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Exposures associated with clandestine methamphetamine drug laboratories in Australia

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Abstract: The clandestine manufacture of methamphetamine in residential homes may represent significant hazards and exposures not only to those involved in the manufacture of the drugs but also to others living in the home (including children), neighbours and first responders to the premises. These hazards are associated with the nature and improper storage and use of precursor chemicals, intermediate chemicals and wastes, gases and methamphetamine residues generated during manufacture and the drugs themselves. Many of these compounds are persistent and result in exposures inside a home not only during manufacture but after the laboratory has been seized or removed. Hence new occupants of buildings formerly used to manufacture methamphetamine may be unknowingly exposed to these hazards. Children are most susceptible to these hazards and evidence is available in the literature to indicate that these exposures may result in immediate and long-term adverse health effects. The assessment of exposure within the home can be undertaken by measuring contaminant levels or collecting appropriate biological data from individuals exposed. To gain a better understanding of the available data and key issues associated with these approaches to the characterisation of exposure, a review of the published literature has been undertaken.

Keywords: biological monitoring; clandestine drug manufacture; drugs of abuse; exposure.

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Introduction

Illicit drugs such as amphetamine-type stimulants (ATS) (1) are manufactured in Australia within clandestine laboratories that range from crude, makeshift operations using simple processes to sophisticated operations. These laboratories use a range of chemical precursors to manufacture or "cook" ATS that include methylamphetamine, more commonly referred to as methamphetamine ("ice") and 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"). In Australia the primary ATS manufactured in clandestine drug laboratories is methamphetamine (2), which is the primary focus of this review. Clandestine laboratories are commonly located within residential homes, units, hotel rooms, backyard sheds and cars, with increasing numbers detected in Australia each year (744 laboratories detected in 2013–2014) (2). Unlike the legal manufacture of industrial and pharmaceutical chemicals, clandestine drug operations do not involve any care in the storage, handling and disposal of chemicals and wastes nor any responsibilities in relation to health and safety during and after the cook. Many of these laboratories are within urban communities where there are significant hazards (including chemical exposures) to cooks, other residents, neighbours, law enforcement and other first responders and the general public who may visit or reoccupy the premises.

Environmental exposures to illicit ATS drugs and chemicals used to manufacture them are not well defined, particularly for children. From its initial establishment through its ultimate re-occupancy, a clandestine drug laboratory typically goes through a number of phases where there is the potential for environmental exposures to the manufactured drug and a wide range of chemicals associated with the manufacture of these drugs. These phases include (3):

- An operational phase, with the potential for exposure to a large number of chemicals including the manufactured drug.
- A discovery phase, where the lab is "seized" by police and chemicals and equipment are removed. Residents

may remain on the premises, or return immediately after police have completed their investigations, and be exposed to a wide range of chemicals that remain in the premises.
– A post operation/discovery/remediation phase, where exposures may be associated with a former laboratory that was undetected (so not remediated); was a known laboratory but not remediated; or was a known laboratory that has not been adequately remediated. In these premises exposure can occur to persistent chemical and drug residues inside and from dumped waste materials outside (4–6).

The greatest hazard, both in relation to likelihood of exposure and concentrations that may be present, occurs during the operational phase. This is where the potential for inhalation of airborne contaminants (including methamphetamine and gases that include acidic, corrosive and toxic gases) and direct contact with primary chemicals, wastes and drug products, and the presence of physical hazards that may be flammable, reactive of explosive may occur (7, 8). The clandestine manufacture of ATS places several groups of people at risk including adults (such as the drug "cooks"), children, neighbours, police, forensic scientists and emergency workers (7, 9–11). Children living in proximity to clandestine laboratories operated by parents or family members are at increased risk of injury and adverse health effects (9, 12).

Australia has developed guidelines relating to the assessment and remediation of contamination (3, 13) that include human health risk-based guidelines for indoor air, indoor surfaces and outdoor environments in residential, commercial and public open space areas (3). These guidelines consider physical assessment and remediation of property/premises formerly used for the manufacture of ATS. However, there is limited guidance on assessing and managing individual exposures and health risks (particularly in children) during the operation of the laboratory, immediately after seizure or if the property is not remediated and is re-occupied.

In Australia, the *Law and Justice Legislation Amendment* (*Serious Drug Offences and Other Measures*) *Act 2005* [the SDO Act (14)] includes offences, that carry custodial sentences, for endangering children during activities associated with the manufacture of controlled drugs or precursors. Most Australian state legislation and initiatives focus on penalties and harm reduction measures associated with drug use, possession and trafficking, with some provisions for offences that relate to manufacture, or equipment or precursors used for manufacture of drugs (7). One state, Western Australia, has introduced stronger legislation that specifically provides a minimum term of 12 months of imprisonment for anyone who causes harm to a child through the manufacture of drugs (15). Outside of criminal offences specifically related to harm caused during the manufacture of an illegal drug, the laws that relate to the protection of the health of the general public who may be exposed to contamination in a former ATS drug laboratory are enforced by local authorities including councils (13, 16, 17), and typically relate to "nuisance" issues or premises not being in a safe or healthy condition (e.g. NSW Local Government Act 1993, Western Australian Health Act 2011, Victorian Public Health & Wellbeing Act 2008 and South Australian Public Health Act 2011). These instruments (and others) generally provide limited powers to prevent a property being re-occupied prior to remediation.

Ultimately it is the role of the property owner to ensure their property is suitable for occupation. Legislation is available in various states that require a landlord to provide residential premises that are clean and fit for habitation (e.g. NSW Residential Tenancies Act 2010, Victorian Residential Tenancies Act 1997, Queensland Residential Tenancies and Rooming Accommodation Act 2008 and South Australian Residential Tenancies Act 1995). Such legislation typically states that the tenant must not use the premises for any illegal activity or purpose.

To better understand the potential for exposure in premises where ATS, specifically methamphetamine, have been manufactured, this review has been undertaken to identify the available information that relates to characterising exposure within homes used to manufacture methamphetamine and adverse health effects.

Background information on clandestine drug laboratories in Australia

General

ATS are a group of psychostimulant drugs that are related to the parent compound, amphetamine, and have a wide range of common/street names (18). The manufacture of methamphetamine involves a relatively simple chemical processes that use highly flammable, very toxic and corrosive chemicals (7). The first clandestine ATS laboratories were found in San Francisco and the surrounding Bay area around 1962 with the first Australian clandestine ATS laboratory reported to be in Sydney in 1976 (19). The number of clandestine drug laboratories detected in

Australia have since increased year-on-year with numbers of detections over the past decade shown in Figure 1. The number may be higher than this as data from New Zealand indicates that 32% of frequent drug users in 2011 indicated that they cooked (or had an attempt at cooking) their own drugs (20). It is estimated that approximately only 1 in 10 laboratories are detected in Australia (21).

The Internet contributes to local methamphetamine production due to the increased ease of access to chemical precursors, equipment and information (9). Scales of clandestine drug manufacture range from easily transportable small-scale 'boot labs' (so-called because they can fit into the boot of a car for easy transportation) and smaller addict-based laboratories to more permanent large-scale laboratories (22) with the distribution of different sized laboratories detected in 2013–2014 illustrated in Figure 2.

From 2008 to 2013 between 68% and 71% of the clandestine laboratories in Australia were detected in residential areas with the rest from commercial/industrial, rural areas and vehicles (1, 2, 18, 23–25). The increasing detection rate of clandestine laboratories, particularly in urban residential areas in Australia, has resulted in an increase in media reports, particularly in relation to injuries and public risks associated with explosions, exposures by police during seizures, the presence of children at these premises and general community concerns.

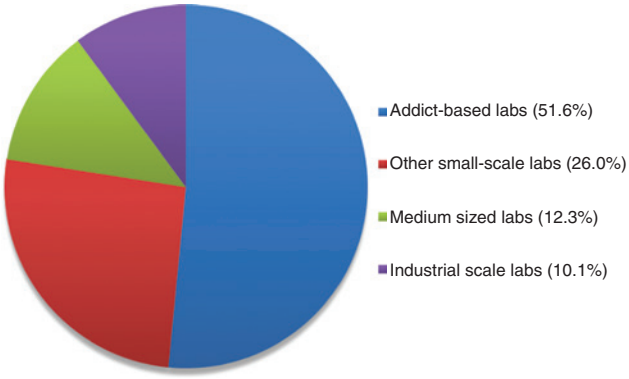

Figure 2: Size and production capacity of clandestine drug laboratories detected in Australia in 2013/2014 (2).

Drugs manufactured and common methods

Since the late 1970s over 100 "recipes" or methods used to manufacture ATS have been identified by the Australian Crime Commission (3) in support of the national Clandestine Drug Laboratory Remediation Guidelines (13). Of the clandestine laboratories detected in 2013–2014 (2) 78.9% were associated with the manufacture of ATS with <1% associated with the extraction of precursor chemicals pseudoephedrine and ephedrine. Most of the ATS laboratories seized, (99%) were associated with the manufacture of methamphetamine and amphetamine, with the remainder associated with the production of MDMA.

Pseudoephedrine is the preferred primary precursor for the manufacture of methamphetamine due to the ease of conversion (21), where the reaction required involves the removal of a single hydroxyl group from the pseudoephedrine molecule to produce methamphetamine (refer to Figure 3) (21).

There are four main methamphetamine manufacturing methods that have been identified in Australia (1–3, 7, 19, 23–25) with clear geographic distributions:

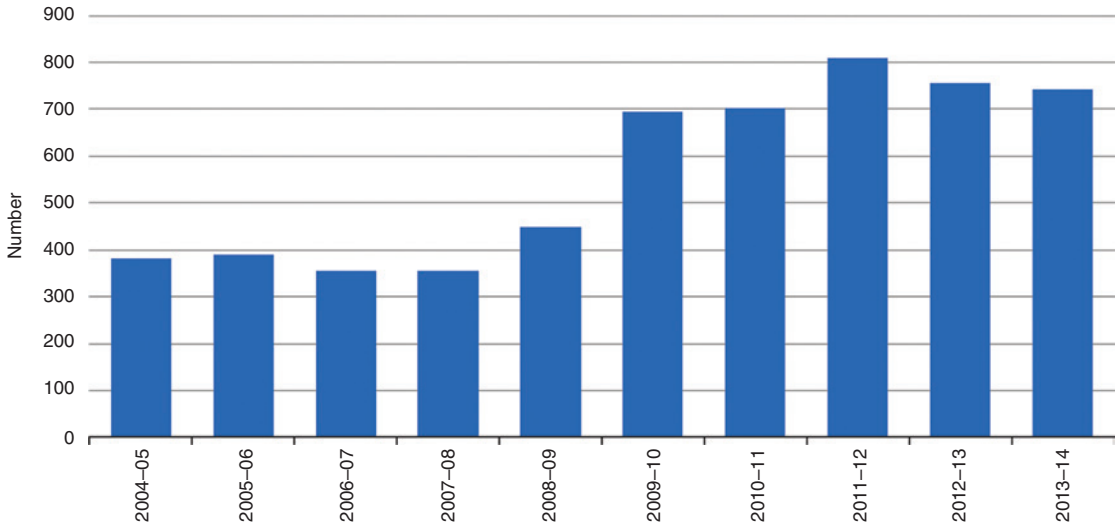

Figure 1: Number of clandestine drug laboratory detections in Australia: 2005/05–2013/14 (2).

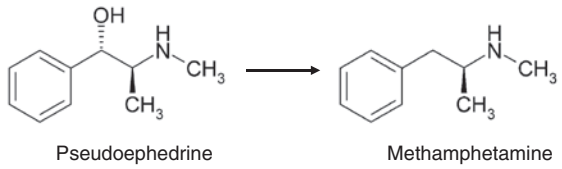

Figure 3: Reduction of pseudoephedrine to methamphetamine.

- Hypophosphorous (or Hypo) method (which is a variation of the red phosphorous method) where ephedrine or pseudoephedrine, iodine and hypophosphorous acid are used. This is the most common method of methamphetamine manufacture in Australia accounting for approximately 63% of identified ATS laboratories in 2013–2014, primarily in the eastern states (2, 21).
- Ammonia ("Birch" or "Nazi") method where ephedrine or pseudoephedrine is reduced in a chemical process involving anhydrous ammonia and lithium or sodium metal. Despite the hazards associated with this method, it is quick and efficient (21) and accounts for approximately 21% of the identified ATS laboratories in 2013–2014, principally in Western Australia (2, 18).
- Red phosphorous (or Red P method) method where ephedrine or pseudoephedrine is reduced using red phosphorous (extracted from match box striker plates) and hydriodic acid. This method accounted for approximately 7% of identified ATS laboratories in 2013–2014, primarily in the eastern states (2).
- Phenyl-2-propanone (P2P) method (not common in Australia), using either the Leuckart method or the "Hells Angels'" method where P2P is reduced using formamide, ammonium formate, formic acid, methylamine, mercuric chloride, aluminium foil and methanol. This method accounted for approximately 4.5% of identified ATS laboratories in 2013–2014, primarily in the eastern states (2).

Activities that give rise to contamination and exposure pathways

During the manufacture of methamphetamine, a range of chemicals are used as precursors, produced as by-products, and drug products may be present in air as volatiles or gases, deposit on surfaces within the home or be present in liquid waste that may be dumped down drains, stored in various containers indoors or dumped outside (to soil or water) (3). There are many general reviews that identify a range of chemical hazards associated with the manufacture of methamphetamine that include the use of corrosive, explosive, flammable and toxic chemicals (5, 12, 26–32).

More generally, the manufacturing of methamphetamine from ephedrine and pseudoephedrine (most common and preferred method in Australia) has the potential to result in contamination from the storage and use of precursors and chemicals, gases released during various stages of manufacture, methamphetamine residues and waste materials.

Use and storage of precursors and chemicals: The collection, often illegal (33), and storage precursor chemicals including (1) cold and allergy medications, drain cleaner, rock salt, battery acid, lithium batteries, pool chloride, iodine, lighter fluid, matches, fireworks, distress flares, antifreeze, propane and paint thinner. Waste materials may also be stored within the premises. Given the illegal nature of the manufacturing process these chemicals are often stored in unlabelled and unsuitable containers (including containers with no lids or food containers) that result in accidental ingestion (34) or leaks and spills; or dumped into drains, soil or waterways (29, 35). Precursor chemicals have been found at high concentrations in kitchen appliances such as microwaves (36), where contamination of food items prepared in these areas can occur. Methamphetamine has been detected in chicken removed from a refrigerator where it was adjacent to a jar of methamphetamine solution (37).

Chemicals used in the manufacture of methamphetamine include volatile solvents (8, 27, 34) that result in direct irritation, inhalation exposures and systemic absorption.

Gases released during manufacture: Cooks using the ammonia method readily produce ammonia gas (38). Cooks using the red phosphorous and hypophosphorous methods produce phosphine gas (39). Both of these gases are toxic and in enclosed spaces, can reach high concentrations resulting in direct irritation and inhalation exposures/systemic absorption and injuries (40, 41). Phosphine in particular has poor odour warning properties and unwitting fatal exposures have been reported (42). Hence bystanders and neighbours may recognise some 'chemical odours' such as pungent ammonia yet may not notice other more harmful gases or vapours.

Gases that are produced during the cooking process are absorbed into porous materials and may off-gas over time resulting in inhalation exposures after the cook has been completed. Limited data are available on this off-gassing process, its duration and its role with respect to exposure and health risks.

Release of iodine residues: Iodine is released (27) during the manufacturing process (red phosphorous and

hypophosphorous methods) and forms a surface residue that often stains the walls of a room where the drug was manufactured. These surface residues can result in exposures via dermal absorption and ingestion following transfer to hands and objects.

Methamphetamine residues: Methamphetamine is generally produced as the free base or the hydrochloride salt. Methamphetamine base is an insoluble oil at room temperature and is the first product of illegal manufacture. It is not suitable for injecting and is difficult to snort (43). Hence it is converted to its hydrochloride salt, usually by bubbling hydrogen chloride gas through an alcohol or diethyl ether solution of methamphetamine base (3, 8). This process is referred to as "salting out" is associated (44) with the release of respirable (predominantly <1.0 μm diameter) aerosols of methamphetamine (and hydrochloric acid) that can be directly inhaled or transported throughout the premises and residues deposited on surfaces (hard and soft). Contaminants present in these residues may be absorbed through the skin (45, 46) or ingested (from placing hands or objects in the mouth).

Waste materials: It has been estimated that for each kilogram of methamphetamine manufactured, 6–10 kg of waste are produced (8) that is often dumped in drains or outside, directly into the soil.

In the event of a fire or explosion contamination from precursors, intermediates, products, wastes and combustion products are more readily and rapidly spread throughout the premises and to neighbouring homes. Emergency personnel are potentially exposed to these contaminants if not properly protected.

Fate and transport of methamphetamine indoors

The fate and transport of methamphetamine indoors has been studied more extensively than other chemical intermediates, wastes and products. The behaviour of methamphetamine indoors has been determined from studies (including "controlled cooks") where levels of methamphetamine on indoor surfaces and other materials have been measured.

Release and transport of methamphetamine residues: Methamphetamine is released as an aerosol during the production process and transported in air to locations distant from the site of synthesis. Hence surface residues associated with methamphetamine production are found throughout the premises not just in the room(s) used for manufacture (36, 38, 39, 47) consistent with the distribution of methamphetamine residues from smoking (48).

The initial product of methamphetamine synthesis is the free base form of the drug, which is volatile and does not persist in the environment for any significant period of time (49). The hydrochloride salt is persistent in the environment, although its stability is pH dependant (49). At a pH in excess of 4 or 5, the hydrochloride salt is more unstable and the more volatile free base is formed (49).

Activity in a residence where methamphetamine has been manufactured can result in re-suspension of respirable fractions resulting in the potential for ongoing inhalation exposures (50).

Distribution of methamphetamine residues: Methamphetamine residues on wall surfaces increase in concentration with height above the floor (51). It is not clear if the distribution of methamphetamine residues is solely due to the manufacture of the drug or if there is a contribution from the occupants who also may have smoked the drug (common in the US where the study sites are located).

Methamphetamine is absorbed into porous surfaces including concrete and paint on surfaces that include gyprock walls (plasterboard or drywall) (52, 53) and carpets (54). Elevated levels have been found in painted plasterboard surfaces (51, 55), with lower levels found in the plasterboard paper (front and back), and no detections within the gypsum itself (51).

Methamphetamine adsorbed into gyprock walls can desorb over time (depending on temperature and humidity) contributing to ongoing exposures in a home (52, 53).

Persistence: Without remediation, residues may persist for months at least, and result in exposures and contamination of clothing of all individuals who enter the premises (36, 47, 50, 53, 56). An initial study (57) on the persistence of methamphetamine residues on wall surfaces over time has indicated a reduction of approximately 50%–60% after 47 days and up to 80% after 179 days (with no remediation). The persistence is expected to vary depending on a wide range of factors that include pH, temperature and humidity.

Removal and remediation: It is suggested that washing of surfaces removes a significant portion of methamphetamine surface residues, in particular dislodgeable residues which would be re-suspended with activity in the premises (55). Hence following initial cleaning of a premise the potential for fine particles of methamphetamine that can be re-suspended and inhaled is expected to be very low and not expected to be of concern. There are, however, no published data to specifically support this outcome. Work

in the United States (57) and South Australia (Edwards pers. comm.) suggests that some surface contamination is easily removed, however, deeper contamination in porous materials (including surfaces such as plasterboard, concrete, plywood) can be more intractable and has required repeated attempts at washing, with and without detergents and/or bleaches, before surfaces have been tested and found to be effectively remediated. Data from New Zealand (55, 58) indicates that the washing is effective in reducing methamphetamine contamination of glass windows, is partially effective for PVC, laminate or ceramic surfaces but has no significant effect on wallpapered, painted or varnished surfaces. Stronger cleaners that contain oxidisers (such as those that contain sodium hypochlorite or quaternary ammonia) have been found to be more effective in the cleaning of these surfaces (55). These cleaners have a very high pH, and given the pH-dependant stability of the more persistent methamphetamine hydrochloride salt, their effectiveness is consistent with both the cleaning process and potential conversion of the residue to the more volatile base.

The efficacy of paint encapsulation in the remediation of methamphetamine residues on plasterboard has been found to depend on the type of paint used. Encapsulation with latex paint has not been shown to effectively seal methamphetamine residues in place (51, 53, 55). Oil-based paints have been found to be more effective with the studies available indicating almost 100% still encapsulated 4 ½ months after painting (55).

Residues on porous clothing materials have been found (55) to be effectively removed with normal household washing, with a single standard wash removing more than 95% of methamphetamine contamination.

Exposure issues associated with methamphetamine laboratories

General

Anyone involved in the manufacture of methamphetamine, or who accesses the premises used in its manufacture, has the potential to be exposed to physical hazards, precursors, intermediates (including gases), waste products and methamphetamine via inhalation, dermal absorption, ingestion and accidental injection (where users are also present). In addition approximately 20% of laboratories discovered in homes (59) result in explosions with severe injuries and exposures occurring within the premises and to neighbours.

Drug cooks

Limited published data are available on drug cooks whose exposure to physical hazards, precursor chemicals, intermediates and wastes (including gases generated) and methamphetamine during and after manufacture is expected to be significant. Many cooks do not take basic laboratory precautions such as wearing personal protective equipment (PPE) and have limited knowledge of the consequences of mixing many of the chemicals, particularly in the presence of heat/open flames (27, 33). In addition poor ventilation, common in illegal laboratories to avoid detection, increases the risk of exposure to high concentrations of chemicals and by-products in air as well as fires and explosions (41, 42, 60). Given the illegal nature of the manufacturing operation no specific data are available in relation to the use of PPE.

A review of hospitalisation data from the US (61) showed that exposure of cooks resulting in injuries that required hospitalisation were primarily from clandestine laboratories in their own residence with methamphetamine, ammonia and hydrochloric acid the most commonly reported chemical exposures.

First-responders and forensic investigators

First-responders (including police, fire fighters, ambulance and emergency personnel) are exposed to chemicals during discovery of clandestine laboratories in vehicles, police raids on domestic or commercial premises or when fire fighters respond to a fire or explosion, or indirectly where these personnel treat contaminated and injured individuals within or removed from the laboratory (11, 62). Exposures by first-responders are higher during initial entry into these premises, often when the presence of the laboratory is unknown (11), compared with exposures that may occur in areas outside of, and adjacent to, the laboratory.

Acute effects have been published, primarily from the US, by police, fire fighters and investigators at seized methamphetamine laboratories (40, 63), with a 7–15 fold increased risk of illness reported (64). Adverse health effects and injuries in first-responders to unknown methamphetamine laboratories (with or without fire or explosion) have been reported (29, 65) most commonly by police officers (70%), emergency medical personnel (11%), firefighters (10%) and hospital personnel (9%). Chemicals exposures most commonly reported by first responders in the US are derived from inhalation, with exposure to ammonia and hydrochloric acid accounting for 54%–58%

of the injuries, and exposure levels to phosphine gas reported well-above occupational limits (11, 42, 62). Other exposures may occur by skin contact and by touching clothing of contaminated individuals removed from the methamphetamine laboratory (11, 29, 40).

The use of PPE by first-responders in the US is poorly reported and may be as low as 15% (11, 29, 60) with only 25% of personnel decontaminating at the scene (36). PPE may be available on a planned raid of a clandestine laboratory, however, the level of chemical exposure is often not known and the need for "speed and surprise" and the possibility of hostile actions and "booby-traps" (66) from occupants of the premises during the raid limit use of PPE (63). Some guidance is available (64, 67) for emergency medical personnel in relation to the identification and management of exposures in clandestine laboratories, however, protocols adopted by various members of police, investigators, fire-fighters and medical staff are specific to these organisations and may not consider these aspects.

Once a laboratory has been seized exposures by those involved in the further investigation of the site can still occur. These investigations include the assessment phase where physical and chemical hazards are evaluated and the contents of the laboratory are determined; and the processing phase where evidence is collected and chemicals are removed (68). Entry during these phases is longer than the initial seizure phase and while PPE may be used during these exposures (at different levels depending on the risk) there is limited information on long-term health effects associated with repeated investigations/exposures. As with first-responders there are no published data on biological monitoring that may be undertaken to evaluate exposures by long-term investigators to methamphetamine.

Children

Children are more sensitive and considered to be at higher risk than adults who may also be present within a clandestine drug laboratory as their physiological (early life developmental processes) and behavioural characteristics [crawling, mouthing of hands and objects, floor play (59)] result in a higher level of contact with contaminated surfaces (34, 69–73). Children have higher metabolic and respiratory rates (69, 71) and the developing CNS is more sensitive than adults when exposed to some chemicals. Gastrointestinal absorption differs and the development of the skeletal system results in the accumulation of some metals (34).

Children do not have the same sense of danger as adults and will not understand the implications of playing with or near chemicals used in the manufacture of methamphetamine and will not be experienced with ways of escaping from emergencies such as fires and explosions (71).

Between 25% and 40% (61, 74–77) of homes seized in the US were reported to have children present. The number of children in these premises in the US has been observed to be increasing with the rate doubling between 1999 and 2002 (78). This may be due to the increased awareness of issues associated with exposures by children, and increased reporting of children in these premises through the introduction of Drug Endangered Children Programs in the US. Data from Australia are limited (8, 79), but anecdotal reports suggest children are commonly found in clandestine drug laboratories and that these children have been exposed to chemicals and drugs present in these homes (7). Statements from children removed from these premises (34) that indicate that drugs were often manufactured in the kitchen, with drugs and precursors often stored in unlabelled food containers (34, 59) or in baby's cots (80), with children (particularly older children) often enlisted to assist in manufacture. In one case a child described assisting a parent during manufacture of methamphetamine where fumes were present and only the adult was using a respirator. These types of exposure are chaotic and not controlled, and differ significantly from the type of exposure that occurs with the medical use of ADHD drugs or even drug use (not smoking).

Neighbours

In the US, most clandestine methamphetamine laboratory incidents occurred in residential areas, with a quarter reporting injuries, of which a third are reported to be to the general (unspecified) public (81). In Australia, 71% of laboratories detected were in urban residential areas (18, 82).

Based on US data from 2000 to 2004 (83), approximately 13% of methamphetamine events (reported as emergencies) required evacuation of people from neighbouring premises (with 1–300 people evacuated) for a median of 3 h. Vapours emitted from ventilation exhaust fans are at high enough concentrations to corrode metal fittings (72), and these vapours are commonly discharged from premises directly towards neighbours. Waste chemicals dumped in wastewater, drains, roadside waste and in public areas comprise corrosive, toxic and flammable

chemicals and pose a significant hazard to the general public and the environment (62).

While information is limited in Australia in relation to exposures by neighbours, a number of more recent newspaper articles have highlighted concerns in relation to these exposures (82, 84, 85). In addition a number of clandestine laboratories have been detected on the basis of complaints from neighbours in relation to strange odours (86, 87).

No quantitative data is available in relation to the levels of contamination that may be present within neighbouring premises.

Health effects

The available data (34, 61, 70, 73, 75, 88) are considered sufficient to support that a range of individuals, including children in clandestine drug laboratories are at high risk for injury and illness associated with immediate hazards such as fires, explosions and chemical incidents, as well as acute and chronic exposure to the range of chemicals used to manufacture the drugs as well as the drugs themselves.

Acute hazards and effects

In relation to the operation of clandestine drug laboratories, the most significant adverse effects are those derived from immediate acute hazards. These hazards include:

- The uncontrolled and unprotected storage and use of volatile, flammable or reactive chemical precursors. These chemicals may be explosive when mixed.
- The release of high concentrations of toxic gases (where these depend on the method of manufacture but may include ammonia or phosphine) into a room or home where ventilation is limited and there is the potential for unprotected exposures.

Explosions and fires in clandestine drug laboratories have resulted in the death of cooks (33, 42, 60, 89, 90) and children living in the home (74) or significant chemical, thermal and inhalation injuries (72, 83, 89, 91–96) that often require higher levels and longer duration of treatment when compared with other burns injuries (27, 97).

Effects consistent with those derived from the range of chemicals and drugs stored and used in the clandestine laboratory include: death; burns and irritation of skin, eyes, nose and throat; lacrimation; pulmonary oedema; coughing; chest pain; shortness of breath; nausea/vomiting; dizziness; headache; anxiety; bad taste and lethargy (5, 31, 34, 61, 71, 74, 83, 98). Exposures to high concentrations of solvents are associated with liver and kidney effects (5). Accidental ingestion of methamphetamine by children has been associated with (7): agitation [most common (99)], tachycardia [second most common (99)], hypertension, hyperthermia, rhabdomyolysis, altered mental status, roving eye movements, cortical blindness, ataxia, constant movement, seizure, flailing head, neck and extremities, hyperactivity (30), acute respiratory symptoms (100) and increased irritability/inconsolable crying (73). Children removed from homes used for the manufacture of methamphetamine are often reported to smell "like cat urine" as a result of the by-products of methamphetamine production (59, 75, 101, 102).

The most common acute adverse health effects reported by first responders attending methamphetamine laboratories include: chemical burns; collapse; abdominal pain; headache; respiratory irritation and effects (including breathlessness, bronchitis, cough, emphysema, pneumonia and wheezing); skin irritation; central nervous system effects and mood swings (11, 35, 65, 66, 68, 86, 102–105). A volunteer fire-fighter's lung capacity was found to decrease by 85% after attendance at an explosion at a methamphetamine laboratory (11). The available studies suggest that 93% of first-responders are likely to seek medical treatment for effects and injuries reported from methamphetamine laboratories (61). No data is available that provide results of any biological monitoring that may have been undertaken to further evaluate the potential for exposure by first-responders.

Chronic effects

Chronic health effects of exposure to methamphetamine are very poorly understood (71), particularly in relation to environmental exposures to low concentrations, compared with high doses associated with drug use. However, they may include: neurochemical changes in areas of the brain that are associated with learning, potentially affecting cognitive function, behaviour, motor activity and changes in avoidance responses (106); psychotic, physiological and behavioural/developmental effects that include violent behaviour, depression, irritability, hallucinations, mood swings, paranoia, mood and sleep disorders that are associated with exposure to, or use of, methamphetamine (75, 106–110); as well as effects associated with exposure to the range of chemicals present, that includes cancer and effects on respiratory, renal, hepatic, neurological, developmental and reproductive

systems (5). Exposures by first-responders have resulted in chronic respiratory (including asthma and significantly decreased lung function), gastrointestinal, neurological and immune system effects (29, 63, 102, 111).

Children removed from homes where methamphetamine has been manufactured (112–116) have been reported to display a range of behavioural issues including academic difficulties (12), developmental delay (78), a higher incidence and risk of externalising (acting out) problems (112–116), aggressive behaviour (112–116), post-traumatic or dissociative symptoms (114, 115) and internalising problems (115). In addition children in environments where methamphetamine, and other drugs or abuse, are used or manufactured can also be exposed to a wider range of other chemicals, neglect, criminal behaviour, abuse (emotional, physical and sexual) that place these children at risk of developmental, behavioural and other mental health problems (114, 115, 117–120).

It is not clear whether early developmental/behavioural issues of methamphetamine exposure observed in children resolve over time, or lead to long-term developmental problems and a predisposition for addictive behaviours (including drug abuse) later in life (73). Prenatal exposures (i.e. drug use) to methamphetamine have been associated with behavioural problems in children (increased emotional reactivity, anxiety/depression, externalising and attention-deficit/hyperactivity disorders) in children aged 3 and 5 years (121) suggesting the potential for long-term development effects. There are few studies available, however, where follow-up data has been collected. The most extensive study involved a study on prenatally exposed children from birth to 14 years of age in Sweden (122–126). While there are limitations with the study (small size of 65 children and no control group) at 4 years of age the study suggested that the children exhibited aggressive behaviour that seemed to correlate with longer in-utero exposure periods. The study identified that parental drug and alcohol use (prenatal and while the children are growing up), along with other family factors influence children's growth and development. The study does not specifically correlate only prenatal methamphetamine exposure with long-term developmental or behavioural effects as these are confounded with a wide range of other factors associated with parental abuse of drugs and alcohol, criminality, mental health issues, poverty and family living arrangements.

A study of potential developmental effects (motor skill and cognitive function) of prenatal exposure on 166 children aged 1, 2 and 3 years (74 exposed and 92 in the control group) (127) found that at 1 year of age the methamphetamine exposed children had fine-motor skill deficits. However, these effects (as well as other cognitive functions) were not apparent at 3 years of age.

A neuroimaging study of 26 methamphetamine exposed (prenatal) and non-methamphetamine exposed children (128) suggested an abnormality in energy metabolism (increased creatine in the striatum) in the brains of children prenatally exposed to methamphetamine. These changes were not found to be associated with any increase in reported behavioural changes in the children. Further studies have identified that methamphetamine exposure during brain development affects the hippocampus (responsible for higher cognitive functions) (129) and results in cognitive impairments (130) and delayed long-lasting memory deficits (131) in adolescent mice.

Confounding factors for evaluating chronic effects of exposure

Numerous papers (4, 30, 71, 77, 114, 116, 117, 132–136) highlight issues associated with child welfare, drug use and methamphetamine manufacturing. Children from homes where there is drug abuse and manufacturing frequently live in squalor, neglect and abuse (69, 71, 73, 135, 136) where lack of stimulation, poor nutrition, unsanitary conditions and medical problems associated pre- and post-natal exposure to drugs and chemicals (12, 69). Children from homes with a history of parental drug abuse or from a home with domestic violence were 3–3.5 times more likely to test positive to illicit drugs in urine or hair (137). When evaluated, children in methamphetamine homes showed higher levels of aggression than others where it is suggested that there is the need to assess the mental health of children removed from methamphetamine homes (112, 116). It is suggested that the combination/accumulation of multiple risk factors have a greater negative impact on psychological development (71) than the individual factors alone.

The U.S. Drug Endangered Children Program that was created by the San Diego District Attorney's Office as a solution to the increasing problem of children removed from their parents as a result of the parents arrest for methamphetamine production (74). The multi-agency programme that includes procedures/protocols for the decontamination and medical assessment of children removed from these homes, and issues associated with the removal of children from these homes has been adopted in some form by a number of US states (30, 70, 75–77). Europe has established the European Network for Children Affected by Risky Environments within the Family (ENCARE), however, this programme focuses more on children living with parental

alcohol misuse or domestic abuse. No such programmes are known to be present in any Australian state.

Quantification of exposure

General

The most common approach adopted for the quantification of exposures by children, and others, to the presence of methamphetamine and other chemicals associated with the manufacture of methamphetamine is to measure concentrations in media relevant to exposure such as indoor air and surface residues. Chemical intakes of these chemicals are then estimated on the basis of the measured concentrations and parameters that estimate physiological characteristic (such as body weight), behavioural patterns (such as the time spent in contact with contaminated surfaces) and absorption. This approach is consistent with national risk assessment guidance in Australia (138). The approach is adopted in Australia (3, 13), New Zealand (139) and many states in the US (49, 140–151) for the derivation of assessment and remediation criteria for methamphetamine laboratories. These guidelines have been established to be protective of exposures to children, the most sensitive individuals who may be exposed to contamination.

It is noted that the development of a remediation criteria for methamphetamine on surfaces inside a home is based on a post-remediation exposure scenario (49). This scenario assumes that some remediation of a property has occurred that removes dusts and other contaminations that could become re-suspended in the air, and that "reservoirs" of methamphetamine contamination (such as contaminated air conditioning filters and ducts and fans) are not present (49). As a result the key pathways of exposure addressed in the development of the guidelines relate to dermal contact with surfaces and objects (accounting for approximately 80%–95% of total intake) and ingestion of contamination from mouthing hand and objects (3, 49). It is also assumed that since remediation has been undertaken, the remaining contamination degrades on indoor surfaces and depletes over time with cleaning such that exposures are considered to be sub-chronic (occurring for <10% of a lifetime) (152). Exposures in former drug laboratories were not considered to be chronic.

To quantify chemical intakes from exposures within a former methamphetamine laboratory requires having enough information and data to define (a) where and how children may contact these chemicals in the home; (b) absorption of chemicals via the skin; (c) how much surface residue sticks to the skin and other objects and can then be swallowed when placed in the mouth; and (d) once ingested, how much is absorbed by the body. While evaluations are available that generally address key factors that influence exposures by children to environmental contaminants (153), there are a data gaps in this information and more specifically in the data directly relevant to exposures to methamphetamine contamination derived from former clandestine laboratories. These data gaps include (153) methods for monitoring and measuring children's exposures and activities, collection of activity pattern data for children (relevant to all routes of exposure), collection and use of data on environmental contaminant concentrations on all media of concern [that may need to include carpets and soft furnishings (151)], whether exposures associated with indoor air levels of methamphetamine of importance, dermal transfer coefficients and the long-term persistence of surface residues. In addition data are lacking on the level of exposure that may occur in a former drug laboratory where no remediation has occurred.

Some of these data gaps have been addressed using assumptions or estimates in the development of Australian and international guidelines by using information obtained on the behaviour and potential for exposure to pesticides inside homes (49, 151). The relevance of these assumptions is not known, particularly where the nature and behaviour chemical contamination from the operation of a clandestine laboratory is likely to differ from known pesticide applications.

More recent studies are available defining potential exposures from indoor air, dermal contact, transfer efficiencies and absorption (46, 54, 154–156). These data suggest:

- There is the potential for methamphetamine in indoor air to accumulate in skin oil, clothing, bedding, upholstery and fabric adding to potential oral intakes by young children mouthing these types of items (156). In addition there is the potential for significant dermal absorption (155). Indoor air pathways have not been considered in the development of existing guidelines.
- The proportion of methamphetamine that may be transferred from surfaces to skin is higher than assumed in the development of existing guidelines (46, 54, 154).

The approaches commonly used to evaluate exposure involve the characterisation of contamination in the environment where exposure may occur (i.e. measure the

exposure concentration on/in different media) and/or use biological data to evaluate how much contamination has been taken into the body during exposure.

Measurement of exposure concentrations

No data are published or available from other sources in relation to levels of contamination within clandestine laboratories in Australia. Most of the published data are available from the US, specifically a number of studies conducted by the National Jewish Medical and Research Center. These studies have provided measurements of contamination levels from seized laboratories (noted to be a limited data set collected after the laboratories were seized, not operational) and from "controlled cooks".

The controlled cooks enabled the measurement of methamphetamine in air and on a range of surfaces (hard, soft and clothes) within the cook area and in other areas of the premises away from the cook area, as well as volatile organic compounds (VOCs), acids, iodine and phosphine in air. These studies are relevant to a range of methamphetamine cook methods and generally address three phases of the operation – cooking of methamphetamine (prior to salting out phase), salting out of methamphetamine and at the completion of the cook.

A summary of the data from the available published studies is presented in Tables 1–3. These relate to the presence of methamphetamine, and some other chemicals associated with the manufacture of methamphetamine, in air and on a range of surfaces from controlled or simulated cooks where some data relate to simulated activities in the premises following a cook. It is noted that that level of contamination reported is dependent on the cook method and the volume of drugs produced. The higher concentrations have typically been reported in actual laboratories where there has been an explosion. Hence there is a wide range of levels of contamination reported from these studies.

None of the published studies provide any data on health effects experienced or biological data from any of the individuals exposed.

Assessment of aerosol sizes generated during controlled cooks (44) indicates that most of the methamphetamine aerosols present in air after a cook are respirable, with up to 90% <1 μm in diameter.

A number of limitations have been identified in relation to the available data, in particular:

- The majority of the studies conducted by the National Jewish Medical and Research Center (36, 38, 39, 47, 48, 50, 56) used occupational-exposure based analytical methods. These methods may not be adequately sensitive for the assessment of environmental exposures by more sensitive individuals such as children.
- Few of the available studies relate to samples collected from actual seized laboratories (36, 47, 157). The majority of the data is from controlled cooks that are associated with the manufacture of small quantities of methamphetamine [noted to be approximately 3 g (44)]. There are no data that enable an assessment of the relationship of quantitative measures from the controlled cooks to those that may be derived from actual laboratories where larger quantities of methamphetamine are produced.
- There are no specific data that cover a range of housing types (including different layouts and ventilation), consideration of different actions/activities that may be undertaken by the cooks during manufacture (that may change the generation and distribution of contamination in a property), and consideration of different qualities manufactured.
- A limited number of test subjects were evaluated for measurement of residues on individuals (personal samples) conducting a range of indoor activities following the controlled cook of methamphetamine (56). This limits the overall conclusions that can be drawn from the data presented.
- No data are available in relation to the potential for systemic absorption of methamphetamine (characterised by biomonitoring data) by anyone involved in the cooking of the drugs, seizure of the laboratory and subsequent investigation of any of the premises evaluated or from exposures that may occur in the premises should no remediation occur.

Exposures in clandestine laboratories are not just limited to the manufactured drug itself. Most of the available data relates to the presence of methamphetamine in the environment, with some studies also reporting precursors and by-products that include ephedrine, pseudoephedrine, iodine, hydrogen chloride gas, ammonia gas, phosphine gas, total volatile organic compounds and amphetamine. None of the studies provide analysis of all precursors, intermediates, wastes and products of the manufacture of methamphetamine that contribute to the mix of chemicals to which anyone within the laboratory, including children may be exposed (158). Reviews of the wide range of chemicals that may be associated with the manufacture of methamphetamine (3, 159), on the basis of the nature, behaviour (including persistence) and availability of data that can be used to characterise exposure, identified a number of key chemicals that can be used as reliable indicators for the manufacture and exposure to chemicals

Table 1: Summary of methamphetamine and other chemicals in indoor air.

Location/activity	Range of maximum concentrations reported in air (μg/m³)					References
	MA	Hydrogen chloride	Phosphine	Ammonia	Iodine	
Data from seized laboratories (cook methods not specified)						
Range of different rooms from seized laboratories – after the cook	0.17–7.3	190–200	nd to 358.6	–	10–23	(36, 47, 51)
Suspected clandestine drug laboratories (9 locations)	0.2–3	–	–	–	–	(58)
Data from controlled cooks – anhydrous ammonia method						
Within cook area						
– Cook phase	10.1–34	–	–	–	–	(38)
– Salting out	127–680	–	–	–	–	
– Post cook	7.6–79	895–1044	–	90,500–286,000	–	
Away from cook area						
– Cook phase	2.4–42	–	–	–	–	(38)
– Salting out	12–158	–	–	–	–	
– Post cook	7.6	596	–	<46,000–255,000	–	
Data from controlled cooks – red phosphorous and hypophosphorous methods						
Within cook area						
– Cook phase	<0.19	119–313	–	–	nd to 29	(36, 39, 44, 47, 50)
– Salting out	680–5500	220–30,000	–	–	nd to 25	
– Post cook	79–5500	75–14,600	nd to 18,000	–	52–1600	
Away from cook area						
– Cook phase	<0.17	30	–	–	nd to 5	(44, 47, 50)
– Salting out	960–4000	390–6710	–	–	–	
– Post cook	2.6–4200	30–313	–	–	5–156	
Day following cook for no activity, medium and high activity (up to 18 hrs post cook) (1 cook) (red phosphorous method)	70 (no activity) –210 (high activity)	nd to 67	–	–	nd to 26	(44, 50)

MA, Methamphetamine; nd, not detected (variable analytical limits or reporting); –, no data reported for analyte.

from methamphetamine laboratories. These key chemicals include those commonly reported in the available studies.

A laboratory study (160) in relation to the recovery of pseudoephedrine and methamphetamine residues from impermeable surfaces (glass, stainless steel, adhesive vinyl laminate, stone benchtop, varnished floor wood, painted metal sheet and varnished benchtop wood) suggested that methamphetamine can be used as a surrogate to represent both methamphetamine and pseudoephedrine (where methamphetamine has been synthesised) on impermeable surfaces from clandestine drug laboratories. It is noted that data from actual seized laboratories (36) suggests this is reasonable for most surfaces with the exception of appliances within kitchens (such as microwave ovens) that are used in the manufacture of drugs where the proportion of pseudoephedrine (precursor more likely to be used in these appliances) has been found to be higher than methamphetamine. Methamphetamine could not be used as a surrogate if the laboratory were only used for the manufacture or extraction of pseudoephedrine.

Sampling and analysis issues

A range of analytical methods have been used in the measurement of contamination (on surfaces and in different materials) associated with clandestine laboratories (157, 160–166).

For the measurement of contamination on surfaces in premises, wipe sampling methods are commonly used. A study of the efficacy of wipe sampling methods (167) identified that it was appropriate to use either methanol or isopropanol wipes for the collection of the samples and that the presence of dust or paint on the wipe samples did not interfere with the analytical results. The recovery of methamphetamine from surfaces using wipe sampling is variable depending on the nature of the surface. Recoveries

Table 2: Summary of amphetamine and precursor residue levels on hard surfaces.

Location/activity	Range of maximum contaminant surface residues reported (μg/100 cm²)				References
	MA	AMP	EPH	PSE	
Data from seized and suspected laboratories (cook methods not specified)					
Walls and surfaces that include benches, tables, floors, fans, appliances	0.1–6093 to 16,000 after explosion	1.2–34	6.6–120	99–1400	(36, 47, 51, 157)
Ventilation fans	0.2–450	nd to1.2	nd to 6.6	0.5–99	(36)
Kitchen appliances (microwaves, burners, ovens, refrigerators	nd to 16,000	nd to 33	nd to 1200	nd to 51,000	(36)
After 3 rounds of decontamination	0.14–1.05	–	–	–	(158)
Data from controlled cooks–anhydrous ammonia method					
Various surfaces (3 cooks)	0.08–160	–	–	–	(38), (47)
Data from controlled cooks–red phosphorous method					
Various surfaces (2 cooks)	6.1–68*	–	–	–	(44, 50)
Data from controlled cooks–hypophosphorous method					
Various surfaces (painted wall, glass, mirror) up to 7 feet from cook area (2 cooks)	0.078–23	–	–	–	(39)
Various, including within hotel room	0.1–860	nd to 3.2	nd to 0.5	nd to 2.6	(36, 47)

MA, Methamphetamine; AMP, amphetamine; EPH, ephedrine; PSE, pseudoephedrine; nd, not detected (variable analytical limits or reporting); –, no data reported for analyte; *, surface residue levels similar immediately post cook, 13 h post cook, 16 h post cook and 18 h post cook.

of methamphetamine residues from surfaces have been reported to be <100% (51, 167), with specific studies indicating variability between 15% for porous surfaces and 80% for smoother surfaces (160).

In relation to the analysis of methamphetamine, the available studies suggest the variability between laboratories ranges from 3%–30% (167) to 1%–50% (51).

These studies indicate that sampling and analysis methods can detect the presence methamphetamine, with the level of recovery varying between porous and smooth surfaces. In addition some variability in the levels reported by different laboratories (between 1% and 50%) can occur. This should be considered where quantitative data from different surfaces and laboratories is compared.

Measurement of exposure using biological data (Biomarkers)

General

Amphetamines are readily absorbed via inhalation [with between 67% and 79% (168) and 90% (169) absorbed into the blood stream], ingestion [with oral bioavailability noted to be in the range of 67.2% (170, 171) to 85% (172)] and dermal pathways (45). Following intake, amphetamines are rapidly distributed to the major organ systems including the brain as it readily crosses the blood-brain barrier (170). In general amphetamines are weak bases with low protein binding (173) and have a high volume of distribution which means almost all of the total amount of drug available in plasma may diffuse across cell membranes and lipid layers to tissue matrices with lower pH values than blood (174). Saliva/oral fluid, sweat and breast milk are more acidic than plasma, hence amphetamines are readily distributed to these fluids (174, 175).

Extensive reviews of the metabolism of methamphetamine and amphetamine are available in the literature (170, 176). These mechanisms do not appear to be changed by chronic exposure (177). The major pathways of methamphetamine metabolism involve (170, 176, 177):

- n-demethylation to form amphetamine, that can then be metabolised via several pathways
- aromatic hydroxylation to form 4-hydroxymethamphetamine and then 4-hydroxyamphetamine and 4-hydrocynorephedrine
- β-hydroxylation to form norephedrine.

There are a number of metabolites that are produced from these mechanisms, with amphetamine and 4-hydroxymethamphetamine being the major metabolites detected in urine. In addition amphetamine is a major drug of abuse, and it may also be present as an impurity or mixture with methamphetamine. Evaluating the presence and ratios of methamphetamine and amphetamine, both of which have relatively long elimination half-lives

Table 3: Summary of amphetamine and precursor residue levels on individuals, clothes, soft furnishings and toys.

Location/activity	Range of maximum contaminant residues reported (μg/sample, many as μg/100 cm²)				References
	MA	AMP	EPH	PSE	
Data from seized laboratories (cook methods not specified)					
Window furnishings and sofa	0.84–120	nd to 1	nd	0.9–12	(36)
Carpet	132–2045	–	–	–	(51)
Data from controlled cooks–red phosphorous, hypophosphorous and anhydrous methods					
Personal samples from cooks (2–7 cooks)					
– Cook phase	nd to 19.3	–	–	–	(36, 38, 39, 47, 56)
– Salting out	nd to 580	–	–	–	
– Post cook	0.2–150	–	–	–	
Personal samples from investigators (5 cooks)					
– Cook phase	nd to 0.14	–	–	–	(56)
– Salting out	2.54–580	–	–	–	
– Post cook	1.1–150	–	–	–	
Personal samples – post cook (5 cooks)					
– Police	nd to 1.6	–	–	–	(56)
– Fire fighter	0.46–56	–	–	–	
– Juvenile	nd to 1.18	–	–	–	
– Child (simulated crawling by adult)	0.2–29	–	–	–	
Personal wipe samples –post cook					
– Low activity	0.075–1.7	–	–	–	(44, 50)
– Medium activity	0.32–56	–	–	–	
– High activity	0.59–44	–	–	–	
Personal samples after decontamination (2–7 cooks)	0.43–10.2	–	–	–	(38, 39, 56)
Dog (5 cooks)	1.89	–	–	–	(56)
Baby clothes near cook (2 cooks)	6.4–500	–	–	–	(39)
Toys (including teddy bear)	6.4–1300	–	–	–	(36, 39)
Carpet	3.93–13	–	–	–	(36)
Carpet – vacuum samples (μg per m²)	54–270	–	–	–	(44, 50)

MA, Methamphetamine; AMP, amphetamine; EPH, ephedrine; PSE, pseudoephedrine; nd, not detected (variable analytical limits or reporting); –, no data reported for analyte.

in the body making them detectable in various biological matrices, provides an indication of systemic absorption of methamphetamine and/or amphetamine. Following intake of pure methamphetamine, the presence of amphetamine relates to the metabolism of the primary drug and the ratio of methamphetamine to amphetamine should be >1 (178). Hence the presence of both methamphetamine and amphetamine in biological matrices are commonly used as indicators of systemic absorption of methamphetamine.

Methamphetamine, amphetamine and their metabolites are excreted primarily in urine, with 55%–69% excreted in the first 24-h after exposure (170). Based on studies associated with doses typically associated with drug use, an average of 30%–40% of a methamphetamine dose is excreted unchanged and the remainder is eliminated as metabolites (170). As amphetamines are weak bases, renal excretion is variable and is dependent on pH. Excretion can be increased by urinary acidification, and decreased by urinary alkalinisation (170, 174).

Due to the rapid absorption and excretion of methamphetamine and metabolites the detection times for methamphetamine in most biological matrices are short. The detection times differ depending on whether exposure occurred from a single dose, repeated doses or chronic exposures. Most data are available following a single dose where the detection time is reported to range from 24 to 48 h in plasma to 87 h in urine (177). Limited data are available in relation to repeated doses of methamphetamine, however, the detection time is in the range of 3 days in saliva/oral fluid to 8 days in urine and sweat (177, 179–181). Accumulation of amphetamines in a keratin matrix is more complex (174) but has been shown to provide a stable measure of temporal exposures with the distribution of drugs along the shaft of the hair expected to reflect historical month-by-month exposures (174).

In relation to the potential for biomarkers to be used as a reliable measure of environmental exposure to methamphetamine (and amphetamine that may be present as an impurity or as a major metabolite of methamphetamine), review of these biological matrices has considered the following factors that are considered to be important for utilising the data in a study that relates to evaluating potential environmental exposures:

1. The potential for the biomarker to be present in the matrix sampled, and be a stable measure of exposure;
2. The potential for the biomarker to report positive detections, if exposure occurred, at the point in time when samples can be collected (may be longer than a week);
3. The potential for data to be easily collected; and
4. The potential for the analysis to be able to report detections, if exposure occurred, that relate to environmental exposures from the clandestine drug laboratory.

These aspects have been considered further in relation to the use of blood and urine, saliva/oral fluid, sweat and hair for the potential assessment of environmental exposures. The use of these matrices for the assessment of exposure to amphetamines in the literature has primarily focused on users, with limited data available for environmental exposures. Where data is available that relates to environmental exposures much of it is presented as a positive or negative finding, rather than a quantitative value.

Blood and urine

Blood plasma is the most direct quantitative measure of the level of methamphetamine and amphetamine within the body at a point in time following exposure. The half-life of methamphetamine in plasma varies from 9.1 to 13.1 h with a window of detection for the presence of the drug in plasma up to 24 h (181) following exposure. In plasma, after oral administration of methamphetamine, concentrations of the metabolite amphetamine are lower than methamphetamine with the 24-h area under the curve (AUC_{24}) for amphetamine showing a typical dose-response relationship (169, 171, 181).

As urine is the primary mechanism of elimination following exposure to amphetamines, it is most commonly used for the purpose of assessing and quantifying workplace exposure, driving related offences and criminal cases (181–183). Analyses of urine for exposure to methamphetamine are only considered positive if the levels are above a pre-determined cut-off limit and the metabolite amphetamine is also detected. The cut-off limit is above the detection limit and allows for low levels to be present either directly or as metabolites from prescribed medicines (182, 184). Methamphetamine and amphetamine concentrations in urine are generally higher than reported in blood plasma and, while rapidly cleared from the body, can remain quantifiable for longer periods of time after multiple doses, with detections reported after 46–196 h (181).

The testing for methamphetamine and amphetamine in urine is often conducted upon hospital admission to evaluate drug use. Methamphetamine cooks treated in hospital for various injuries associated with drug manufacture commonly (around 91%) test positive for amphetamines (29, 89).

One study is available where urine samples have been collected from 104 children removed from methamphetamine laboratories (37). The children were tested at emergency medical departments immediately after removal from the premises where 46% of the children reported positive detections (reported as detections only, no quantitative data) for methamphetamine. Of the children who tested positive, 85% were 8 years old and younger. No child tested positive more than 6.5 h after removal from the laboratory highlighting the importance of the ability to collect urine samples within the window of detection. No information or data is available from this study on the levels of methamphetamine (and precursors) within the homes from which the children were removed.

Given the rapid clearance of methamphetamine and metabolites from the body, blood plasma or urine are not considered to be a suitable indicator of former environmental exposures, where sample collection may only be possible more than a week (and likely longer) following the cessation of exposure.

Saliva/oral fluid and sweat

Saliva/oral fluid has been identified as an easily accessible and suitable biomonitoring method for the assessment of drugs of abuse (179). A number of studies have indicated that oral fluid methamphetamine concentrations are higher than blood plasma (169, 171, 179, 181), however, there was a poor correlation between saliva/oral fluid and plasma methamphetamine concentrations reflecting high intra and inter-individual variability. While some attempts have been made to better define saliva-plasma ratios (S/P) for methamphetamine (171, 185) the measure is generally not considered to be a reliable quantitative measure of exposure, and is only considered to be a suitable matrix for screening for drug use (181).

The testing of sweat using sweat patches is a non-invasive method of biomonitoring, however, only a limited number of studies are available that assist in the understanding of methamphetamine and amphetamine excretion in sweat (180, 186). Testing conducted with other drugs has identified some uncertainties associated with the method that include potential for time-dependant drug loss due to drug degradation, reabsorption to the skin, volatile losses and contamination on the skin (180, 187). In relation to methamphetamine and amphetamines, the available studies indicate that sweat testing is an effective and reliable test for detecting drug use, however, significant intra- and inter-individual variability indicated it should only be used as a qualitative screening test to report positive detections rather than a quantitative test (180, 186).

Given the rapid clearance of methamphetamine and metabolites from the body, and the variability issues identified in relation to the use of saliva/oral fluid and sweat, these media are not considered to be a reliable quantitative method for the assessment of environmental exposures.

Nails

Few studies are available that specifically address the use of nails as an analytical media for the detection of drugs (188). The available studies indicate that fingernail and toenail clippings have been found as reliable as hair for the detection of methamphetamine and amphetamine in users, as these drugs are well accumulated in the nail matrix, stable in the nail, retained for a long period of time, show a good correlation with hair concentrations (174, 188, 189). The mechanism of deposition at the nail matrix is complex (188, 189), hence analysis of nails are considered to be a less reliable indicator of temporal trends than hair. However, analysis of nails may provide an alternate method of evaluating environmental exposures to methamphetamine.

Hair

General

The incorporation of drugs and metabolites into hair has been found to provide a reliable basis for evaluating historical use or exposure (190). The mechanisms by which drugs and their metabolites are incorporated into hair are complex and not fully understood (190). Conceptually it is believed that drugs and their metabolites (as well as other trace elements) are incorporated during metabolic activity and cell division associated with the anagen (i.e. formation of the hair shaft) growing phase of the hair (190). There are three recognised routes by which drugs are incorporated into the hair, as illustrated in Figure 4. These include incorporation of drugs from the circulatory system (191); absorption from sebum and sweat bathing the hair; and from external contamination (190).

Within the hair itself, the drugs and metabolites are incorporated/bound into the keratinaceous matrix of the hair shaft during protein synthesis. In the hair shaft, the materials form a stable drug bolus that remains embedded in the hair matrix. Different drugs have different affinities and binding capabilities which vary depending on drug pKa, structure, size, lipophilicity, protein binding capacity and melanin affinity (190). The lipid solubility of a drug is a critical factor for the transport of the drug from the blood stream across the cell membrane and into the growing hair (190).

In sufficiently long hair, sectional analysis can provide a timeline of drug exposure/use (191, 192). The drug is incorporated into the hair matrix as it grows with the growth rate approximately 2.8–3.2 mm per week (an

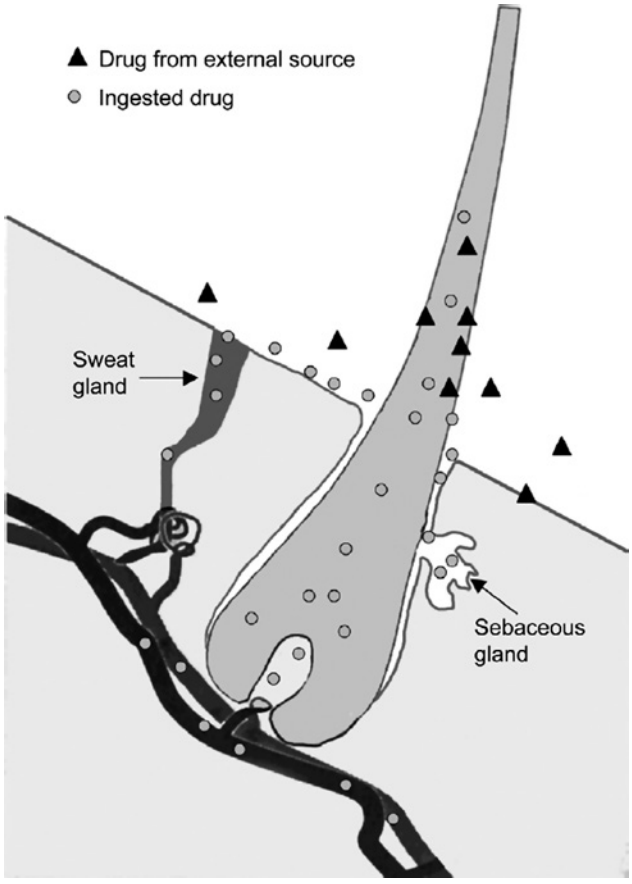

Figure 4: Routes of drug incorporation into the hair follicle (190).

average of 1 cm/month) and clearance of the drugs from the follicle cells during the 5–8 days after exposure (174). The testing of drugs in hair has a long window of detection and the samples can easily be collected and stored under a range of normal conditions (193).

The window of detection is limited by the length of the hair (relevant to systemic absorption where the window of detection can range from weeks to months) and, where environmental exposures are concerned, the cleanliness of the hair (deposition onto hair) (193).

Factors that can affect the stability of drugs in hair relate to the morphology and physicochemical properties of the hair as well as external factors such as exposure to sunlight and weathering, dying, bleaching or treatment of hair and curling or straightening (which damages the hair shaft) (190).

Incorporation of amphetamines in hair

Hair testing is considered to be a reliable biological and stable marker for cumulative and temporal measure of exposure to amphetamines, with a long window of detection making it suitable for the assessment of exposure even after a long period of time has elapsed since exposure occurred.

The first study in relation to the incorporation of methamphetamine in hair was in 1954 in a guinea pig, with a large number of animal studies further conducted to evaluate the incorporation of amphetamines into the keratin matrix to investigate the pharmacokinetics (174).

Amphetamines absorbed into the keratinaceous matrix have been found to be tightly bound and are stable over long periods of time (191, 192). Amphetamines, and other contaminants that are externally deposited or not tightly bound can be removed through a series of ethanol or isopropyl alcohol washes followed by phosphate buffer washes (192). By analysing the concentrations recovered from the washes to the concentrations recovered from the hair matrix, a determination can be made that distinguishes passive or environmental exposures/contamination from systemic absorption (191, 194). Deposition of amphetamines from air, such as from smoking or from the suspension of amphetamine residues in a home during vacuuming or from the operation of a contaminated air conditioning unit, could be a potential route of entry into hair (195).

More specifically in relation to methamphetamine exposures, analysis of both methamphetamine (from systemic absorption and deposition) and amphetamine (metabolite following systemic absorption only) has been used as a quantitative method of differentiating between the types of exposure (196). From the intake of methamphetamine, the ratio of amphetamine to methamphetamine in hair is reported typically to be approximately 1:10 (174), however, it is noted that this ratio has been found to increase with the duration of drug abuse (192) and presumably environmental exposures.

Melanin has been proposed as an important factor in the incorporation of amphetamines in hair (174, 197, 198). While the nature of the interaction has not been established a significant correlation has been observed in controlled human studies (199).

Dose response

In general, hair analysis can be used to approximate dose. The mechanism of entrapment suggests that there should be a pharmacological relationship between the intake of a drug and the amount of drug or metabolite recovered from hair (191). A positive linear relationship between dose and hair concentration has been identified for cocaine and medicinal drug use (200) with segmented analysis of hair used to evaluate changes in dose over time (201, 202). In relation to use of methamphetamine, a positive dose-response relationship has been demonstrated with rat hair (203), in drug users (204) and in a controlled study (199).

The relationship from these studies, however, may not be used to determine dose from the hair analysis alone as a number of researchers have reported substantial inter-individual variability in hair concentrations (191). It is suggested (191) that some of these variability issues may be due to the variety of assay protocols utilised in these studies or melanin concentrations in hair (where a significant correlation has also been observed) (199). Regardless of the variability observed it still holds that the higher the dose the higher the concentration in hair. Hence where a single competently executed assay protocol is used it has been found to provide a useful tool in rank-ordering doses (191).

Published data on use of hair analysis to assess environmental exposures for children

Hair analysis for drugs has been used in a small number of cases of suspected child abuse where proof of harm was required to be demonstrated (205).

Published reports on the use of hair analysis for evaluating environmental exposures (i.e. not drug use) to methamphetamine in children are limited (98, 193, 205–207). The available data have provided evidence of exposure by children as summarised below:

– In general, approximately 35%–73% of biological samples, as urine and/or hair samples collected from

children exposed to methamphetamine in the home (from drug use or manufacture), reporting positive detections results for methamphetamine, amphetamine, pseudoephedrine and/or ephedrine exposures (30, 37, 70, 71, 78, 88, 133, 207).
- More specifically, between 45% and 73% of children [with 100% from one small study of four children (208)] exposed to methamphetamine via drug use or manufacture tested positive for methamphetamine in hair (70, 73, 196, 207). In some cases (where data are reported) positive detections were reported in hair where no detections were reported in urine (73).
- Hair analysis of a child injured from the ingestion of caustic liquid (drain cleaner) in the US (where methamphetamine was manufactured in the home) reported detections of methamphetamine (1.7 ng/mg) and amphetamine (0.16 ng/mg) (98).
- Hair analysis data from New Zealand (207) from children removed from clandestine drug laboratories reported 73% detection of methamphetamine in hair above 0.1 ng/mg and low level detection (10%) of methamphetamine determined to be present from external contamination/deposition (i.e. in the hair wash). The levels of methamphetamine reported in children ranged from 0.1 to 131 ng/mg, with higher concentrations reported in children under 5 years of age.

The actual incidence of positive detections of methamphetamines in hair samples, however, may be under reported as many jurisdictions do not conduct medical testing on children, or on all children, removed from clandestine laboratories and/or do not report these data (due to privacy issues) (78).

The level of exposure that corresponds with the detection of precursors and drugs in biological samples is not known and is generally poorly understood (4, 12, 34, 37). A study by Weisheit (27) considers that exposures to chemicals other than methamphetamine within clandestine drug laboratories is of greater concern on the basis that doses of methamphetamine expected to be absorbed by a child from contaminated surfaces is lower than doses received during drug use, and that methamphetamine is often administered to children with behavioural problems (such as ADHD). While these arguments suggest a relative understanding of potential exposures, they do not take into account the voluntary nature of drug use and monitored/controlled use of ADHD medications. Nor is the statement based on any evidence of the exposure levels that may occur within a former clandestine drug laboratory. Children exposed to methamphetamine in an operational or former clandestine laboratory have no choice (12) in relation to drug exposures and their intake and health is not monitored and managed.

Analysis methods

In relation to the quantification methamphetamine and amphetamine in hair samples, there are a wide range of methods (192, 193, 196, 206, 209–216) that rely on the sampling of different quantities of hair (that have the potential to affect the laboratory quantitation limit), potential inclusion of segment analysis (for evaluation of exposure over time), utilisation of different extraction methods and inclusion of methods for the evaluation of deposited and/or absorbed contamination. The washing of hair during analysis needs to be undertaken with caution as some methods have the potential to damage the hair shaft and affect the reporting of absorbed methamphetamine and amphetamine (194).

Where an analytical method is required for the quantification of methamphetamine and amphetamine in hair, it is important that these issues are evaluated and resolved to ensure that data is sufficiently robust.

Summary

On the basis of the literature review undertaken it is clear that the operation of clandestine methamphetamine laboratories results in the presence of a wide range of hazards and risks within the premises including the contamination of all indoor surfaces and materials with methamphetamine residues. The operation of these laboratories has the potential to result in significant hazards (primarily fire, explosion and release of high concentrations of toxic gases) and other acute exposures by individuals who have chosen to conduct the illegal activities (cooks). However, these activities also has to potential to expose a range of other individuals, who have not chosen to take on these illegal activities, to the same hazards and risks. These individuals include children (considered to be the most sensitive group in relation to exposure), neighbours, police and first-responders to a fire or explosion, forensic and other local investigators (including local council officers) and any residents who may live in these homes before remediation or if no remediation is conducted.

It is important that these risks are understood such that appropriate measures can be implemented to manage exposures and/or determine the need for medical evaluation and intervention, particularly if there is the potential for harm to have occurred. This is particularly relevant

to children, who are most vulnerable group who have no choice in where they live, and are exposed to varying levels of hazards and chemical contamination in the clandestine laboratory. While limited, the available literature provides supporting evidence that shows that children living in these homes are exposed to the drugs manufactured, and that these exposures have resulted in adverse acute and chronic health effects, including long-term behavioural issues. More data are needed to better define these exposures, however, the limited data available suggest that further evaluation and the development of appropriate protocols for the assessment and management of these children needs to be established in Australia.

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