new scientific evidence on health risks?

Any health-based guidance value (exposure limit), or concentration limit based on a health-based guidance value should be qualified as being derived based on currently available information. If significant new information becomes available, it should be considered and weighted as to its relevance for revision of the existing limits.

What is international best practice in setting exposure limits?

Unfortunately, procedures for deriving exposure limits are not uniform across organisations and it is not unusual for different organisations to derive different exposure limits from the same toxicological data. These differences are usually due to the application of more or less conservative uncertainty factors.

Does ESR recommend a "bright line" approach to a maximum inhabitable level, or a different approach?

What does ESR recommend as a maximum inhabitable level, above which a tenancy should be terminated due to the health risk?

How does ESR recommend that a maximum inhabitable level should be applied in practice, particularly where that level is present in only part of the premises?

ESR does not consider that there is sufficient evidence to define a maximum inhabitable level for methamphetamine. No evidence is available of severe health effects associated with third-hand methamphetamine exposure.

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