Government of **Western Australia**
Department of **Health**

Technical paper:

Public health risks of methylamphetamine smoke houses

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Environmental Health Directorate

Public Health and Aboriginal Health Division

Department of Health, Western Australia

October 2021

Suggested citation:

Parker E, Howell J (2021). Technical paper: Public health risks of methylamphetamine smoke houses. Perth: Department of Health WA.

Acknowledgements:

This work would not have been possible without the support of Mirella Goetzmann, Peter Franklin, Pierina Otness and others within the Chemical Hazards Unit of the WA Department of Health, as well as the Public Health Division of the North Metropolitan Health Service. The authors would like to thank Paul Newell, Jackie Wright, Brad Prezant, John Martyny, and Glenn Morrison for their expertise and advice; and several Department of Health-accredited service providers, specifically ChemCentre, Hill Laboratories, Occuhealth, MTK Group and Envirolab Services, for advice and/or provision of non-identifying data.

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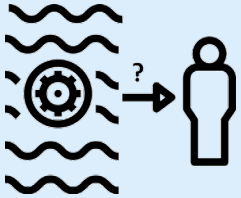


Data on health impacts from third hand exposure to meth are lacking

Methylamphetamine in Western Australia

Methylamphetamine is a highly-addictive stimulant drug, which is illegal to possess, manufacture, sell, or use outside of a prescription under current laws in Western Australia (WA). Despite this, 2.1% of Western Australians report recently using the drug; the highest percentage among all states and territories in Australia.

Contamination of homes

Smoking of crystal methylamphetamine ('ice') can release several contaminants into the surrounding environment, the most concerning of which is the methylamphetamine vapour itself. The vapour can settle as residue on surfaces within the home and can persist for several years.

Many governments around the world, including Australia, have set guidelines for remediation of homes used for the clandestine manufacture (clan lab) of methylamphetamine. Very few of these have explicitly extended their advice to cover situations of contamination from smoking the drug. The nature of surface methylamphetamine contamination from smoking is similar to that from manufacture; however the levels detected in smoke houses are considerably lower than levels detected in clan labs (the vast majority of methylamphetamine smoke residues being less than 5µg per 100cm^2).

Methylamphetamine exposure and health

Methylamphetamine is known to cause a wide range of health impacts among first-hand users, and has been associated with health impacts in those exposed second-hand (specifically, children living with users, and first responders attending incidents in clan labs). Although research in the area has been sparse, it has been assumed that methylamphetamine can cause health impacts on a third-hand, passive basis for those moving into homes where the drug was previously made or smoked.

Informing a local approach

This work has re-visited the toxicological evidence for human methylamphetamine exposure, and applied local exposure parameters to estimate received doses for adults and infants at risk in Western Australia in relation to residues from smoking the drug. This risk assessment and the current weight of scientific evidence indicates that human health risks from most residential exposure to methylamphetamine smoke residues are low as reflect the relatively low levels of this type of contamination. Our assessment supports the current Health Investigation Level of 0.5µg/100cm^2, but highlights the need for a tiered clean-up standard commensurate with health risk.

Introduction

Purpose

Recreational usage of methylamphetamine in Western Australia (WA) remains high (1), and concerns about property contamination from smoking the drug are increasing. This technical paper was completed to inform guidance on:

- Public health risks posed by residual methylamphetamine from smoking within homes; and
- Remediation and decontamination of methylamphetamine smoke houses, commensurate with public health risk.

Background

Smoking of methylamphetamine in Western Australia

Methylamphetamine is a highly addictive stimulant, and a common drug of abuse in WA. In the 2019 National Drug Strategy Household Survey (NDSHS), 2.1% of Western Australians reported methamphetamine or amphetamine use in the previous 12 months (1). This number has steadily declined from a peak of 5.8% in 2001 (2), however, WA continues to have higher a percentage of users than all other states and territories in Australia (3).This situation is also generally supported by other sources of information such as the National Wastewater Drug Monitoring Program Reports.

Half of Australian users reported that crystal methylamphetamine is the predominant form used (1). Among these, more than 75% reported that smoking is the main method of use (4), and almost 30% reported using on a daily or weekly basis (1). Methylamphetamine was estimated to have cost the Australian community $5 billion in the 2013-14 financial year (5), and was responsible for 0.56% of total disease burden in Australia in 2015 (6).

Contamination of homes

Residential properties can become contaminated with residues from the clandestine manufacture or smoking use of methylamphetamine. These residues may pose health risks for existing and future occupants of the home. In 2019, approximately three quarters of methylamphetamine smoking in Australia occurred in private homes (7). Methylamphetamine smoking involves heating the crystallised drug to produce a vapour, which is inhaled (8). Vapours can deposit on surfaces, leaving residues in a similar manner to those resulting from tobacco or cannabis smoking indoors. Methylamphetamine surface residues have been shown to persist for months or years (9).

Health concerns

Methylamphetamine is known to have a range of therapeutic effects for those on prescribed doses, as well as acute, sub-chronic and chronic health effects on illicit users (10). Health effects have also been described for those exposed to clandestine methylamphetamine laboratory activities in a second-hand manner (e.g. children living in the home at the time of manufacture (11), or first responders to accidents, both with and without personal protective equipment (12, 13)) .

There are increasing concerns about health impacts resulting from third-hand exposures (e.g. for occupants of homes that were previously used to manufacture methylamphetamine), though supporting evidence is scarce. Reported health impacts include skin and eye irritation, cough or asthma-like symptoms, respiratory infections, sleep issues, headaches, behavioural effects,

mood effects, and memory difficulties (14). There is growing concern, despite a lack of observational evidence, that contamination from smoking of methylamphetamine within a home could result in similar adverse health effects (15).

Objectives

This health risk assessment will aim to:

1. Estimate the degree of residential property contamination resulting from smoking of crystalline methylamphetamine within the home.
2. Estimate the likelihood and possible form of health effects resulting from third-hand exposure to contamination from smoking of crystalline methylamphetamine in residential properties.
3. Estimate public health risk due to third-hand exposure to contamination from smoking of crystalline methylamphetamine within homes, based on typical patterns of contamination, exposure and response.

Although undoubtedly of interest, this report will not cover the additional risks of:

- contamination from methylamphetamine smoking in a residence where manufacture has also occurred (see enHealth guidance on clandestine laboratories (8));
- concurrent contamination from smoking of multiple drugs with plausible health effects (for example, tobacco and cannabis); and
- health impacts from first-hand or second-hand exposure to methylamphetamine smoking.

Overview of contamination from smoking methylamphetamine

Chemicals of potential concern

The smoking of crystal methylamphetamine (normally as hydrochloride salt) theoretically releases a number of chemicals to the environment. This includes methylamphetamine itself, as well as impurities and adulterants in the material, and pyrolysis products generated when the drug is heated during smoking (Appendix 2).

Methylamphetamine

Methylamphetamine is the primary chemical of concern for this assessment. It is a chiral molecule, and exists as one of two optical isomers: the very biologically active dextro-methylamphetamine (d-) enantiomer, and the much less active levo-methylamphetamine (l-) enantiomer (16). Crystal methylamphetamine hydrochloride salt can contain varying proportions of the two (16). When produced from ephedrine or pseudoephedrine precursors, the resulting drug can be close to 100% pure d-methylamphetamine (16). When produced via phenyl-2-propanone (P2P), the resultant methylamphetamine contains approximately half of each isomer, i.e. the drug is about half as potent compared with the former method (16). An additional step of P2P manufacture is able to chemically separate the isomers, increasing the proportion of d-isomer going on to be sold; this results in varying isomeric proportions (16).

In Western Australia, crystal methylamphetamine hydrochloride salt is around 72% pure d-methylamphetamine (17). A proportion of the remainder is hydrochloric acid (very roughly 19% as a basic molar stoichiometric ratio, with the actual proportion dependent on many factors), variable amounts of the l-isomer, and variable presence of adulterant or impurity (18). This level of d-methylamphetamine in the WA marketed drug suggests that the potency of any material deposited from smoking would be comparable with that resulting from manufacture.

Impurities

Despite the generally high purity profile of crystallised methylamphetamine in WA, the drug can contain a number of impurities, dependent predominantly on the method of manufacture (Appendix 2, Table S3). For a majority of these compounds, little is known about behaviours during conditions of pyrolysis, capacity to persist for any length of time in ambient environmental conditions, or any plausible health risks following dermal contact, ingestion or inhalation.

In WA, methylamphetamine production typically employs the Nazi-Birch method (17) using pseudoephedrine as the key precursor. This approach generates one major impurity, 1-(1,4-cyclohexadienyl)-2-methylaminopropane (CMP) (19). CMP is known to metabolise to methylamphetamine in soils, with a half-life typically less than one week (20). Capacity for vaporisation and environmental deposition following smoking remains unclear. CMP is detectable in urine samples that are positive for methylamphetamine (21), suggesting that the compound is both absorbed and excreted by the human body following methylamphetamine use, with unknown pharmacodynamics in transit.

In other states and territories methylamphetamine normally is manufactured from pseudoephedrine by phosphorous reaction methods. They may well produce other impurities (17) which will not be discussed here any further.

Most imported crystal methylamphetamine used in WA, and likely other Australian jurisdictions, is thought to have been produced from P2P via Leuckart or reductive amination methods (17, 22, 23). These approaches have a greater array of potential impurities (Appendix 2, Table S3). Several of these impurities are known to emit toxic substances upon heating, specifically: p-bromotoluene (carbon monoxide and hydrogen bromide (24)); bibenzyl (toluene and trans-1,2-diphenylethene (25)), 1-phenyl-2-propanol (toluene and indene (26)), P2P (acrid smoke (27)),

N-benzylmethamphetamine (hydrogen chlorine and nitrogen oxides (28)) and dibenzyl ketone (toluene (29)). The half-life of most of these vapours is less than five days, though hydrogen bromide and hydrogen chloride are stable as gases and are theoretically amenable to environmental deposition (30, 31).

Impurities within the drug material will not be discussed further in this health risk assessment, as there is both considerable variability in the impurities present in any given sample of crystal methylamphetamine, relatively low levels, and little evidence to date suggesting that environmental contamination from vaporisation of trace amounts of these compounds within homes poses a credible threat to the health of future inhabitants.

Adulterants

Data from Victoria and Queensland suggests that the adulterants, cutting agents, or bulking agents most commonly found in methylamphetamine samples in Australia include sugars (glucose, lactose, sucrose and mannitol), caffeine, isopropylbenzylamine, methylsulfonyl-methane (MSM), other common recreational drugs (MDMA, cocaine and heroin), and a variety of other pharmaceuticals (including paracetamol and ephedrines) (32, 33). Of these, isopropylbenzylamine and MSM are most likely to be present in crystal formulations, as their salts have similar physical properties to methylamphetamine (34, 35).

Aside from the known effects of the recreational drugs and pharmaceuticals, most of these compounds are considered biologically benign. The only known reported cases of adverse health effects from adulterated methylamphetamine have related to lead within drug administered intravenously (36), and inhalation of powdered drug containing talc or starch (37). Potential adulterants within crystal methylamphetamine will not be discussed further in this health risk assessment.

Pyrolysis products

The heating of pure crystallised methylamphetamine causes aerosolisation of the drug, enabling consumption via inhalation. Although heating crystals to the point of pyrolysis (decomposition) is not the intent, several pyrolytic degradation products may be inadvertently generated in the process of smoking (Appendix 2, Table S4). Several of these are known to exert toxicity through common mechanisms, contributing to cumulative effects. Specifically, dimethylamphetamine (DMA) metabolises to methylamphetamine inside the body (38), and amphetamine exerts biological effects through receptor mechanisms in common with methamphetamine (39). Most of the pyrolysis products are known to have adverse effects on health, though most (with the possible, but low likelihood, exception of benzene (40)) are unlikely to persist within a household environment for any length of time that would permit a third-hand health risk.

Summary: Although smoking of methylamphetamine has the potential to release numerous impurities, adulterants and pyrolysis products into the environment, the sole chemical of potential concern to be explored in this health risk assessment is methylamphetamine. Methylamphetamine has known biological effects, and is known to persist long-term within residential homes under usual environmental conditions. In circumstances of contamination from manufacture, others (15, 41) have likewise determined that methylamphetamine itself is the most important persistent environmental contaminant, and that remediating to the levels required for methylamphetamine will also adequately remediate any other contaminants.

Patterns of contamination within a home

During smoking, escape of methylamphetamine vapour may occur at the point of heating in the pipe (minimal), escape of vapour from the mouth during inhalation (minimal), or exhalation of vapour (thought to be the predominant source) (18).

Vapours can deposit on surfaces, usually as crystallised salt (the original form) or less commonly as base oil liquids, both of which may remain on hard surfaces or be absorbed into porous surfaces (8). The extent of contamination depends on location of the smoking event, layout and size of the premises, and the use of ventilation fans and air conditioning systems (42).

Methylamphetamine vapours produced by smoking are likely to deposit at highest concentrations in the room where smoking takes place (42). Data from New Zealand suggest that common living areas, such as the kitchen, lounge and dining areas, typically have the highest levels of contamination within the home, indicating where smoking often occurs (43). Contamination of access ways such as entrance halls and hallways suggests that contamination readily migrates to nearby areas (43). People smoking in private may also contaminate associated bedrooms and toilets

Russell et al. (2019) suggest that methylamphetamine surface contamination may be more concentrated toward the ceiling (for example, on surfaces such as rafters/beams, and door frames) (43). Ventilation fans and air conditioning systems may have the highest levels of contamination and, as conduits of contaminated air, can cause ongoing spread of contamination throughout the premises (44).

Although methylamphetamine vapour degrades rapidly in air (with a half-life of one hour) (45), the crystal salt is considered non-volatile and has been shown to persist as a surface residue for months or years (9). In terrestrial environments, methylamphetamine is known to strongly adsorb to soils containing organic carbons, with a biodegradation half-life of 131-502 days, which offers some insight into how long the chemical may persist in indoor environments (45).

The amount of methylamphetamine persisting on common household surfaces is likely to decay over time, in an almost exponential pattern (46). This is compatible with evidence suggesting that methylamphetamine may gradually desorb from surfaces over time, re-aerosolising and potentially causing ongoing exposure to third parties via inhalation (47). In addition to desorption, levels on surfaces may decline as a result of ongoing cleaning, transfer to occupants, or transfer to items of clothing which are then laundered (41).

Summary: Smoked methylamphetamine that is not absorbed during inhalation may deposit on or penetrate into surfaces within the environment, at highest concentrations near the smoking event but with a degree of spread to neighbouring areas. This contamination may persist for months or years, with gradual depletion over time. Methylamphetamine may also be present in air, most likely resulting from continued desorption from surfaces.

Exposure considerations

Population at risk

Estimated size of the receptor population

This report is limited to individuals exposed to methylamphetamine contamination on a third-hand basis; that is, it excludes individuals smoking methylamphetamine first-hand, as well as those inhaling chemicals second-hand at the time of the smoking, for which the exposure is greater and the health risks are established.

All people living in residential properties in which previous residents smoked methylamphetamine are theoretically at risk of exposure from environmental contamination. By making a number of assumptions, it is possible to extrapolate the number of households that may be impacted by (i.e. subject to) smoking of methylamphetamine in WA (Table 1). A five year period was selected to account for movement of people over time, and to reflect a reasonable estimate of persistency of methylamphetamine within a home environment.

Assumptions include:

- 2.1 - 3.0% of the WA population aged 14 and over used meth/amphetamines each year over the last 5 years (1)
- Around half (49.8 - 57.3%) of meth/amphetamine users report that crystal meth is the predominant form used (1)
- Most (67.6 - 77.8%) of crystal meth users predominantly smoke the drug (1)
- Most (73.7 - 78.1%) crystal meth users report smoking in private homes (1)
- One home is affected per smoker; this balances the chances that users may smoke in more than one home (estimated at 40.2% (48)), may co-habit with other meth smokers and smoke predominantly at home, or may smoke socially at gatherings and never at home. Overall an expert consensus was 1 house: 1 user.
- The proportion of people moving houses across years is as per the 2016 Australian Census (17.7% over 1 year, and 46.6% over 5 years (49), with a linear relationship in between); individuals did not move more than once during this period, and users moved into previously uncontaminated homes.

These things considered, around 2.7% of the 1.07 million households in WA (50) may have been contaminated to variable extents by methylamphetamine smoking in the past five years (Table 1). Some of these may have already been remediated, and many would likely fall well below the surface levels of contamination that trigger remediation. Nonetheless, at a standard household size of 2.6 individuals (50), more than 75,000 individuals could theoretically be at risk of environmental exposure to third-hand methylamphetamine at any time. Using the same approach with Australia-wide inputs, approximately 1.5% of dwellings and more than 370,000 occupants may be impacted across the country.

The main exposed populations might be divided into the smokers themselves, their partners or other concurrent occupants, and occupants of the home subsequent to the smoking activity. The smokers' main exposure will be first-hand but there will also be second and third hand impacts. The non-smoking partners or other people present will be second and third-hand recipients. Subsequent occupants will primarily be in the third-hand exposed group. So possibly more than half the exposed population, the ones subject to the highest meth levels, will be participants or complicit in the smoking.

An important additional consideration is that smoking rates vary greatly across the relevant population. A 2019 survey of drug use (48) indicated that for methylamphetamine, the use rate

(including smoking) and proportion of the relevant population were: more than once a week – 16.9%; about once a month – 16.4%; every few months – 19.9%; and once or twice a year – 47%. For the latter two groups, and subject to our subsequent contamination level discussion, it may be that the associated smoke impacts are negligible.

Sub-populations at highest risk

People living in public housing (approximately 4% of households in WA (51)) or living in certain geographic areas may be more vulnerable, due to an increased risk of encountering environmental contamination with methylamphetamine than the general population. This assumption is based on anecdotal reports from methylamphetamine testing service providers about the homes they most frequently assess; there is no supporting data available.

Infants and children (approximately 6.6% are aged under 4 years in WA (52)) are considered to be the most vulnerable population, due to high contact time with the floor, high frequency of hand/object-to-mouth behaviours, high volumes of gas exchange relative to body weight, and high likelihood of remaining in the home on a continuous basis (41, 53). Similarly, individuals who are the primary cleaners of the home, and who chew fingernails may have greater exposure (14). Other individuals, who do not work, work from home, or who are caregivers for others within the home, may also be more exposed due to increased time spent in the contaminated environment.

Table 1: Estimate of number of properties and people impacted by third-hand exposure to methylamphetamine in Western Australia

	2015	2016	2017	2018	2019
WA population aged >14 (52)	2,049,058	2,059,450	2,071,975	2,086,995	2,109,715
Assumption: % from NDSHS 2019, WA specific, which has values for 2013, 2016 and 2019. Fit line used to estimate interval years.					
% reporting meth/amphetamine use in the previous 12 months	3.0%	2.7%	2.4%	2.2%	2.1%
Popn using meth/amphetamine in the previous 12 months	61,472	55,605	49,727	45,914	44,304
Assumption: % from NDSHS 2019, Australia-wide figures, which has values for 2013, 2016 and 2019. Fit line used to estimate interval years.					
% of meth/amphetamine users where crystal is usual form	56.6%	57.3%	56.4%	53.9%	49.8%
Popn using crystal meth in the previous 12 months	34,793	31,862	28,046	24,748	22,063
Assumption: % from NDSHS 2019, Australia-wide figures, which has values for 2013, 2016 and 2019. Fit line used to estimate interval years.					
% of crystal meth users where smoking is main method of use	68.8%	67.6%	68.7%	72.1%	77.8%
Popn smoking crystal meth in the previous 12 months	23,938	21,538	19,268	17,843	17,165
Assumption: % from NDSHS 2019, Australia-wide figures, which has values for 2013, 2016 and 2019. Fit line used to estimate interval years.					
% of meth users usually smoke within private dwellings	78.1%	78.1%	77.4%	75.9%	73.7%
Popn smoking meth within private dwellings each year	18,695	16,822	14,913	13,543	12,651
Assumption: on balance, one dwelling is impacted per user.					
Estimated number of private dwellings impacted each year	18,695	16,822	14,913	13,543	12,651
Assumption: The proportion of people moving houses across years is as per the 2016 Australian Census. Fit line used to estimate interval years.					
Estimated number of new dwellings impacted over 5 years	18,695	2,977	2,640	2,397	2,239

	Totals
Total dwellings in WA impacted by meth smoking over 5years	**28,948**
Total population impacted by meth smoke houses over 5years	**75,265**

Individuals who carry hypofunctional alleles of cytochrome P450-2D6 (CYP2D6) are thought to be more susceptible to acute and potentially sub-chronic effects from methylamphetamine due to slower metabolic clearance of the drug, and higher accumulated levels after exposure (54). These 'poor metabolisers' comprise around 5.4% of Australians; a figure which may quadruple when considering those whose CYP2D6-led metabolism is inhibited by concurrent medications (55). It also seems probable that renal impairment would restrict methylamphetamine clearance.

Summary: In a reasonable case scenario, around 2.7% of households in WA might have been contaminated to some degree by, or at least subject to, methylamphetamine smoking over the past five years. This would mean that more than 75,000 individuals may have been exposed to methylamphetamine, including those where this may be primarily third-hand. Roughly 15% of Western Australians are at higher-than-average risk of exposure to or adverse health impacts from environmental methylamphetamine based on age, genetic predisposition and/or use of the social housing system.

Levels of contamination resulting from smoking

Smoke house surface contamination

Four major sources of data (three observed sources and one modelled) have contributed to a multiple lines of evidence approach to estimating levels of surface contamination that might result from smoking methylamphetamine.

Firstly, Russell et al. (2019) looked at over 13,000 surface swab results from more than 1000 properties in New Zealand, where testing had been carried out for suspicion of use of methylamphetamine, but where manufacture was not suspected (43). The mean concentration of all positive surface wipes was 2.7µg/100cm^2 (43). The average 'highest' level within a home was 8.1µg/100cm^2 (43). Of all positive surface swabs, 51.2% were ≤0.5 µg/100cm^2, 70.3% were ≤1.5µg/100cm^2, and 98.8% were ≤30µg/100cm^2 (43). The distribution of observed surface contamination levels in this paper has been estimated in Figure 1 using available parameters.

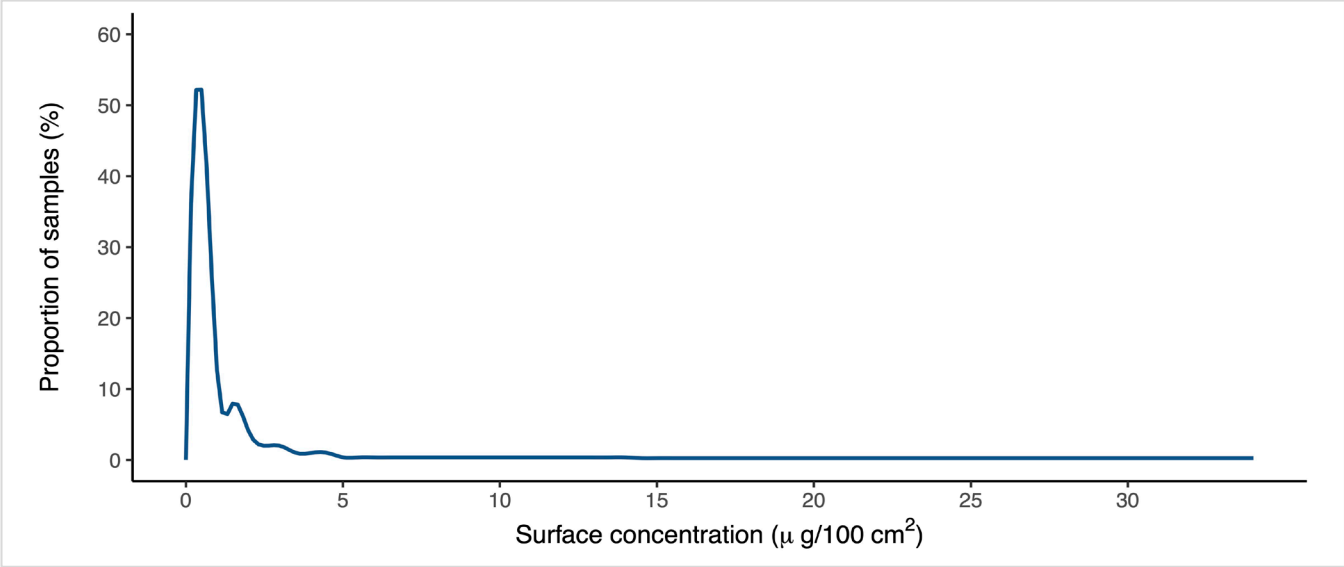


Figure 1: Modelling of the distribution of methylamphetamine concentrations across all positive samples collected from homes in New Zealand (from Russell et al. (2019) (43))

Secondly, testing reports from 55 properties that were recently tested following suspicion of use, but not manufacture, of methylamphetamine were obtained from Department of Health-accredited service providers. Most of these properties were in Western Australia (n=43), with the remainder from Queensland and Victoria. The mean concentration of positive surface wipes was also 2.7ug/100cm^2 in these properties, corroborating the New Zealand data. The average 'highest' level within these homes was 14.48ug/100cm^2, which is higher than reported in New Zealand and may reflect differences in testing practices or patterns of use, or may be a function of smaller sample size. In this sample of properties, 29.0% had a mean surface swab result ≤0.5 µg/100cm^2, 58.2% had mean ≤1.5 µg/100cm^2, 83.6% had mean ≤5 µg/100cm^2 and 100% had mean ≤30 µg/100cm^2.

Thirdly, aggregated data provided by two different Australasian laboratories, inclusive of all methylamphetamine tests that they had undertaken in respective time periods, are presented in Table 2. These values lack contextual information, and may be skewed toward lower concentrations by potential inclusion of post-remediation samples, and toward higher concentrations by potential inclusion of samples from sites of methylamphetamine manufacture. The results are largely consistent with the previously discussed work and among other things demonstrate that 90.7% and 88.4% of samples, respectively, measured less than 5.0 µg/100cm^2. One significant difference is that for Laboratory 2 an inordinate proportion of results,

64.1%, were ≤0.02 µg/100cm^2 (Limit of Detection) which may reflect testing as part of a survey rather than based on suspected contamination.

Table 2: Surface concentration results for all samples tested for methylamphetamine (µg/100cm^2) provided by two different Australasian laboratories

	Laboratory 1	Laboratory 2
Time period	Jan 2017 – March 2018	Jan 2019 – Dec 2020
n (samples)	Unknown, likely 100s	78
% 0 - 0.02	12.3	64.1
% 0.02 - <0.5	49.2	5.1
% 0.5 - <1.5	15.9	11.5
% 1.5 - <5.0	13.3	7.7
% 5.0 - <10.0	4.5	3.8
% 10.0 - <20.0	2.7	7.7
% 20.0 - <50.0	1.4	0
% 50.0 - <100.0	0.4	0
% 100.0 - <500.0	0.26	0
Mean	3.94	Estimated 1.82*
Maximum	39,243	unknown

*Based on midpoint value and proportion of each range.

By way of comparison with the above “real” contamination values, it is possible to try to estimate the amount of meth that could be deposited on adjacent surfaces during smoking. This was done by Martyny et al. (2008) (42) when undertaking simulated methylamphetamine smoking research. For a range of simulated smoking frequencies they measured air and surface levels of methylamphetamine contamination. They converted their readings into “real” numbers by subtracting the amount of methylamphetamine absorbed by the smoker, 67.3% or 90.3% (56, 57), to arrive at, among other things, average surface contamination levels. These were 0.08ug/100cm^2 or 0.02ug/100cm^2, respectively for a single smoke of 100 mg of methylamphetamine in a 100m^2 surface area space (motel room).

Although not done by the researchers, it is possible to calculate that less than 5% of the methylamphetamine smoke appears to have deposited on surfaces, with the balance remaining in air, decomposing or being vented.

A similar surface contamination calculation can be done for Australia, based on the Martyny et al findings, but assuming a single smoke dose of 185mg based on a 2019 Australian illicit drug survey (48) and using an inhaled dose of 79%, the midpoint of the above percentages. This would produce an average surface contamination value of about 0.08ug/100cm^2. This result would of course vary with room size, ventilation conditions, temperature, surface materials and other relevant parameters.

If methylamphetamine was smoked regularly the level of contamination would increase, noting that this may not always occur in the same room or under similar conditions. Any contamination increase based on smoking frequency will be offset to varying degrees by natural or artificial removal processes. The 2019 Australian illicit drug survey (48) also provides an indication of use rates for the relevant population. About two thirds of methylamphetamine users took it at most several times a year. Based on the above, it would be difficult for that population to cause surface contamination in excess of the HIL level of 0.5ug/100cm^2. Of the remaining population, about half used methylamphetamine at least once a week and the rest once a month.

In a more extreme situation, likely for a small part of the user population, if they smoked methylamphetamine once a day in the same room and not allowing for removal processes, the methylamphetamine surface contamination average level might reach 365 x 0.08 = 30ug/100cm^2.

Furthermore, if the whole user population was included on a proportional basis, and the corresponding or reasonable assumed smoke rates ascribed to each, a surface methylamphetamine contamination of nearly 3ug/100cm^2 can be calculated. Again one room and no decay is assumed.

Although these estimates are quite speculative and derive from other sources of information, the results have some consistency with the measured levels provided earlier in this section.

It is worth drawing attention to other factors associated with taking and interpreting surface contamination measurements. It is likely that in many cases that the testing was prompted by a suspicion of contamination rather than a more general survey. Consequently, any associated contamination may have been relatively recent and therefore not subject to a prolonged period for the impacts to have diminished through natural or artificial removal processes.

Also, most testers will be focussing on those areas or materials that may provide the most effective indicators of contamination, such as shiny impervious surfaces such as metals, light switches and gloss painted materials. These surfaces however, may not comprise the bulk of the contaminated materials in an area. Normally the bulk of areas will be the walls, which often may be more permeable and less readily yield up the contamination by testing.

So these factors may if anything increase the levels of contamination associated with the averages we have determined in comparison with what exposed populations may experience over time.

Smoke house air contamination

Methylamphetamine concentrations in air are seldom obtained and published, and those that exist generally relate to sites of manufacture rather than smoking. Martyny et al. (2008) performed a simulated smoking experiment and estimated that air levels of methylamphetamine would be between 37 and 131ug/m^3 immediately after a single smoke (42). These levels are much lower than those observed during (520-760 µg/m^3) and 24 hours after (70-210 µg/m^3) controlled manufacture (58).

The latter experiment showed that airborne methylamphetamine levels are likely to decrease over time, with particularly marked early decreases following peak levels during the cook (58). This is supported by a series of investigations by the Minnesota Pollution Control Agency, looking at three separate former clandestine laboratories over time. At the first site, levels between 0.22-7.3 µg/m^3 at 3 months post-last cook decreased to a maximum of 0.046 µg/m^3 (and other samples mostly undetected) at 12 months post-cook, despite demolition activities at the time of the second lot of samples which were expected to cause resuspension of airborne methylamphetamine and increase observed levels (59). At the second site, levels between 0.303 and 3.19 µg/m^3 at 3.5 years post-last cook decreased to undetectable levels at 4.5 years despite renovations and air conditioner cleaning being undertaken at the time (59). At the final site, levels of between 0.12 and 0.35 µg/m^3 at 5.75 months post-cook decreased to undetectable levels at 9.5 months post-cook, only becoming detectable again at levels of 0.097 – 0.2 µg/m^3 during remediation activities including removal of insulation and sanding of wooden floors (59). No corresponding surface contamination levels were provided for these sites.

Wright et al. (2020) reported methylamphetamine levels in one house between 0.53 and 8.3 µg/m^3, corresponding with surface levels ranging between 0.52 and 49µg/100cm^2 (and up to

250 µg/100 cm^2 detected on the air conditioning unit), approximately ten years after manufacture of methylamphetamine in the home was suspected (47). Another investigation which lacked contextual information relating to the duration and recency of manufacture found methylamphetamine levels in air between 0.2 and 3.0µg/m^3 at three sites, only where surface concentrations were equal to or greater than 60µg/100cm^2 (60). Measurable levels in air in the longer-term are likely to stem from gradual desorption from surfaces over time, rather than persistence in the airborne state. To date, no estimates of desorption rate exist.

To supplement this information, the Department of Health has started work with some of its accredited service providers to obtain real-life observed levels of airborne methylamphetamine from smoke houses who had recently been identified as having surface contamination present. Only one house has been sufficiently assessed as yet and contextual details such as frequency of smoking and time since last smoking event were not available.

The house was a rental which had been vacated some months before the surface and air sampling took place. The surface results throughout the house ranged from 0.27 µg/100cm^2 to 22µg/100cm^2. The distribution of the contamination based on 18 house samples was quite widespread and indicated a pattern consistent with heavy smoking of methylamphetamine e.g. 14µg/100cm^2 in the toilet. Active sampling was done over 5 hours at three locations adjacent to contamination levels of 18-22µg/100cm^2. It is noteworthy that these readings were all taken from relatively small areas of high yielding surfaces e.g. kitchen cabinetry, and contamination of the much larger associated wall areas was between, 1.4µg/100cm^2 to 7.4µg/100cm^2, albeit based on single samples for each.

The resulting air readings ranged from 0.2µg/m^3 to 0.43µg/m^3. These results seem to be reflective of the level of contamination of the larger space of each room, and the fact that highest reading was in a room with the air conditioner set on 30 degree Centigrade.

The only other site where the Department of Health conducted air monitoring failed to get a measurable amount in air. This was likely because the analytical method used at the time was not sufficiently sensitive. For the most contaminated location where the monitoring failed to get a reading, 71µg/100cm^2, the limit of detection can be calculated to be 1.2 µg/100cm^2.

The above varying contamination situations and lack of information about sampling arrangements and conditions make it difficult to draw conclusions about the air levels of a methylamphetamine likely to associated with methylamphetamine surface residues. However, for smoke residues such levels are likely to be low (<1µg/m^3) even when nearby surfaces exhibit relatively high levels (up to 22 and 71 µg/100cm^2 in these homes). Although levels may be higher in the period immediately following a smoking event, third-hand exposure to future occupants of the home would usually occur after a period of weeks to months when levels in air would predominantly result from ongoing low level surface desorption.

<u>Summary</u>: Properties contaminated by methylamphetamine smoking are very likely to have average surface contamination levels of around 3µg/100cm^2, with 'hotspots' in rooms of heavy use that may reach 10-15µg/100cm^2. Levels exceeding 30µg/100cm^2 occur very rarely and would indicate heavy and frequent smoking activities. The degree and persistence of methylamphetamine contamination in air requires further investigation, however it is reasonable to assume that higher surface concentrations would enable a desorption rate sufficient to release measurable quantities of methylamphetamine to air. In smokehouses that no longer have active smoking, these levels are likely to be low (<1µg/m^3). Levels both on surfaces and in air will decay naturally over time.

Levels in context – what is acceptable?

There have been two comprehensive assessments of toxicity of methylamphetamine from environmental sources. These suggested that doses below 0.00027mg/kg/day (61) and 0.004 mg/kg/day (53) of methylamphetamine, respectively, would be protective of adverse health effects in vulnerable populations (infants and children), with at least a 300-fold safety margin included. These were developed with clandestine laboratories in mind as the source, using dermal and oral exposure routes. Though now dated (2009 and 2005 respectively), these assessments have not been superseded, and can be considered relevant for contamination from smoking in addition to manufacture. Surface contamination levels of 1.5µg/100cm^2 (41) and 0.5µg/100cm^2 (53) were calculated to result in doses just below the respective health protective reference doses. The assessment by the California Environmental Protection Agency (EPA) used human studies exclusively (61) and thus, of the two, may be the more relevant.

Recently, experts in New Zealand have argued that both estimates are over-precautionary (15). On the other hand, some Australian research suggests assessments based only on surface contamination, and therefore not accounting air contamination, may underestimate environmental risk (47).

In 2011, the Australian Government released the Clandestine Drug Laboratory Remediation Guidelines, which formally recommended a Health Investigation Level (HIL) of 0.5µg/100cm^2 for methylamphetamine in settings of known manufacture (62). This level was based on a 2009 paper by Environmental Risk Sciences (commissioned by the Australian Crime Commission) and designates the concentration above which further investigation and evaluation of contamination is indicated (63). The only other jurisdiction known to employ a HIL or 'screening level' is Colorado, USA, where any positive results over 0.2µg/100cm^2 require further investigation (Table 4) (64).

Despite the intention of the HIL, the 0.5µg/100cm^2 level has broadly been interpreted across Australia as a clean-up standard, with remediation efforts typically aiming to bring surface levels below this number. Western Australia is the only jurisdiction within Australia where this level is explicitly applied to situations of contamination from smoking in addition to manufacture (65). Outside of Australia, only Colorado, Minnesota, Kentucky and New Zealand stipulate that their guidance extends to contamination from smoking.

New Zealand and many States in the US have elected to specify clean-up standards or remediation thresholds. In the US, these values typically fall between 0.1 and 1.5µg/100cm^2 (Table 4). Several jurisdictions employ tiered approaches. In Colorado, the default clean-up standard is 0.5µg/100cm^2, except for areas of limited human exposure where the standard is 4.0µg/100cm^2, and painted surfaces which can be encapsulated by further painting, where the standard is 1.5µg/100cm^2 (64). In Minnesota, clandestine laboratories must be remediated to a strict standard of 0.1µg/100cm^2, whereas homes contaminated by smoking require cleaning to achieve levels of only 1.5µg/100cm^2 (66). New Zealand has adopted a similarly tiered distinction, requiring remediation to levels below 1.5µg/100cm^2 for homes used for manufacture, but below 15µg/100cm^2 for homes where manufacture is not suspected (67). This latter threshold is substantially higher than elsewhere in the world, justified on the basis of claimed substantially lower risk from use alone, without the presence of other chemicals of concern related to manufacture (15).

Regions outside of Australia, New Zealand and North America have comparatively little active regulation on methylamphetamine contamination. This potentially reflects patterns of availability and use in these regions, as well as the relative importance of methylamphetamine contamination among other competing priorities. To date, methylamphetamine use in the United

Kingdom (68) and Europe (outside of Czechia, Slovakia and Germany) (69) has been far surpassed by use of other stimulants, which have greater availability and are less stigmatised.

Comparatively, many countries in Africa, Asia, and South and Central America are foci of methylamphetamine production and use (70-72); however, these regions generally also face major challenges with respect to population health and development. Consequently, methylamphetamine contamination from manufacture or use within homes may be considered a lesser priority, or may be challenging to regulate with available resources.

Table 4: Summary of HILs, reference doses and clean-up standards for methylamphetamine residue contamination

	Health investigation level / screening assessment level (µg/100cm^2)	Clean-up standard / remediation threshold (µg/100cm^2)	Reference dose / health based reference value (mg/kg/day)	Ref
Australia	0.5	*0.5**		(62)
New Zealand - manufacture - use		 1.5 15		(15, 67)
Alaska, US		0.1		(73)
Arizona, US		1.5		(74)
Arkansas, US		0.05		(75)
California, US		1.5	0.00027	(41, 61)
Colorado, US - standard - limited exposure areas - encapsulated areas	0.2	 0.5 4.0 1.5	0.01 to 0.004	 (64) (53)
Connecticut, US		0.1		(76)
Hawaii, US		0.1		(77)
Idaho, US		0.1		(78)
Indiana, US		0.5		(79)
Kansas, US		1.5		(80)
Kentucky, US		0.1		(81)
Michigan, US		0.5		(82)
Minnesota, US - manufacture - use		 0.1 1.5		(66)
Montana, US		0.1		(83)
Nebraska, US		0.1		(84)
New Mexico, US		0.1		(85)
North Carolina, US		0.1		(86)
South Dakota, US		0.1		(87)
Tennessee, US		0.1		(88)
Utah, US		1.0		(89)
Virginia, US		1.5		(90)
Washington, US		1.5		(91)
West Virginia, US		0.1		(92)
Wyoming US		0.75		(93)

Note: * = the Australian national guidelines imply that the stated HIL should also act as a clean-up standard (62).

It is important to note that although governments around the world have had remediation standards in place, some for more than 15 years, there have been no controlled trials, cohort studies or even ecological studies to suggest that different standards have resulted in better or worse health outcomes for future occupants.

Summary: From a health perspective, methylamphetamine contamination from smoking is indistinguishable from contamination from manufacture, and the same health-based reference doses should apply, and arguably the health action levels. The two established reference doses have 300-fold safety factors applied. Remediation standards vary considerably around the world; Australia has an implied standard of 0.5µg/100cm^2.

Potential health effects and toxicity

Pharmacology and pharmacokinetics

Profile

D-Methylamphetamine, formally known as (2S)-N-methyl-1-phenylpropan-2-amine, is a chemical compound classed as a 'substituted amphetamine', containing a methyl substituent in the amino group (Figure 2). Methylamphetamine is a sympathomimetic amine with central nervous system stimulant activity. It acts by both facilitating the release of catecholamines, particularly noradrenaline, dopamine and serotonin, from nerve terminals in the brain and by inhibiting their uptake (94). This leads to an increase in synaptic concentration of these neurotransmitters and results in increased stimulation of postsynaptic receptors (94).

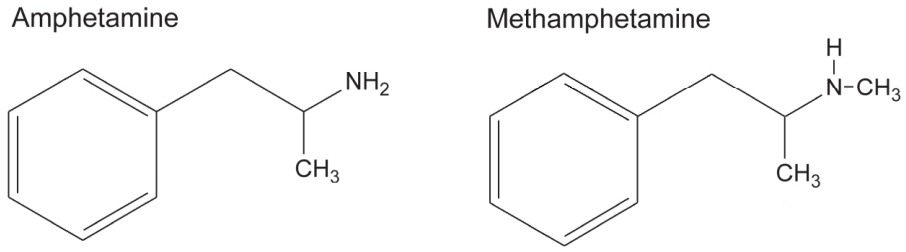


Figure 2: Molecular structures of amphetamine and methamphetamine

Typical dosages

Methylamphetamine has limited pharmaceutical uses. Pure d-methylamphetamine hydrochloride is legally manufactured as 5mg immediate release tablets (95). These are indicated for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD), and the short-term treatment of exogenous obesity (95). Oral dosages for these purposes typically begin at 5mg per day (0.2mg/kg for an average six year-old child; 0.07mg/kg for an average adult) and are typically capped at 25mg per day (1mg/kg for an average six year-old child; 0.36mg/kg for an average adult) (95).

Methylamphetamine is increasingly popular as a recreational drug. The crystal hydrochloride salt form is most commonly smoked, injected, ingested orally, or inhaled intra-nasally (1). When smoked, dosages are higher than for therapeutic use, typically at least 100mg per smoke (1.4mg/kg for an average adult) (48), however frequencies vary from multiple uses per day on most days, to 1-2 sporadic uses over the course of 12 months (1). Australian survey data from 2019 suggests that 185mg was the median volume smoked on days when methylamphetamine was used (48).

Doses resulting from third-hand exposure are dependent on the extent and nature of environmental contamination, as well as numerous factors relating to the receptor population. Models developed by the California EPA, based on a number of highly conservative assumptions, concluded that surface contamination levels of 1.5µg/100cm^2 could achieve dosages less than the reference dose of 0.0003mg/kg per day (at which health effects, therapeutic or adverse, are very unlikely to occur) (41). With varying assumptions, others have argued that even lower levels of methylamphetamine contamination (0.5µg/100cm^2) could approach this reference dose (63). As such, the real methylamphetamine dosages resulting from environmental contamination in the order of 2-30µg/100cm^2 could be orders of magnitude higher, but are unlikely to approach or exceed even the lowest doses used to treat ADHD in children.

Absorption

The absorption of methylamphetamine is route-dependent (Table 5). The dermal route is thought to be predominant in the setting of third-hand exposure to smoke residues (41). Transfer of methylamphetamine to skin from various surfaces is varied, and commonly estimated at 7% in existing models (41, 63). Once transferred to skin, dermal absorption is dependent on pH (with greater volatisation from the skin occurring at higher pH levels, reducing the amount available for absorption (96)), and skin moisture (with greater absorption by moist skin (97, 98)). On the skin, methylamphetamine rapidly penetrates the stratum corneum, which then gradually releases the drug to deeper tissues (97). Peak penetration is reached at 8 hours post-dose (96). Between 1% to 75% of a dermal dose of methylamphetamine is able to transfer to and penetrate the skin barrier in a 24 hour period (97). No research has characterised the effects of secondary barriers (e.g. loss in fatty tissues, or at vascular walls), and no data is available describing serum or target organ concentrations of methylamphetamine achieved via dermal absorption.

The gastrointestinal tract is another source of absorption. In the context of third-hand exposure, oral intake is thought to be most relevant for infants and young children, who exhibit hand-to-mouth and other mouthing behaviours. Methylamphetamine is thought to be readily absorbed from the gastrointestinal tract, with one estimate of 67.2% oral bioavailability proposed (56). The extent of first-pass metabolism is unquantified. Maximum plasma concentrations are achieved at 3.2-3.6 hours post-ingestion, with plasma concentrations of 19.8ng/mL and 37.2ng/mL for initial doses of 9.2 and 18.4 mg respectively (99). The systemic concentrations from oral doses from environmental sources will be many-fold lower than the doses studied in the therapeutic range.

Exposure via inhalation was once considered unimportant due to the non-volatile nature of methylamphetamine. However, the possibility of continued desorption from surfaces within a home has raised the possibility of inhalational risk from methylamphetamine (47). Of the dose delivered to the lungs during smoking, total bioavailability has been estimated at 67% (100) and 90.3% (56). Methylamphetamine appears rapidly in plasma after smoking, reaching levels of 29.0ng/mL by the end of the smoke (30mg initial dose), indicating rapid transfer from alveolar spaces to the blood stream (57). Peak concentrations (47.1ng/mL after a 30mg initial dose) occur approximately 2.5 hours after the drug is inhaled, with levels plateauing for two hours before a steady decline over 48 hours (57). This situation is vastly different to environmental third-hand exposures, where concentrations of methylamphetamine in inhaled air are substantially lower than concentrations inside a smoking pipe. Inhalation of contaminated indoor air is likely to contribute to very low levels of methylamphetamine absorption, but with exposures over longer, more continuous time periods.

Table 5: Summary of absorption efficiency of methylamphetamine by route

Route	Bioavailability after absorption	Time to maximum serum concentration
Dermal	Unknown (likely <75%)	Unknown (likely >8 hours)
Inhalational	67.0 – 90.3%	2.5 hours
Gastrointestinal	67.2%	3.2 – 3.6 hours

Distribution

Once absorbed, the behaviour and fate of methylamphetamine is consistent regardless of the route of initial exposure. Methylamphetamine has a moderate volume of distribution, estimated at 3.2 – 4.6 L/kg (56, 100, 101), and is distributed through most organs (102). Highest uptake occurs in the lungs, liver, brain and kidneys (102). The lipophilic nature of the compound

ensures ready distribution across the blood-brain barrier (103), across the placenta (104, 105), and into breast milk (106).

Metabolism and elimination

In humans, methylamphetamine is metabolised primarily in the liver, by aromatic hydroxylation producing 4-hydroxymethamphetamine (via cytochrome P450 2D6), and N-demethylation to produce amphetamine (also via cytochrome P450 2D6) (107). To a lesser extent, other metabolites include norephedrine, 4-hydroxyamphetamine, 4-hydroxynorephedrine, benzyl methyl ketoxime and benzoic acid (108). The amphetamine metabolite is active, but appears insignificant in terms of clinical effects, reaching fairly low peak plasma concentrations around 12 hours post-ingestion of methylamphetamine (56, 57). Methylamphetamine is excreted predominantly in urine (estimated at 90% (108)), with varying proportions as unchanged drug (ranging from 18% to 55% (10)) and metabolites. Clearance has been estimated between 9.5 and 39.5 L/hour (56, 99-101, 109) in adults, with most estimates at the lower end of this range. Lesser routes of elimination may occur via sweating and faecal elimination (10). Methylamphetamine is considered to be fully eliminated, without substantial bioaccumulation (110).

Pharmacokinetic profile

The pharmacokinetic profile of methylamphetamine from environmental sources was estimated using available parameters from the literature (Figure 3, Table 6). The benefit of modelling the pharmacokinetic profile of methylamphetamine is two-fold: firstly, to understand how doses from multiple exposure pathways might culminate in a total received dose; and secondly, to understand how regular doses might accumulate in the body over time. A non-compartmental model was chosen given the known rapid distribution of methylamphetamine across most body tissues, and also to remain in keeping with previous models (99).

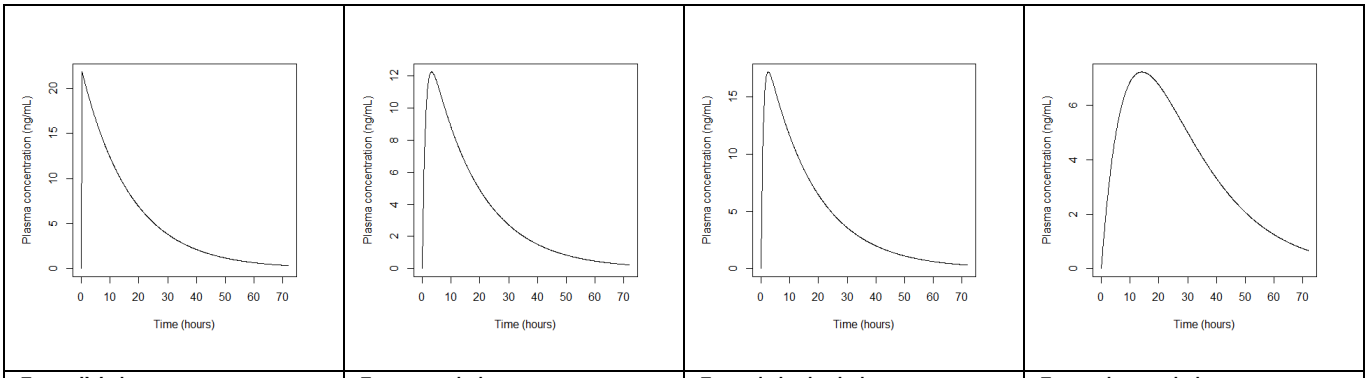


Figure 3: Pharmacokinetic profiles of single 5mg intravenous (IV), oral, inhaled and dermal doses of methylamphetamine in adults

Pharmacokinetic modelling enables estimates of plasma concentrations, usually expressed in nanograms of methylamphetamine per millilitre of blood (ng/mL), to be estimated from various doses and routes. For example, a 5mg dose of methylamphetamine might result in plasma concentrations exceeding 20ng/mL if delivered intra-venously, or less than 8ng/mL if applied dermally (Figure 3). Doses are almost fully cleared within 72 hours, due to high clearance rates.

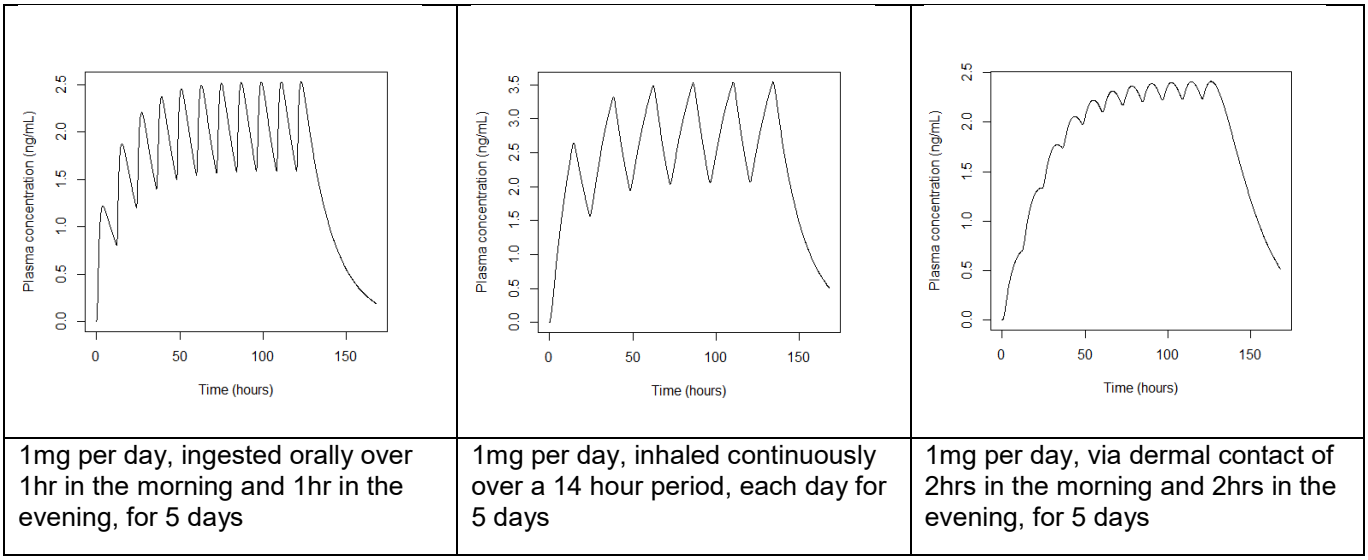
Pharmacokinetic profile of sub-chronic exposures

Under conditions of regular, repeated dosing, methylamphetamine is expected to reach steady-state concentrations in adults within 3-4 days, regardless of route (Figure 4). Exposure to methylamphetamine through multiple routes is likely to be aggregate, increasing overall total

bodily methylamphetamine level. However, concentrations are still expected to reach a steady state within several days.

Table 6: Summary of pharmacokinetic parameters used to develop the models

Route	Oral dose	Inhalational dose	Dermal dose
Bioavailability	67.2%	90.3%	75%
Absorption constant	0.9	1.3	0.085
Half life (absorption)	0.77 hours	0.53 hours	8.1 hours
Tmax	3.2 hours	2.5 hours	14.0 hours
Cmax	12.24ng/mL	17.19ng/mL	7.23ng/mL
Volume of distribution	226.8L	226.8L	226.8L
Half life (elimination)	11.8 hours	11.8 hours	11.8 hours
Clearance rate	13.32L/hr	13.32L/hr	13.32L/hr



1mg per day, ingested orally over 1hr in the morning and 1hr in the evening, for 5 days	1mg per day, inhaled continuously over a 14 hour period, each day for 5 days	1mg per day, via dermal contact of 2hrs in the morning and 2hrs in the evening, for 5 days

Figure 4: Pharmacokinetic profiles of regular repeated dosing through oral, inhaled and dermal exposure to methylamphetamine, assuming a total dose of 1mg per route per day.

<u>Summary</u>: Methylamphetamine can be absorbed into the body via dermal, oral, and inhalational routes. Once absorbed, the kinetics of distribution, metabolism and elimination are alike (i.e. independent of absorption route). Methylamphetamine is rapidly cleared and does not tend to bioaccumulate. Levels in blood are quantifiable, and offer the most accurate measure of received dose. Regular, repeated dosing (reflecting sub-chronic exposure) results in steady-state levels in blood within 3-4 days.

Toxicology

Acute toxicity studies

Ingestion of methamphetamine has several dose-dependent acute physiological (not necessarily harmful) effects. Stimulation of the sympathetic division of the central nervous system by methylamphetamine causes a characteristic ‘fight or flight’ response. Sympathetic neurotransmission causes an increase in heart rate and heart contractility, thereby increasing cardiac output (57). Blood pressure increases because of both increased cardiac output and vasoconstriction (57, 111). Sympathetic stimulation causes increased respiratory rate (10) as

well as bronchodilation (112). Muscular activity is thought to be improved through transient hyperglycaemia and dilation of blood vessels within skeletal muscle (113).

Pupils dilate in response to sympathetic innervation (107), primed for distance vision. Arousal and alertness are increased, manifesting as improved attention and concentration (114, 115). Acute psychological effects include increased stimulation, euphoria, mood and libido (116-118). The hypothalamic-pituitary-adrenal axis responds to methylamphetamine ingestion by increasing levels of circulating stress hormones (such as cortisol and adrenocorticotropic hormone) (119). Conversely, non-essential physiological activities, such as stomach and intestinal function, are inhibited (113). Appetite and food intake is generally reduced (120). These low dose effects form the basis of the pharmacological indications for methylamphetamine.

The health effects of methylamphetamine are commonly described alongside concentrations in blood (Figure 5). This has been necessitated in part by circumstances of illicit use where doses are unreported, but health effects and blood concentrations are both clear. The therapeutic blood concentration of methylamphetamine is estimated to be 20-50ng/mL (121). Higher doses of methamphetamine (above approximately 40mg orally, achieving serum concentrations above 100ng/mL) produce acute effects that exceed what would be considered a normal physiological response. Overstimulation of sympathetic pathways can result in dysphoria, restlessness, anxiety, tremors, dyskinesia and compulsive behaviours (107, 113). Driving offences, and violence and aggression, are most commonly seen at blood concentrations above 300ng/mL (107, 121).

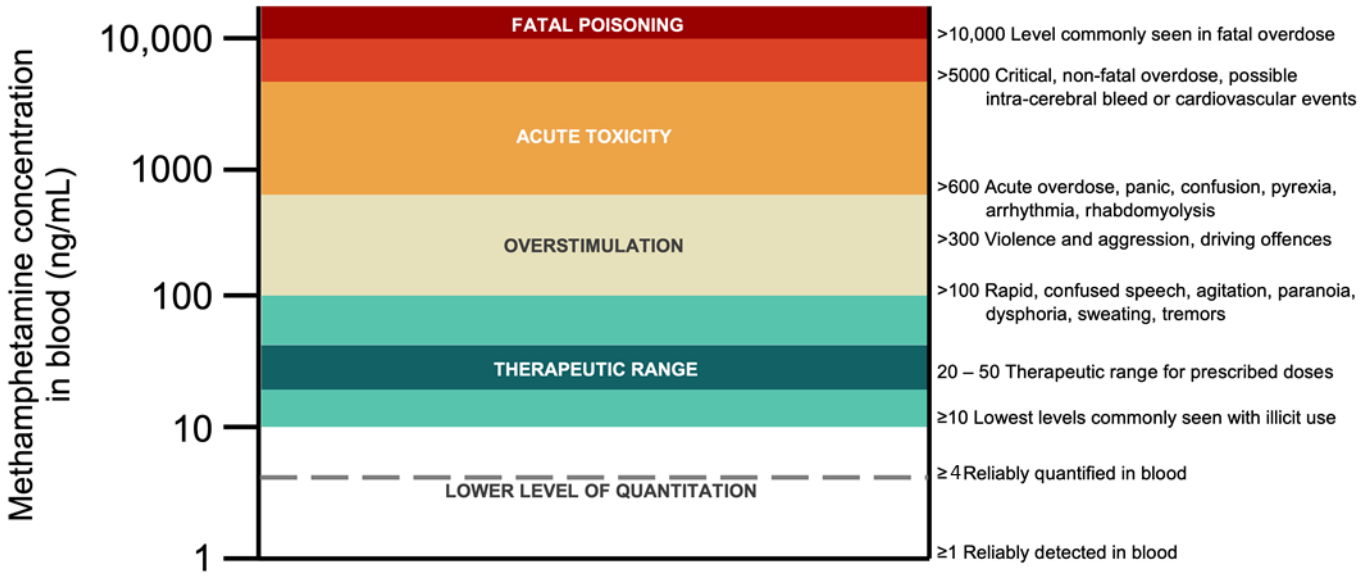


Figure 5: Methylamphetamine concentrations in blood and associated health effects

Acute toxicity from overdosage (blood levels 600-5000ng/mL (122)) presents as restlessness, tremor, hyperreflexia, rapid respiration, confusion, combativeness, abnormal gait, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis from muscle breakdown (10, 107). Gastrointestinal symptoms included nausea, vomiting, diarrhoea and abdominal cramps (10). Cardiovascular effects can include arrhythmias, hypertension or hypotension, pulmonary oedema, and circulatory collapse (10, 107).

Fatal poisoning can result in cardiac dysrhythmias, myocardial infarction, cardiorespiratory arrest, intractable seizures, hypoxic brain damage, hyperthermia, or intracerebral bleed (10, 107, 123). The lethal dose (LD50) has been identified at 43.2 - 95mg/kg in mice (delivered intra-peritoneally) (124-126); the equivalent of over 3g in an adult human. Observations of lethal dose

have varied in humans, and are typically limited to case studies or case series. Deaths are most commonly reported at blood concentrations above 10,000ng/mL (122, 123), however non-lethal doses may be much higher among experienced users.

Sub-chronic toxicity studies

Sub-chronic exposures refer to short-term repeat dose studies, lasting up to 10% of the expected lifespan (127). For methylamphetamine use in humans, this can be defined as periods less than 10 years. This timeframe most closely reflects the duration of exposure that might be seen in third-hand exposures in residential properties.

The California EPA developed models based on a number of health-protective assumptions, and concluded that dosages of methylamphetamine less than 0.0003mg/kg per day, via dermal and oral ingestion routes, were very unlikely to have health impacts, therapeutic or adverse, in the most susceptible population (children 6-24 months of age) (61). This dose would equate to 0.0075mg per day in a 25kg child, which is 666 times smaller than the recommended therapeutic initiation dose for children with ADHD (95) (Figure 6). The reference doses include 300-fold safety margins to account for extrapolation of a LOAEL to a NOAEL (10-fold), variation in individual sensitivity (10-fold) and incompleteness of the database (3-fold).

Outside of modelling, very little information is available regarding the long-term impacts of regular low doses of methylamphetamine in humans. There are no published studies investigating the long-term effects of prescribed methylamphetamine (though data relating to long-term amphetamine use may be relevant), nor any controlled studies looking at the effects of sub-chronic environmental exposure to methylamphetamine in humans.

The only evidence of health concerns from third-hand exposure to methylamphetamine contamination comes from a series of opportunistic case studies of household groups in Australia who discovered their residence was a former clandestine laboratory (14). Time spent in these properties ranged from regular short visits to ten years (14). This work found that common self-reported health complaints in these settings included skin irritation or rashes, eye irritation, respiratory effects (such as persistent cough or asthma-like symptoms), persistent and recurrent respiratory infections, sleep issues, headaches, behavioural effects, mood effects, and memory difficulties (14). It remains possible that these effects were secondary to other contaminants or environmental conditions, or were impacted by positive recall bias given that the residents were already aware that their property had been deemed contaminated. Symptoms were non-specific, varied widely and there was no evidence of increasing health problems with the level of contamination (dose-response effect). There are no published case studies reporting adverse health effects of third-hand exposure from smoking methylamphetamine.

Sub-chronic effects at the higher doses associated with regular illicit methylamphetamine use are better documented. Many of these effects are neuropsychiatric and psychological. Binge-like use has been reported to cause sleeplessness, hallucinations and paranoia (128), irritability and unprovoked aggression (129). High doses in the longer term can cause psychological changes that resemble psychosis (though researchers qualify that it is difficult to avoid confounders as this would require studying individuals using methylamphetamine alone, and without a previous mental health history) (113, 130).

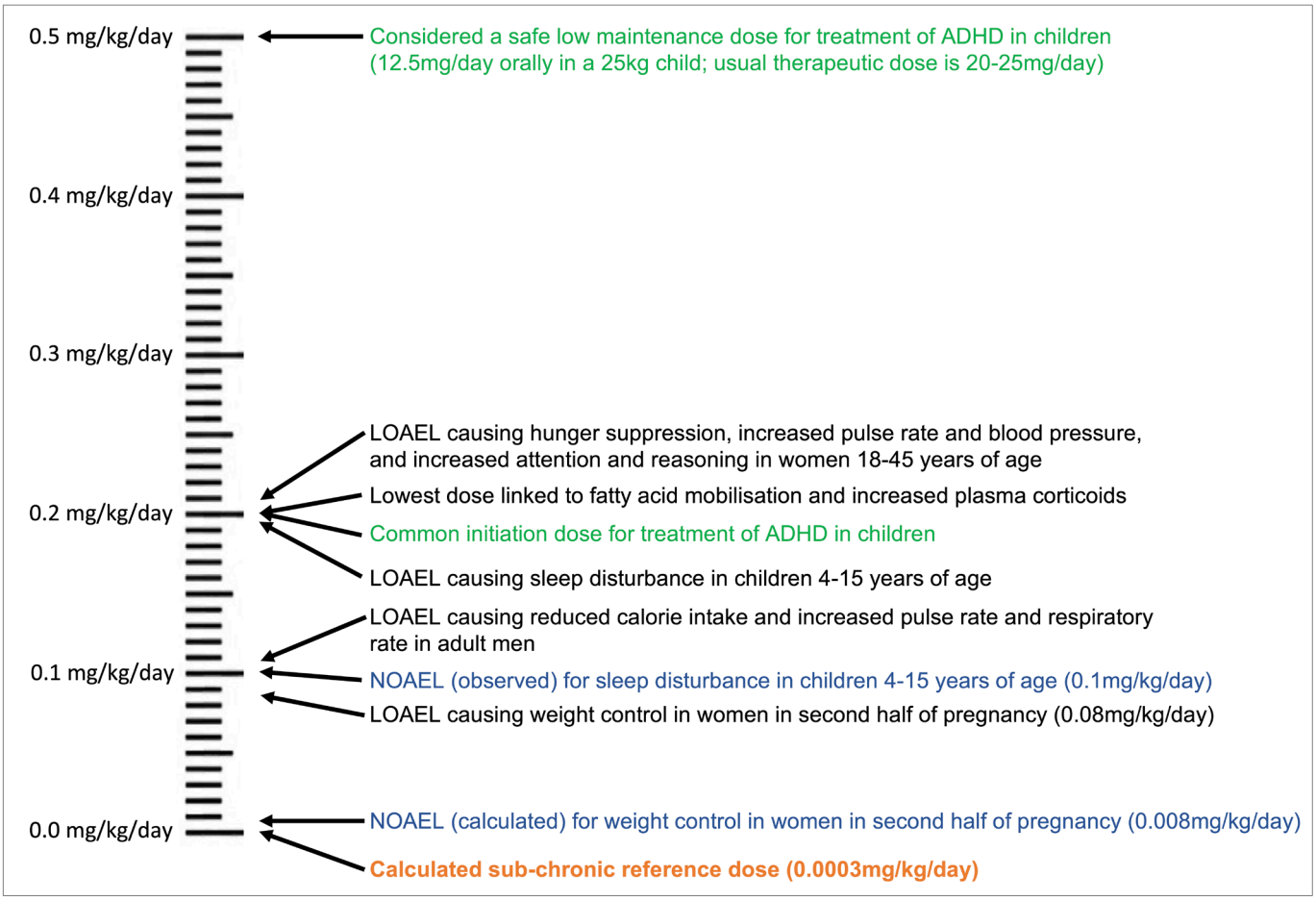


Figure 6: Lowest doses thought to cause health effects on a sub-chronic basis. Note: LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; ADHD = attention deficit hyperactivity disorder

Subjects using methylamphetamine more than four times per week for over two years have larger striatal volumes (131). Dopamine transporter density in the striatum is persistently reduced even after periods of abstinence (132, 133). Regular use can cause sensitisation of the stress hormone response, increasing the intensity and duration of HPA stress responses to daily life stressors (134). Methylamphetamine can increase the expression of inflammatory cytokines, which may prolong and exacerbate neuropsychiatric symptoms (135).

Methylamphetamine can impact immunity by directly suppressing dendritic cells, macrophages and T cell antigen presentation functions, possibly increasing susceptibility to infectious threats (136). Furthermore, the hypertension associated with ongoing methylamphetamine use, as well as high rates of rhabdomyolysis among users, can impair renal function (137, 138).

Chronic toxicity studies

Studies assessing chronic toxicity aim to capture effects of exposures that last the greater part of the lifespan (127). For methylamphetamine, studies of chronic use are commonly defined as periods of greater than ten years (113, 139).

The long-term neurological effects of methylamphetamine are considered to primarily be the result of neurodegeneration of the dopaminergic system (140). In subjects consuming an average of 3g of methylamphetamine per week for 10 years, there is a substantial loss of gray matter in the frontal cortices of the brain, reduced hippocampal volume, and white matter hypertrophy (141). Other brain changes described include structural alterations in the corpus callosum (142), reduced white matter integrity in frontal regions (143), and changes in cerebral

vasculature (144). Lower levels of dopamine transporter and serotonin in certain brain regions have been linked with behavioural symptoms (133, 145). In a post-mortem study, chronic methylamphetamine users had dopamine levels depleted as severely as in Parkinson's Disease patients (146).

These changes in the brain contribute to impaired executive function and result in poor coping skills, including disorganised lifestyle and interpersonal difficulties, irritability, aggressiveness and impulsivity, which often impact social factors such as employment and housing (113).

Long-term methylamphetamine use is associated with numerous severe cardiovascular complications related to chronic hypertension and cardiovascular disease, such as angina, arrhythmias, valvular disease, haemorrhagic and ischaemic strokes, and a high incidence of myocardial infarction (147). If smoked over a long period, chronic bronchitis and pulmonary hypertension can develop (148). Other effects of chronic methylamphetamine use include malnourishment (149), 'meth mouth' resulting from dry mouth, xerostomia and poor hygiene (150), and skin lesions from compulsive scratching (151).

Reproductive toxicity studies

There are no studies examining the potential reproductive toxicity of methylamphetamine in humans. Limited animal studies suggest that methylamphetamine does not impact the oestrous cycle, mating ability or incidence of impregnation of female rats, but does negatively impact both ovarian reserve, and maternal behaviour toward pups (152, 153). In male rats, methylamphetamine administration appears to impair sexual motivation and performance (154), and to reduce spermatogenesis (155).

Developmental toxicity studies

One large population-based study found no increased risk of fetal malformations resulting from maternal use of amphetamines for medicinal purposes during pregnancy (156). A second large population-based study found that methamphetamine exposure conferred statistically significant increases in hypertensive diseases of pregnancy, eclampsia, preterm delivery, small-for-gestational-age, low birthweight, abruption, and intra-uterine fetal death (157). Studies among methamphetamine abusers are often small and tend to be unable to account for confounders (such as poverty, nutrition, maternal mental health status, other health problems, and the use of other drugs). Associations with impaired structural brain development of the child, and impaired cognition and executive function in the child, have been inconsistently reported (158, 159).

Genotoxicity studies

Methylamphetamine is not currently listed as a human carcinogen, nor have the available animal studies demonstrated evidence of carcinogenic activity in rats and mice (160). Small studies have demonstrated genotoxicity in limited contexts, including histidine operon mutagenicity in Salmonella typhimurium strain TA98, and micronucleus in bone marrow erythrocytes of mice (161).

Summary: Methylamphetamine has a broad range of documented health effects in humans. These can be severe and potentially fatal, and can impact individuals across acute, sub-chronic and chronic timeframes. However, data suggesting health effects can occur as a result of sustained low-dose exposure from third-hand environmental sources of methylamphetamine are lacking. There are no new data to reassess/re-evaluate the existing health reference doses. No dose-response relationships have been described for environmental methylamphetamine exposure and health. Health responses are most comprehensively described in relation to blood methylamphetamine concentrations.

Health risk characterisation

Modelling received doses from environmental sources

Previous toxicity assessments have proposed health-based reference doses based on tolerable daily intake of methylamphetamine via dermal and oral routes (53, 61). This assessment takes the approach one step further, using a range of environmental dose and human exposure and susceptibility scenarios to estimate plasma concentrations over time. Distinct from previous toxicity assessments, this model includes three exposure pathways (dermal, oral and inhalational). The model considers sub-chronic durations of one year, and does not include depletion of environmental methylamphetamine concentrations over time; it is therefore likely to overestimate received doses. The model does not factor in changes to metabolism and clearance over sub-chronic durations of exposure (such as due to tolerance) as the influence of these factors is unknown.

Firstly, a series of comparator maximum plasma concentrations (Cmax) were estimated using four previously published dose scenarios (53)(61)(scenarios 1-4; Table 7, Figure 7; see Appendix 1 Table S1 for assumptions). In high risk infants, the 'safe' daily reference doses articulated by the California EPA and the Colorado Department of Public Health and Environment would result in maximum plasma concentrations of 0.03 and 0.3 ng/mL respectively, which are unlikely to be detected with existing assays. The California EPA explores two possible NOAELs based on two different studies. Although there is uncertainty in these NOAEL estimates, the results indicate that low level sub-chronic exposure could feasibly cause plasma concentrations in the quantifiable range (1.9 and 15.7 ng/mL, respectively)

Table 7: Plasma concentrations estimated from previously published dose scenarios

	Scenario details	Cmax (ng/mL)
Scenario 1: Safe level: California	An infant who absorbs 0.0003mg/kg/day of methyl-amphetamine via dermal and oral pathways (see Table 6 of (61)), with pharmacokinetic values reflecting higher-than-average susceptibility, and behaviours that maximise time spent in the home.	**0.03**
Scenario 2: Safe level: Colorado	An infant who absorbs 0.004mg/kg/day of methyl-amphetamine via dermal and oral pathways (see Section 4.4 of (53)), with doses multiplied by 9.6 to achieve the daily total), with pharmacokinetic values reflecting higher-than-average susceptibility, and behaviours that maximise time spent in the home.	**0.30**
Scenario 3: NOAEL: adult, calculated	An adult who absorbs 0.008mg/kg/day of methyl-amphetamine orally (see page 4 of (61)), with typical pharmacokinetic values, and typical behaviour patterns.	**1.92**
Scenario 4: NOAEL: child, observed	A child who absorbs 0.1mg/kg/day of methylamphetamine orally (see page 4 of (61)), with typical pharmacokinetic values, and typical behaviour patterns.	**15.72**

Next, daily doses and maximum plasma concentrations were estimated for six new scenarios of environmental exposure (scenarios 5-10), including two estimates of third and second hand exposure to contamination from clandestine laboratories, as comparators (Table 8, Figure 8; see Appendix 1 Table S2 for assumptions).

Table 8: Estimated absorbed doses and maximum plasma concentration of methylamphetamine for adults and children in homes associated with average and high contamination situations.

	Exposure scenario	Absorbed dose (mg/kg/day)	Cmax (ng/mL)
Scenario 5: Typical adult, typical smokehouse contamination	An adult exposed to average levels (2.7µg/100cm^2) of surface contamination and low level (1µg/m^3) air contamination from methylamphetamine smoking in a home environment -- with dermal, oral and inhalational routes, typical pharmacokinetic values, and typical behaviour patterns.	**0.0003**	**0.05**
Scenario 6: Typical infant, typical smokehouse contamination	An adult exposed to average levels (2.7µg/100cm^2) of surface contamination and low level (1µg/m^3) air contamination from methylamphetamine smoking in a home environment -- with dermal, oral and inhalational routes, typical pharmacokinetic values, and typical behaviour patterns.	**0.001**	**0.05**
Scenario 7: High risk adult, high smokehouse contamination	An adult exposed to high levels (30µg/100cm^2) of surface contamination and moderate level (3µg/m^3) air contamination from methylamphetamine smoking in a home environment -- with dermal, oral and inhalational routes, pharmacokinetic values reflecting higher-than-average susceptibility, and behaviours that maximise time spent in the home.	**0.005**	**1.35**
Scenario 8: High risk infant, high smokehouse contamination	An infant exposed to high levels (30µg/100cm^2) of surface contamination and moderate level (3µg/m^3) air contamination from methylamphetamine smoking in a home environment -- with dermal, oral and inhalational routes, pharmacokinetic values reflecting higher-than-average susceptibility, and behaviours that maximise time spent in the home.	**0.025**	**1.38**
Scenario 9: High risk infant, typical third-hand clan lab contamination	An infant exposed to a typical level of clan lab (50µg/100cm^2) surface contamination and high level (5µg/m^3) air contamination from methylamphetamine manufacture -- with dermal, oral and inhalational routes, pharmacokinetic values reflecting higher-than-average susceptibility, and behaviours that maximise time spent in the home.	**0.042**	**2.30**
Scenario 10: Typical adult, first responder to clan lab incident	An adult exposed to very high levels on surfaces (500µg/100cm^2) and in air (500µg/m^3) for one hour while responding to an incident in an active clandestine laboratory, without PPE. Typical adult values used, except higher inhalation rate typical of moderate exercise.	**0.014**	**3.33**

These results indicate that typical adults and infants living in former smokehouses with average level methylamphetamine contamination (scenarios 5 and 6) may be exposed to small, sub-chronic doses of methylamphetamine, resulting in plasma concentrations below the level of detection (approximately 0.05ng/mL). In scenario 5, the absorbed dose is similar to the

California EPA reference dose (scenario 1), however possible inhalational exposures are included in this model and partially explain the higher Cmax value in scenario 5.

Generally, adults absorb greater absolute doses than children, due to greater body surface area, greater inhalation rates, and a greater time spent awake in the contaminated environment. However, infants absorb greater doses per body weight and consequently achieve higher plasma concentrations of the drug.

High risk adults and infants in situations of higher contamination in the home (scenarios 7 and 8)(likely less than 1% of the exposed population) demonstrate that continuous exposure to higher surface and air contamination (around 30µg/100cm^2 and 3µg/m^3, respectively could feasibly result in concentrations of drug which are detectable in plasma. These are still below the range of values most commonly documented alongside physiological or pathological effects, but are approaching the calculated NOAEL values in scenario 3, noting that these NOAEL values are for small specific groups and may not reflective of risks for a larger and more diverse population.

By way of comparison, high risk infants in clandestine laboratory who are continuously exposed to very high levels, albeit typical of labs, (scenario 9) would have plasma concentrations of methylamphetamine that are higher again. The contamination levels included in the scenario modelling are taken as averages – levels on surfaces and in air are likely to reach substantially higher levels during a cook, and as such the plasma concentrations in infants in this environment are likely to be considerably higher at times, plausibly reach the range of values known to cause health impacts. Attending an incident in a clandestine laboratory for one hour during or shortly after a cook, a first responder (without PPE) might reach similarly high plasma concentrations.

Finally, daily doses and maximum plasma concentrations were estimated for the highest risk group (infants with high susceptibility and behaviours that maximise exposure), at varying surface clean-up thresholds (scenarios 11-18, Table 9).

Given the dominance of dermal exposure in received doses from previous models, a distinction was made between a) remediating all surfaces in living spaces (‘within reach’ of the occupants) to the threshold level, and b) remediating all surfaces in the home to the threshold level. The former would mitigate dermal and oral exposures, but would incompletely address low level air contamination resulting from desorption from non-remediated areas (such as roof spaces). The latter approach would mitigate dermal and oral exposures to the same extent, but would also effectively eliminate inhalational exposures.

In this analysis, cleaning all surfaces back to the current Australian clean-up threshold of <0.5µg/100cm^2 (scenario 18) essentially achieves the California EPA safe reference level for high risk infants in terms of the estimated absorbed dose per day. The Cmax achieved from these ongoing daily exposures is 0.03ng/mL, likely undetectable on current assays. In comparison, cleaning only surfaces within daily human reach would achieve very similar results given that dermal exposure comprises most of the daily dose and that ongoing air contamination via desorption is thought to be low.

Absorbed daily doses increase as remediation criteria become less stringent, but not by a large margin. By cleaning all surfaces within reach to a standard of <5µg/100cm^2, the expected plasma concentration in high risk infants could reach 0.39ng/mL (scenario 11). It is notable that cleaning all surfaces to <1.5µg/100cm^2 (scenario 14) could achieve the same level of health protection as cleaning surfaces within reach to a slightly more stringent standard of <1.0µg/100cm^2 (scenario 15), highlighting the need to focus on these contactable surfaces.

Table 9: Estimated absorbed doses and maximum plasma concentration of methylamphetamine for high-risk infants in homes remediated to a range of clean-up standards.

Remediation scenario	Absorbed dose (mg/kg/day)	Cmax (ng/mL)
Scenario 11: All surfaces within reach <5µg/100cm^2	**0.0053**	**0.39**
Scenario 12: All surfaces <5µg/100cm^2	**0.0027**	**0.26**
Scenario 13: All surfaces within reach <1.5µg/100cm^2	**0.0016**	**0.12**
Scenario 14: All surfaces <1.5µg/100cm^2	**0.0008**	**0.08**
Scenario 15: All surfaces within reach <1.0µg/100cm^2	**0.0011**	**0.08**
Scenario 16: All surfaces <1.0µg/100cm^2	**0.0005**	**0.05**
Scenario 17: All surfaces within reach <0.5µg/100cm^2	**0.0005**	**0.04**
Scenario 18: All surfaces <0.5µg/100cm^2	**0.0003**	**0.03**

In considering the value of simply cleaning the contactable room areas, it should be noted that in the case of clan labs, the contamination levels in the upper areas of a room may be very high and not only pose an inhalation concern but there is the possibility of migration to lower parts of a room and thereby also presenting a risk through the other exposure routes.

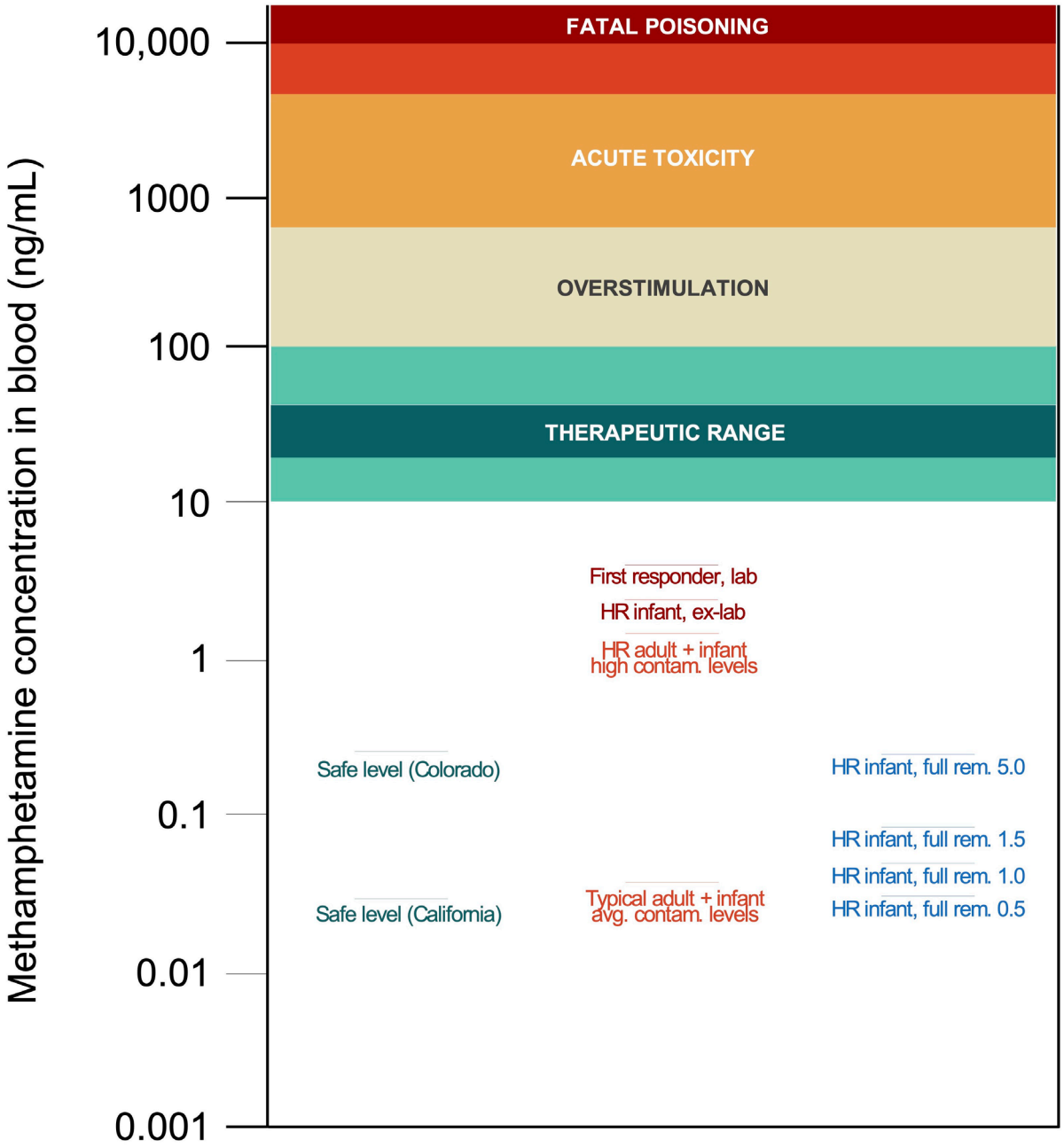


Figure 7: Methylamphetamine concentrations in plasma (ng/mL) in various exposure and remediation scenarios, juxtaposed with approximated thresholds of health effects in humans. Note: HR = high risk; ex-lab = former clandestine laboratory; avg. = average; contam. = contamination; full rem. = full remediation to the cited level (in µg/100cm^2).

<u>Summary</u>: Based on available evidence, exposure to environmental methylamphetamine residues in former smokehouses is unlikely to generate plasma concentrations >1.5 ng/mL, even in the most susceptible individuals and using conservative modelling assumptions. Typical adults and infants living in 'average' smokehouses would have plasma concentrations of methylamphetamine which are undetectable with existing tests; however, it is possible that in some higher risk individuals, plasma methylamphetamine concentrations may reach detectable levels.

The range of plasma concentrations resulting from smokehouse exposures are estimated to fall in the safety margin range between the safe reference doses and the calculated NOAELs for particular studied groups.

In comparison, the health effects attributed to passive exposure among children and first responders in clandestine laboratories may be the result of considerably higher plasma concentrations, approaching the levels where health effects have been described.

Dermal exposure contributes to most of overall received dose in low-level settings, and therefore remediation of 'touchable' living space surfaces might offer greatest benefit.

Determination of hazard risk levels

Assessment of health risk from environmental methylamphetamine exposure due to smoke related methylamphetamine contamination was assessed using the WA Department of Health's Health Risk Assessment (Scoping) Guidelines (162). This assessment is based on both the degree of health consequences and the likelihood that they will occur.

Health consequences for occupants of smoke houses can be designated **Category 5 (Minor)** and consequences for health services can be designated **Category 6 (Negligible/slight)**. See Figure 8. Based on available scientific evidence, these categories would seem a conservative, approach to such exposures. These Categories have the following characteristics:

Health Consequences

- Acute health consequences with
  - No fatalities;
  - No permanent disabilities;
  - Non-permanent injuries requiring hospitalisation for 1-5 persons;
  - No evacuations;
- Chronic health consequences requiring medical treatment for 0-1% of the population at risk.

Health Service Consequences

- <$100,000 in associated health costs.

For health consequences, this reflects the possibility that methylamphetamine could plausibly cause acute and sub-chronic health effects such as sleep issues, headaches, behavioural effects, mood effects and memory difficulties, but given the low doses absorbed from smokehouses, these effects would be unlikely to be severe enough to cause fatalities, permanent disabilities or hospitalisations.

In regard to service consequences, consultations in primary care may be sought, but costs associated with this would not be substantial. These effects would likely be limited to a minority of the exposed population.

The likelihood of health consequences from environmental methylamphetamine exposure associated with smoke residues can be designated as **Level 4 Likely**. The authors consider this a conservative designation, based on the relatively large exposed population in WA, and the potential for unrecognised minor health consequences among susceptible populations. This designation reflects a once in 1-3 year frequency of a non-chronic incident occurring; or (less pertinently) a 31-60% chance of a chronic health effect occurring in the longer-term.

Together, these factors indicate a **Low** inherent risk level (Figure 8), even making use of conservative assumptions. Typically this would still suggest that some mitigation or management of risk may be required, within the scope of routine controls (162).

Likelihood	Consequences					
	Slight/ negligible	Minor	Moderate	Major	Massive	Catastrophic
Almost Certain	Low	Medium	High	Extreme	Extreme	Extreme
Likely	Low	Low	Medium	High	Extreme	Extreme
Possible	Very Low	Low	Low	Medium	High	Extreme
Unlikely	Very Low	Very Low	Low	Low	Medium	High
Rare/remote	Very Low	Very Low	Very Low	Low	Low	Medium

Figure 8: Risk profile of environmental methylamphetamine exposure from smokehouses, based on consequences and likelihood. Figure adapted from (162).

Routine controls in this situation could include: environmental sampling of homes where manufacture and use is suspected; notification pathways and regulatory action for properties where high level contamination from manufacture is suspected; provision of guidance for remediation of low-level contamination; and pathways to access further expert advice where required.

Summary: Based on available evidence, exposure to environmental methylamphetamine residues in former smokehouses carries a low risk to public health, and can be managed within the scope of routine controls.

Discussion and conclusions

Smoking of crystalline methylamphetamine ('ice') may release a number of chemicals into indoor environments, the most persistent and concerning of which is methylamphetamine itself. Vapours that are not absorbed by the smoker can deposit as residues and absorb into porous materials, often detectable for years after smoking ceases. This work has examined evidence regarding the credibility of the health threat from human exposure to these residues.

Based on reasonable estimates of usage from survey data, around 2.7% of households in WA might have been contaminated to some degree by methylamphetamine smoking over the past five years. This would place more than 75,000 individuals at risk of potential third-hand exposure, but with a high proportion of these being smokers or complicit in the activity. Although vulnerability and susceptibility exist on a spectrum, roughly 15% of Western Australians are estimated to be at increased risk of exposure or health impacts from environmental methylamphetamine, based on age, genetic predisposition and/or use of the social housing system.

From a health perspective, methylamphetamine contamination from smoking is indistinguishable from contamination from methylamphetamine manufacture. However, manufacture generally causes higher concentrations and greater spread of contamination from the source; thereby increasing health risk. Other chemical contaminants may also be present at sites of manufacture, depending on methods of production.

At the present time, no analytical markers can reliably distinguish manufacture from use. Both sources can cause detectable and proportionate levels of ephedrine and pseudoephedrine to be found on surfaces. Forensic analysis of residues can assist, for example detection of methylamphetamine hydroiodide can indicate hypophosphorus or red phosphorus methods of manufacture, and trace lithium hydroxide can sometimes be found after Nazi Birch cooks. However, these analytes are likely to offer a high positive predicted value (a positive detection implies manufacture) but a low negative predicted value (a negative result does not accurately reflect the absence of manufacture). As such, in most situations, the health response will likely be guided by methylamphetamine levels alone. However, in Western Australia, the Department of Health's position is that suspected meth residential contamination should be assumed to result from smoking unless there is evidence to the contrary.

The vast majority of suspected smokehouses have average surface levels less than 5µg (mean 2.7µg, median 1.5µg) of methylamphetamine per 100cm^2, with 'hotspots' in rooms of heavy use that may reach 10-15µg/100cm^2, and rarely more The rate of desorption of methylamphetamine from surfaces into air requires further investigation; it remains unclear whether the low levels of surface contamination seen in most smokehouses would release measurable quantities of methylamphetamine to air.

The first-hand health impacts of methylamphetamine use and abuse are reasonably well-documented, with increasing severity of effects at increasing doses and blood concentrations. The second-hand health impacts have limited evidence; some information is available regarding children living in clandestine laboratories, and first responders to incidents involving such sites of manufacture. Evidence pertaining to health impacts from third-hand exposure is thus far limited to case studies of families living in homes that were formerly used for manufacture, with an absence of evidence specifically relating to homes contaminated by smoking alone.

Dose-response relationships for methylamphetamine are most comprehensively described in relation to blood methylamphetamine concentrations. Results of exposure and pharmacokinetic modelling in this work indicate that adults and infants living in former smokehouses would have blood concentrations around 0.05ng/mL. For highly contaminated smoke houses and In

circumstances of high inherent susceptibility as well as behaviours that maximise exposure, levels might be as high as 1.4ng/mL. These both fall in the range of values between the calculated group specific NOAEL (scenario 3) and the reference dose which considers additional safety margins (scenario 1) (61).

In contrast, a first responder who spends one hour inside an active clandestine laboratory might achieve blood concentrations closer to 3 ng/mL, which is above the most-commonly applied NOAEL and approaching the range of documented health effects. This could explain why second-hand exposures have been associated with adverse health impacts, but reports of health impacts from third-hand exposures at lower levels are less common.

Table 10: Knowledge gaps relating to the health effects of environmental methylamphetamine contamination from smoking within homes

Regarding environmental contamination
1. Properties are not routinely tested for methylamphetamine contamination, nor apparently have any random sampling programs been completed (in WA, Australia or elsewhere). The prevalence of households contaminated with methylamphetamine is therefore unknown, and can only be estimated from usage data.
2. There is no centralised data collection system for properties contaminated with methylamphetamine in WA. Testing data is held by private service providers and laboratories in varying formats and with varying contextual information. Information on the degree of contamination within homes is therefore limited to the information that can be gathered from these sources.
3. Structured longitudinal sampling of contaminated properties over months and years has never been reported; therefore information on the natural decay of methylamphetamine concentrations over time is limited to opportunistic cases and small 'in-vitro' experiments.
4. Concurrent surface wipe and air sampling in homes contaminated with methylamphetamine is very limited. There is inadequate information to determine the relationship between surface residues and desorbed air phase methylamphetamine, which is crucial for characterisation of inhalational risk.
Regarding health effects
5. The efficacy of dermal transfer and absorption is poorly characterised (compared with inhalational and oral routes).
6. No published reports have documented blood concentrations among individuals exposed to environmental methylamphetamine, so actual received doses from passive exposure are unknown.
7. Very little information is available regarding the medium to long-term health effects of regular, low doses of methylamphetamine; this includes information relating to the prescribed drug.
8. Susceptible and vulnerable populations have been hypothesised but not appropriately characterised.
Regarding management
9. Aside from concentration levels of methylamphetamine (which can overlap substantially), there are no clear chemical markers distinguishing properties contaminated as a result of smoking from those contaminated as a result of manufacture.
10. Approaches to management of methylamphetamine contamination vary greatly around the world; however, no jurisdictions have evaluated their approach, nor have any research papers sought to evaluate policy effects on health on an ecological scale.

Remediation standards vary considerably around the world; Australia has a Health Investigation Level and implied remediation standard of 0.5µg/100cm^2. This assessment affirms that full remediation to the level 0.5µg/100cm^2 or below would cause blood concentrations in high-risk infants approximately equivalent to those expected at the health-protective California EPA reference dose (61). Increasingly strict remediation standards offer diminishing returns for

health (e.g. the additional benefit of cleaning to 0.5µg/100cm^2 rather than 1.0µg/100cm^2 achieves plasma concentrations that are only 0.02ng/mL lower (0.03ng/mL compared to 0.05ng/mL). Such small reductions in already undetectable plasma concentrations may not be a cost-efficient use of resources.

Given the contribution of dermal exposures to total absorbed doses (47-83% in the scenarios modelled here), prioritising the remediation of 'touchable' living space surfaces would confer the greatest health advantages. However this may not be expedient for highly contaminated situations, especially those associated with clan labs, The current work has not sought to outline remediation standards and processes for Western Australia, but may inform them moving forward.

This assessment has a number of limitations. First and foremost is the availability and quality of the underlying input data (Table 10). Knowledge gaps are an inherent part of risk assessments, and although every effort has been made to incorporate reasonable values into modelling, incomplete knowledge contributes to a degree of uncertainly around risk estimates. Health protection was the foremost guiding principle, with models fitted to scenarios of highest risk (using 95th or 99th percentile values, as available) to promote safety across a highly variable human population. All assumptions have been documented.

There is an additional limitation in the use of the `linpk` package in R for pharmacokinetic profiling in these circumstances, where each profile can have only one absorption rate constant (K_a). Different exposure routes typically have different K_a values, however in this situation where multiple exposure routes were considered simultaneously, the most conservative K_a was selected.

Given these uncertainties, authors have medium confidence in the quality of the models. The assessment may need to be repeated as more information comes to light.

This work was designed to estimate health risk for Western Australians. Data from WA was used where possible, with data from Australia-wide and at times international sources filling in gaps where local data was unavailable. Sources have been attributed throughout. Aside from specific usage differences (for example, the higher proportion of Western Australians smoking methylamphetamine than in other states and territories), the results are likely to be generalisable across Australia, and perhaps to other comparable nations with similar methylamphetamine abuse issues (noting of course, that differences in drug use patterns, behaviour and exposure patterns, climate and building structures should all be taken into consideration).

Based on the findings of this assessment and the balance of available scientific evidence, exposure to environmental methylamphetamine residues in former smokehouses carries a low risk to public health. Although it may sometimes be difficult to determine whether contamination results from manufacture and therefore is more likely to potentially result in health effects, any high levels of contamination should be managed carefully. In any case, routine controls limiting acceptable methylamphetamine concentrations within residential properties remain important. There is room for a common sense approach to remediation that fosters a cost-efficient response commensurate with health risk.

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Appendix 1: Methodology

Overview

This work was undertaken as a desktop health risk assessment, and comprised accessing information from literature, advice from experts, data from colleagues operating in the field, and some primary sample collection from the contaminated homes.

Literature review

A comprehensive review of published and grey literature was completed, using combinations of key words and phrases in PubMed, Google Scholar, and the Google search engine itself. The search was not limited in scope; instead, it was designed to be expansive. Key words were changed based on findings as the work progressed. Non-peer reviewed sources, such as national and sub-national guidelines and reports, as well as sources cited in key papers but not otherwise identified in searches of the literature, were located and reviewed for relevance. All sources have been acknowledged throughout this work.

This work focuses on public health risk within Western Australia. Where available, information and estimates specific to Western Australia (for example, population estimates and survey data regarding usage) have been employed. Where unavailable, information pertaining to Australia as a whole (for example, survey data where numbers for WA alone are too small to be valid, and exposure parameters from the Australian Exposure Factor Guide (163)) have been used. Information and data from international sources have been reported where available and relevant.

Primary surface contamination data

Surface contamination testing data was requested and voluntarily provided by a number of WA Department of Health-accredited service providers for illicit drug contamination (164). All identifying information (relating to owners, occupants, and addresses of properties) were removed prior to data being received by the WA Department of Health. Data was provided in varying formats and has been reported with associated limitations in mind.

Analysis

All statistical analysis was completed in R Studio (version 1.2.5033) using R (version 3.6.0). Graphs were made using the ggplot2 package in R, and pharmacokinetic profile graphs were generated using the `linpk` package in R.

Calculations informing Table 3: estimated environmental deposition and accumulation

Environmental deposition calculation

The estimated surface concentration of methylamphetamine following environmental deposition immediately following a smoke (Dep) was conservatively calculated using:

$$Dep = \frac{Dg \times (1 - Pf) \times (1 - Abf) \times C\mu g}{Area \times Ccm}$$

Where:

- Dg = Volume of drug smoked (g)
- Pf = fraction of volume left in pipe (proportion)

- Abf = fraction of volume absorbed by user's body (proportion)
- Cμg = conversion factor from grams to micrograms (1,000,000)
- Area = surface areas available for deposition (m^2)
- Ccm = conversion factor from m^2 to $100cm^2$ (100)

Assumptions informing Table 7: potential and received dose models

Table S1: Assumptions informing estimates of blood concentrations from previously published dose scenarios

	Scenario 1: Safe level (Cal) 0.0003mg/kg/day Infant – high risk	Scenario 2: Safe level (Col) 0.004mg/kg/day Infant – high risk	Scenario 3: Adult NOAEL 0.008mg/kg/day Adult - typical	Scenario 4 Child NOAEL (observed) Infant – typical
Assumptions (individual)				
Weight [163]	11kg	11kg	70kg	20kg
Absorption rate constant	1.3	1.3	1.3	1.3
Volume of distribution [56, 100, 101]	35.6L	35.6L	226.8L	81.0L
Clearance rate [56, 99-101, 109]	9.5L/hr	9.5L/hr	13.32L/hr	13.32L/hr
Assumptions (exposure)				
Total daily dose	0.0037mg	0.044mg	0.56mg	2.5mg
Daily dermal dose	3.1μg	20.3μg	0μg	0μg
Daily oral dose	0.6μg	23.5μg	560μg	2500μg
Daily inhaled dose	0μg	0μg	0μg	0μg
Time spent at home[c]	24.0hrs/day	24.0hrs/day	NA (oral dose)	NA (oral dose)
Time spent awake at home[c]	14.35hrs/day	14.35hrs/day	NA (oral dose)	NA (oral dose)

Assumptions informing Table 8: potential and received dose models

Table S2: Assumptions informing estimates of exposure doses and plasma concentrations for adults and children in homes of average and high contamination.

	Scenario 5: Adult - typical	Scenario 6: Infant - typical	Scenario 7: Adult – high risk
Assumptions (individual)			
Weight [163]	70kg	11kg	70kg
Surface area of hands [163]	$1070cm^2$	$300cm^2$	$1310cm^2$
Surface area of other exposed skin [163]	$6300cm^2$	$1600cm^2$	$7900cm^2$
Inhalation rate [163]	$0.63m^3/hr$	$0.33m^3/hr$	$0.83m^3/hr$
Volume of distribution [56, 100, 101]	3.24L/kg	3.24L/kg	3.24L/kg
Clearance rate [56, 99-101, 109]	13.32L/hr	11.32L/hr	9.54L/hr

Assumptions (exposure)			
Concentration of methylamphetamine on surfaces	2.73µg/100cm^2	2.73µg/100cm^2	30.0µg/100cm^2
Fraction of methylamphetamine transferred from surfaces to skin [41]	0.07	0.07	0.07
Concentration of methylamphetamine in air	1.0µg/m^3	1.0µg/m^3	3.0µg/m^3
Time spent at home [165]	15.8 hrs/day	17.75hrs/day	23.8hrs/day
Time spent awake at home [165]	7.8hrs/day	4.75hrs/day	18.3hrs/day
Frequency of 20min whole hand-surface contact [63]	5.9/day	14.8/day	5.9/day
Contact rate of hands (20min events per hour awake at home)	0.25/hr	1.04/hr	0.25/hr
Frequency of 20min other exposed skin-surface contact [63]	1.3/day	3.1/day	1.3/day
Contact rate of body (20min events per hour awake at home)	0.06/hr	0.22/hr	0.06/hr
Fraction of the hand that enters the mouth [63]	0.08	0.16	0.08
Frequency of hand to mouth events [166]	0.75/hour	19.6/hour	0.75/hour
Duration of hand to mouth events [165]	0.5 min/event 0.0083hrs/event	2.4 min/event 0.0408hrs/event	0.5 min/event 0.0083hrs/event
Efficiency of mouthing in removing chemical [41]	0.1	0.1	0.5
Days per year exposed	365	365	365
Long-term duration of exposure	1 year	1 year	1 year
Potential exposures			
Potential dermal dose (/kg/day)	0.0001mg	0.0005mg	0.0044mg
Potential oral dose (/kg/day)	0.000002mg	0.000003mg	0.000071mg
Potential inhalational dose (/kg/day)	0.0001mg	0.0005mg	0.0008mg
Potential total dose (/kg/day)	0.0003mg	0.001mg	0.005mg
Potential daily dose (/day)	0.019mg	0.01mg	0.37mg
Absorption rate constant	1.3	1.3	1.3
Dermal bioavailability (%) [97]	57%	57%	57%
Oral bioavailability (%) [56]	67.2%	67.2%	67.2%
Inhalational bioavailability (%) [56]	90.3%	90.3%	90.3%
Estimated absorbed dose (per day)	0.015mg	0.009mg	0.23mg
Estimated resultant blood concentrations			
Steady state Cmax (plasma)	0.058ng/mL	0.057ng/mL	1.35ng/mL
Steady state trough (plasma)	0.038ng/mL	0.023ng/mL	1.13ng/mL

Table S2 (continued)

	Scenario 8: Infant – high risk	Scenario 9: Infant – high risk clan lab	Scenario 10: Adult – typical first responder
Assumptions (individual)			
Weight [163]	11kg	11kg	70kg
Surface area of hands [163]	350cm^2	350cm^2	1070cm^2
Surface area of other exposed skin [163]	1900cm^2	1900cm^2	6300cm^2
Inhalation rate [163]	0.53m^3/hr	0.53m^3/hr	1.56m^3/hr
Volume of distribution [56, 100, 101]	3.24L/kg	3.24L/kg	3.24L/kg
Clearance rate [56, 99-101, 109]	9.54L/hr	9.54L/hr	13.32L/hr
Assumptions (exposure)			
Concentration of methylamphetamine on surfaces	30.0µg/100cm^2	50µg/100cm^2	500µg/100cm^2
Fraction of methylamphetamine transferred from surfaces to skin [41]	0.07	0.07	0.07
Concentration of methylamphetamine in air	3.0µg/m^3	5.0µg/m^3	500µg/m^3
Time spent at home [165]	24.0hrs/day	24.0hrs/day	1 hrs/day
Time spent awake at home [165]	14.35hrs/day	14.35hrs/day	1 hrs/day
Frequency of 20min whole hand-surface contact [63]	14.8/day	14.8/day	5.9/day
Contact rate of hands (20min events per hour awake at home)	1.04/hr	1.04/hr	0.25/hr
Frequency of 20min other exposed skin-surface contact [63]	3.1/day	3.1/day	1.3/day
Contact rate of body (20min events per hour awake at home)	0.22/hr	0.22/hr	0.06/hr
Fraction of the hand that enters the mouth [63]	0.16	0.16	0.08
Frequency of hand to mouth events [166]	19.6/hour	19.6/hour	0.75/hour
Duration of hand to mouth events [165]	2.4 min/event 0.0408hrs/event	2.4 min/event 0.0408hrs/event	0.5 min/event 0.0083hrs/event
Efficiency of mouthing in removing chemical [41]	0.5	0.5	0.1
Days per year exposed	365	365	1
Long-term duration of exposure	1 year	1 year	1 day
Potential dose exposures			
Potential dermal dose (/kg/day)	0.021mg	0.036mg	0.003mg
Potential oral dose (/kg/day)	0.00046mg	0.00076mg	0.00005mg
Potential inhalational dose (/kg/day)	0.0001mg	0.0058mg	0.011mg
Potential total dose (/kg/day)	0.025mg	0.042mg	0.014mg
Potential daily dose (/day)	0.28mg	0.46mg	1.0mg
Absorption rate constant	1.3	1.3	1.3
Dermal bioavailability (%) [97]	57%	57%	57%

Oral bioavailability (%) [56]	67.2%	67.2%	67.2%
Inhalational bioavailability (%) [56]	90.3%	90.3%	90.3%
Estimated absorbed dose (per day)	0.17mg	0.29mg	0.84mg
Estimated resultant blood concentrations			
Steady state Cmax (plasma)	1.38ng/mL	2.30ng/mL	3.33ng/mL
Steady state trough (plasma)	0.30ng/mL	0.50ng/mL	NA

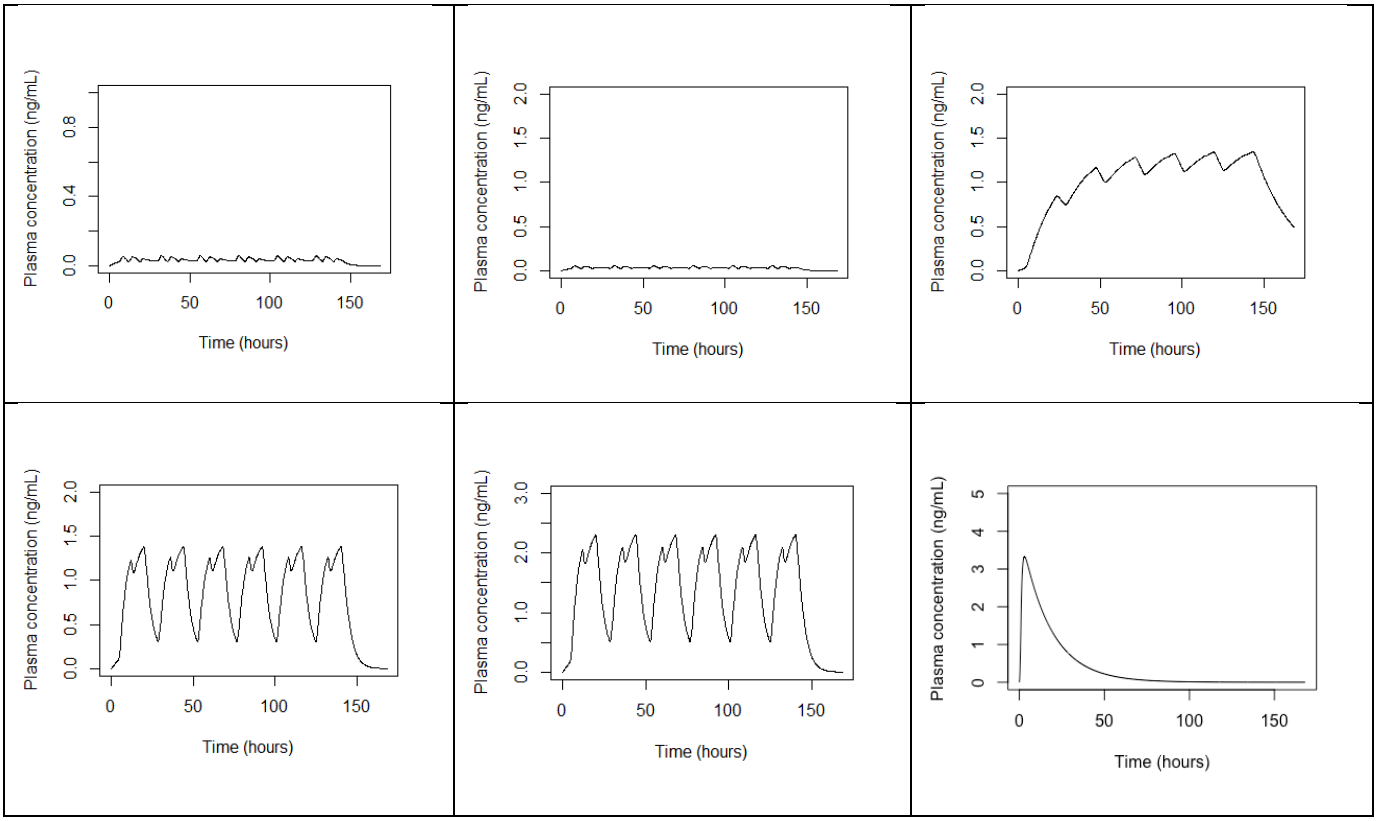

Figure S3: Pharmacokinetic profiles of plasma methylamphetamine levels during scenarios 5-10. The x axis reflects time over six days.

Calculations underlying scenario modelling

Dermal exposure is a sum of exposure via hands (Dh) and more infrequent exposure via other exposed body parts (Db), which can be calculated using:

$$Dh = \frac{C \times SAh \times CRh \times FTSS \times ET \times EF \times ED}{BW \times AT}$$

$$Db = \frac{C \times SAb \times CRb \times FTSS \times ET \times EF \times ED}{BW \times AT}$$

Where:

- C = measured concentration of chemical on surfaces within the home (mg/cm^2)
- SAh = surface area of the hands (cm^2)
- SAb = surface area of other exposed body parts (cm^2)
- CRh = frequency of 20 minute whole hand-surface contact (events per hour)
- CRb = frequency of 20 minute [all] exposed body part-surface contact (events per hour)
- FTSS = fraction of chemical transferred from surfaces to skin for every 20 minute exposure (proportion)
- ET = duration of exposure per day (hours)
- EF = event frequency (days per year exposed)
- ED = duration of exposure considered (years)
- BW = body weight (kg)
- AT = averaging time (days)

Oral exposure (Oh) via hand-to-mouth activity builds on the dermal equations, and can be calculated using:

$$Oh = \frac{DLh \times HF \times 1-(1 - MRE)^{(FQH \times tHM)} \times ET \times EF \ ED}{BW \times AT}$$

Where:

- DLH = dermal loading of the hands (mg/cm^2)
  $= C \times \frac{SAh}{2} \times CRh \times FTSS$
- HF = fraction of the hand that enters the mouth (proportion)
- MRE = efficiency of the mouth at removing chemical from the hands (proportion)
- FQH = frequency of mouthing events (events per day)
- tHM = duration of mouthing events (days)

Similarly, inhalational exposures (Ia) can be calculated using:

$$Ia = \frac{Ca \times InhR \times ETa \times EF \times ED}{BW \times AT}$$

Where:

- Ca = measured concentration of chemical in air within the home (mg/m^3)
- InhR = inhalation rate (m^3/hour)
- ETa = duration of exposure per day (hour)

Example calculation: Scenario 5

Calculating dermal exposure via hands:

$$Dh = \frac{C \times SAh \times CRh \times FTSS \times ET \times EF \times ED}{BW \times AT}$$

$$Dh = \frac{2.73x10^{-5} \times 1070 \times 0.25 \times 0.07 \times 7.8 \times 365 \times 1}{70 \times 365}$$

$$Dh = \frac{1.45}{25{,}550} = \mathbf{5.67x10^{-5}}$$

Calculating dermal exposure via body:

$$Db = \frac{C \times SAb \times CRb \times FTSS \times ET \times EF \times ED}{BW \times AT}$$

$$Db = \frac{2.73\times10^{-5} \times 6300 \times 0.06 \times 0.07 \times 7.8 \times 365 \times 1}{70 \times 365}$$

$$Dh = \frac{2.06}{25{,}550} = \mathbf{8.05x10\text{^}\text{-}5}$$

Total dermal dose = Dh + Db = 5.67x10^-5+ + 8.05x10^-5 = **0.0001372mg/kg/day**

Calculating oral exposure:

$$DLH = C \times \frac{SAh}{2} \times CRh \times FTSS$$

$$DLH = 2.73\times10^{-5} \times \frac{1070}{2} \times 0.25 \times 0.07$$

$$DLH = 2.56\times10^{-4}$$

$$Oh = \frac{DLh \times HF \times 1\text{-}(1 - MRE)^{(FQH \times tHM)} \times ET \times EF\ ED}{BW \times AT}$$

$$Oh = \frac{2.56\times10^{-4} \times 0.08 \times 1\text{-}(1 - 0.1)^{(0.75 \times 0.0083)} \times 7.8 \times 365 \times 1}{70 \times 365}$$

$$Oh = \frac{0.057}{25{,}550} = \mathbf{2.25x10\text{^}\text{-}6\ mg/kg/day}$$

Calculating inhalational exposure:

$$Ia = \frac{Ca \times InhR \times ETa \times EF \times ED}{BW \times AT}$$

$$Ia = \frac{0.001 \times 0.63 \times 15.8 \times 365 \times 1}{70 \times 365}$$

$$Ia = \frac{3.63}{25{,}550} = \mathbf{0.001\ mg/kg/day}$$

Total exposure = dermal exposure + oral exposure + inhalational exposure

= 0.0001372 + 2.25x10^-6 + 0.001

= **0.000282 mg/kg/day**

= **0.01974 mg/day** (in this 70kg individual)

Calculating air contamination proportional to surface contamination levels for the remediation scenarios:

$$Ca \text{ (in } \mu g/m^3) = \frac{C \text{ (in } mg/cm^{2)}}{0.02}$$

Method for estimating pharmacokinetic profile

Total daily doses (in µg) were divided over a 24 hour period dependent on exposure assumptions for that scenario. For example, in scenario 5:

- The dermal dose (9.62µg) was divided over the duration that the person was awake (7.8 hours), with times estimated across the day e.g. continuous exposure between 6-8am, and between 4:12-10pm.
- The oral dose (0.16µg) was divided over the duration that the person was awake at home (7.8 hours), with times estimated across the day e.g. continuous exposure between 6-8am, and between 4:12-10pm.
- The inhalational dose (9.95µg) was divided over the duration that the person was at home, even if asleep (15.8 hours), with times estimated across the day e.g. continuous exposure between 4:12pm and 8am.

This dose exposure scenario analysed using R package `linpk`, with the following code (manually changed to include the relevant clearance rate, absorption rate constant and volume of distribution:

```
y <- pkprofile(t.obs = seq(0, 168, length.out=1000), cl = 13.32, ka=1.3, vc = 226.8, dose = scen5)

plot(y, xlab="Time (hours)", ylab="Plasma concentration (ng/mL)", ylim=c(0,1))

halflife(y)

secondary(y)
```

Appendix 2: Impurities and adulterants present in crystal methylamphetamine, by production method

Table S3: Impurities that may be found in methylamphetamine

Source compound	Method of manufacture	Impurity	Pyrolysis info	Health info
From ephedrine or pseudo-ephidrine	Nazi-Birch or One Pot	1-(1,4-cyclohexadienyl)-2-methylaminopropane (CMP)	No	Some
	Nagai	(2E)-N-methyl-3-phenyl-N-(1-phenylpropan-2-yl)prop-2-enamide	No	No
		Iodoephedrine	No	No
		Iodopseudoephedrine	No	No
		N-methyl-N-(α-methylphenyl)amino-1-phenyl-2-propanone	No	No
		(Z)-N-methyl-N-(a-methylphenylethyl)-3-phenylpropanamide	No	No
		cis-1,2-dimethyl-3-phenylaziridines	No	No
		trans-1,2-dimethyl-3-phenylaziridines	No	No
		1-phenyl-2-propanone	Some	Some
		1,3-dimethyl-2-phenylnaphthalene	No	No
		1-benzyl-3-methylnaphthalene	No	No
		1-methylamino-1-phenyl-2-chloropropane	No	No
		N-acetylmethamphetamine	No	Some
		N-formylmethamphetamine	No	No
		cis-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		trans-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		1-propenylbenzene	Yes	Yes
		2-propenylbenzene	No	Yes
		Methylamphetamine dimer	No	No
	Emde	1-methylamino-1-phenyl-2-chloropropane	No	No
		1-dimethylamino-1-phenyl-2-chloropropane	No	No
		(+)-chloropseudoephedrine	No	No
		(-)-chloroephedrine	No	Some
		cis-1,2-dimethyl-3-phenylaziridines	No	No
		trans-1,2-dimethyl-3-phenylaziridines	No	No
		Methylephedrine	No	Yes
		N-formylephedrine	No	No
		N-formylmethamphetamine	No	No
		N-acetylephidrine	No	Some
		N,O-diacetylephedrine	No	No
		N-acetylamphetamine	No	Some
		N-acetylmethamphetamine	No	Some
		N-methyl-1-(4-[2-(methylamino)propyl]phenyl) -1-phenylpropan-2-amine	No	No
		1- methylamino-1-phenyl-2-chloropropane	No	No
		Dimethylamphetamine	Yes	Some
		N-dimethyl-3,4-diphenylhexane-2,5-diamine	No	No
		cis-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		trans-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		Ephedrine	No	Yes
		Methylamphetamine dimer	No	No
	Moscow	1-methylamino-1-phenyl-2-chloropropane	No	No
		cis-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		trans-3,4-dimethyl-5-phenyl-2-oxazolidone	No	No
		1-propenylbenzene	No	No
	All	Chlorpheniramine (from pseudoephedrine tablets)	No	Yes
From norpseudo-ephedrine or	Emde	(+)-chloromethylpseudoephedrine	No	No
		(-)-chloromethylephedrine	No	No
		1-propenylbenzene	Yes	Yes

norephedrine		2-propenylbenzene	No	Yes
		1-dimethylamino-1-phenyl-2-chloropropane	No	No
From 1-phenyl-2-propanone	Leuckart	N, α-α'-trimethyldiphenethylamine	No	No
		N-ethylamphetamine	No	Yes
		N-ethylmethamphetamine	No	No
		N-formyl-α-benzylphenethylamine	No	No
		Dibenzylketone	Yes	Some
		α-benzyl-N-methylphenethylamine	No	Some
		α-benzylphenethylamine	No	Some
		p-bromotoluene	Yes	Yes
		α,α'-dimethyldiphenylamine	No	Some
		N,N-di-(β-phenylisopropyl)amine	No	No
		N,N-di-(β-phenylisopropyl)formamide	No	No
		N,N-di-(β-phenylisopropyl)methylamine	No	No
	Reductive amination	1-phenyl-2-propanone	Some	Some
		1-phenyl-2-propanol	Some	Some
		1-phenyl-1-amino-2-hydroxypropane	No	No
		1-phenyl-1,2-diaminopropane	No	No
		3,4-diphenyl-3-butenone	No	No
		N-cyanomethyl-N-methyl-1-phenyl-2-propylamine	No	No
		N-(¬β-phenylisopropyl) benzyl methyl ketimine	No	No
		1,3-diphenyl-2-methylaminopropane	No	Some
	Both	trans-N-methyl-4-methyl-5-phenyl-4-penten-2-amine	No	No
		N-butylamphetamine	No	No
		N-cyclohexylamphetamine	No	No
		N-formylamphetamine	No	No
		N-formylmethamphetamine	No	No
		N-benzoylamphetamine	No	No
		N-benzoylmethamphetamine	No	No
		N,N-dimethylamphetamine	Yes	Some
		Amphetamine	Yes	Yes
		N-benzylamphetamine	No	No
		N-benzylmethamphetamine	Some	Yes
		Bibenzyl	Yes	Yes

Table S4: Pyrolysis products of methylamphetamine

Group	Pyrolysis product	Environmental persistence	Potential for health impacts
Amphetamine-like structures	Amphetamine (approx. 28.7% of initial MA)	Volatises slowly at room temperature, will degrade in air with a half life of 3 hours. May volatise from dry but not wet soil. Detected in air of homes 2 years post-contamination (?possible to be ongoing degradation of methamphetamine)	Acute: Sympathomimetic effects: increased body temperature, blood pressure, pulse rate; insomnia, loss of appetite, physical exhaustion, nervousness, irritability, talkativeness, changes in libido, dizziness, headaches, increased motor activity, chilliness, pallor or flushing, blurred vision, mydriasis, and hyper-excitability. Exacerbation of motor or phonic tics, Tourette's syndrome, dyskinesia, seizures, euphoria, dysphoria, emotional lability, and impotence Chronic: psychosis that resembles schizophrenia: paranoia, hallucinations, violent and erratic behaviour. Bioconcentration in aquatic organisms is low.
	Dimethylamphetamine (DMA) (approx. 5-10% of initial MA)	Stable in wastewater for at least 24 hours, otherwise unknown	CNS stimulant; lethal dose (50%) in mice 180 mg/kg 53-56% excreted unchanged or as metabolites in urine (humans). Potential cumulative effects with MA (Sato 2004)
	Benyzlethyltrimethylammonium (BEMA)	Unknown	Unknown
Substituted benzenes	Benzene	Evaporates quickly into air, will be degraded in air by photo-chemically produced hydroxy radicals with half life of 13 days. Expected to volatise from soil. 47% biodegraded in soil after 10 weeks. Very water soluble and can be removed from an environment using water	Immediately dangerous to life and health = 500 ppm; affects bone marrow causing aplastic anemia, excessive bleeding and damage to the immune system; known human carcinogen and is linked to an increased risk of developing lymphatic and hematopoietic cancers, acute myelogenous leukemia, as well as chronic lymphocytic leukemia. Readily absorbed via lung, & about 40-50% is retained. Dermally absorbed at rate of 0.4 mg/sq cm/hr
	Toluene	Rapidly volatises to air; will be degraded in air by photo-chemically produced hydroxy radicals, nitrate radicals and ozone molecules with half life of 2 days. Common indoor pollutant (paint, adhesives, varnishes)	Absorbed through skin 14 to 23 mg/sq cm-hour; orally (nearly 100%). 67-72% eliminated in urine as metabolites. Suspected reproductive toxicity, drowsiness/dizziness, skin, eye and respiratory irritation.

			Fatigue, sleepiness, headache, nausea. Respiratory depression. Low level ability to bioconcentrate in fatty tissues.
	Ethylbenzene	Will be degraded in air by reaction with photo-chemically-produced hydroxyl radicals and nitrate radicals with half lives of 2.3 and 56 days, respectively. Expected to volatise from dry or moist soils. Can be removed from air by wet deposition.	Respiratory, skin and eye irritation, dizziness, depression. Possible increase in cancers in animals, not currently a human carcinogen.
	Styrene	Common pollutant. Will be degraded in air by photo-chemically produced hydroxy radicals, ozone and nitrate radicals with half lives of 6.6 hours, 24 and 2.7 hours respectively. Expected to volatise from water within 4 days and biodegraded from soil within 2 weeks.	Irritation of eyes, skin, respiratory system, headache, weakness, exhaustion, dizziness, confusion, malaise, drowsiness, unsteady gait, defatting dermatitis, possible liver injury, reproductive effects. Low to high bioconcentration.
	Methylstyrene (Cis and trans)	Will be degraded in air by photo-chemically produced hydroxy radicals and ozone with half lives of 7 hours and 2-4 hours respectively. Expected to volatise from dry and most soils. Expected to volatise from water with half life 4 days.	Skin, eye, respiratory irritation, Low bioconcentration.
	Cumene	Common pollutant; will be degraded in air by photo-chemically produced hydroxy radicals with a half life of 1.5 hours. Expected to volatise from dry and wet soils, or biodegrade within 2 days. Expected to volatise from water with half life 6 hours.	Acute: headaches, dizziness, drowsiness, slight incoordination, narcosis and unconsciousness; skin and eye irritation, potent CNS depression. Moderate bioconcentration.
	Propyl benzene	Will be degraded in air by photo-chemically produced hydroxy radicals with a half life of 2 days. Wet deposition is possible. Volatisation from and biodegradation in soil may occur. Expected to volatise from water with half life 4 days.	Irritating to eyes and mucous membranes. CNS depression, headache, anorexia, weakness, incoordination, confusion, unconsciousness
	Prop-2-enylbenzene	Low water solubility, unlikely to persist in environment	CNS depression, coma, aspiration risk
	1-Phenyl-2-Propanone	Will degrade in air with half life of 5.7 days, high mobility from terrestrial environments	Acute: ataxia in mice; lethal dose (50%) in mice 540mg/kg
Multi-ring aromatics	Bibenzyl (1,1'-(Ethane-1,2-diyl)dibenzene)	Unknown	Acute: watering eyes, behavioural change, diarrhoea
	3-methylisoquinoline	Unknown	Acute: skin, eye, and respiratory irritation,

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