Comments on "Background notes relating to the nature and health significance and persistence of trace of methamphetamine on indoor surfaces" by Dr Nick D Kim, Senior Lecturer, School of Public Health, College of Health, Massey University

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The background note uses extant information to propose a level of surface contamination with methamphetamine which could be viewed as the lowest plausible health-effects concentration. While the general approach taken appears valid, some aspects of this analysis invite further elaboration.

Reference dose/health-based reference value

To simplify terminology these values will be collectively referred to as health-based exposure values (HBEVs). Two HBEVs are referred to in the background notes:

- A reference dose (RfD) of 0.3 μg/kg bw per day, derived by the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency (CEPA) (Salocks, 2009).
- A reference value of 5-70 μg/kg bw per day, derived by staff from the Colorado Department of Public Health and Environment (CDPHE) and the US Environmental Protection Agency (USEPA) (Hammon and Griffin, 2007). While this value range is referred to as a 'reference value' by the study authors, it is derived in a similar manner to a reference dose.

The RfD derived by OEHHA, CEPA is based on the study "Control of Weight Gain in Pregnancy, Utilizing Methamphetamine" (Chapman, 1961). This was a double-blind placebo-controlled trial of the efficacy of methamphetamine for controlling weight gain during pregnancy. Four dose groups were included, receiving methamphetamine doses of 0.0, 0.08, 0.15 and 0.17 mg/kg bw per day. At the conclusion of the study, the dose levels had changed slightly due to weight loss/gain by some participants. Weight gain was significantly different in all treatment groups compared to the control group. While some side-effects were noted the overall prevalence did not appear to be dose-related, with similar total side-effects in the control and high-dose groups.

Babies born to mothers who had lost weight "appeared normal and healthy". All electrocardiogram and laboratory results for all patients evaluated were within normal ranges.

OEHHA, CEPA judged maternal weight loss to be an adverse effect, giving a Lowest Observed Adverse Effect Level (LOAEL) of 0.08 mg/kg bw per day (Salocks, 2009). Three components of uncertainty were applied in deriving a RfD:

- Extrapolation from the LOAEL to a No Observed Adverse Effects Level (NOAEL) (x10). Uncertainty factors for LOAEL to NOAEL extrapolation are usually in the range 3-10, with higher factors used if the effect seen at the LOAEL in considered serious.
- Inter-individual uncertainty factor (x10)
- (In)completeness of database (x3)

These factors result in an overall uncertainty factor of 300 and a RfD of 0.00026 mg/kg bw per day (rounded to 0.0003 mg/kg bw per day or 0.3 μg/kg bw per day).

In the context of the Chapman study, there must be some questions as to whether the weight loss seen represents a true adverse effect. Similarly, it must be questioned whether this effect is sufficiently serious to warrant application of a 10-fold uncertainty factor for extrapolation from LOAEL to NOAEL. However, derivation of a RfD based on the Chapman study has two advantages; it was carried out in humans and requires no interspecies extrapolation, and doses were administered by the oral route.

The reference value derived by CDPHE/USEPA was derived using benchmark doses ($BMDL_{10}$ – the lower 95th percentile confidence limit for a dose giving a 10% change in response compared to baseline) derived from animal reproductive and developmental toxicity studies (Hammon and Griffin, 2007). $BMDL_{10}$ values were in the range 1.5 to 20 mg/kg bw per day, with the lowest $BMDL_{10}$ relating to decreased foetal weight. A total uncertainty factor of 300 was applied to the $BMDL_{10}$ values, made up of components for inter-species extrapolation (x10), inter-individual extrapolation (x10) and database deficiencies (x3). This resulted in a range of reference values from 0.005 to 0.066 mg/kg bw/day, rounded to 5-70 μg/kg bw per day.

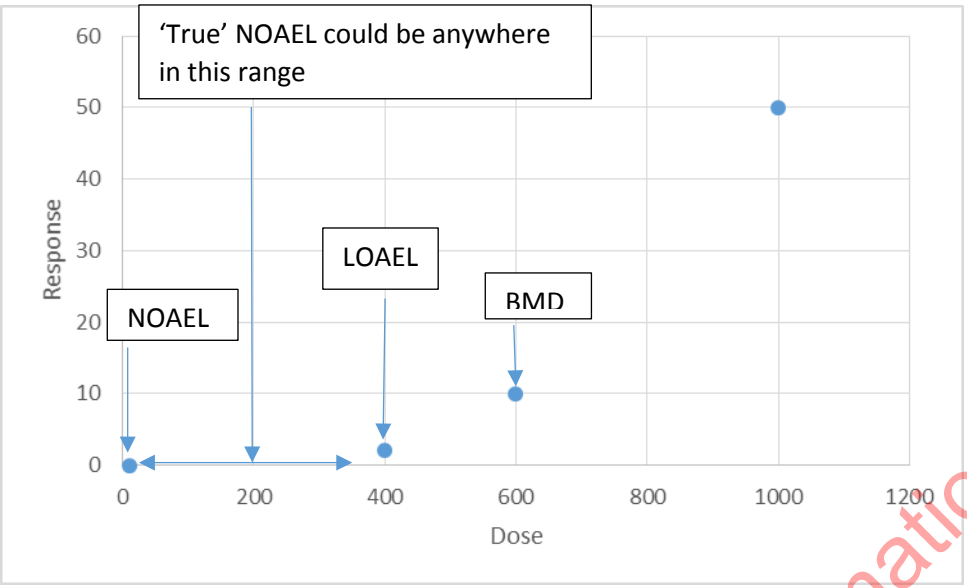
It should be noted that all animal studies used non-oral routes of dose administration (intravenous, intraperitoneal or subcutaneous) and are not immediately comparable to the routes of exposure to methamphetamine that would occur in a contaminated house.

In the background notes, Dr Kim chose to use the latter reference values (CDPHE/USEPA) as a reference point for human methamphetamine exposure, rather than the human-derived OEHHA RfD. The rationale for this decision was that "an RfD provides a level at which long-term exposure is without appreciable risk, a health-based reference value provides the lowest level at which the first onset of the most sensitive possible health effect may begin to occur". I believe that this overstates the difference between these two approaches. The CDPHE/USEPA study bases the derived HBEV on benchmark doses, from animal studies. There has been a general move to the use of benchmark doses, rather than NOAELs, because the benchmark dose can be determined with some confidence by interpolation of the dose response curve, while the NOAEL is the highest dose at which no adverse effect is seen and is not necessarily a point on the dose-response curve (see attached illustrative Figure 1). While uncertainty factors are applied to a NOEAL to arrive at a HBEV that is without appreciable risk (but not 'without any risk'), benchmark doses are most often compared to human estimated exposures, with the resulting margin of exposure (MOE) being a measure of the level of concern associated with the human exposure. The study of Hammon and Griffin essentially predefines a MOE of 300. MOEs of this magnitude, for threshold effects (non-carcinogenic) would usually be considered to represent a low level of toxicological concern. I believe that 'without appreciable risk' and 'a low level of toxicological concern' cannot be viewed as distinctly different expressions of the level of risk.

In my opinion, Dr Kim's choice of the higher HBEV requires a more substantial rationale than has currently been provided. In the absence of a clear reason to choose one HBEV over another, a conservative approach to risk assessment would suggest that the lower HBEV should be used as the reference point for assessing risks.

Given the approximately 17-fold difference between the two HBEVs, this decision had a major impact on Dr Kim's conclusions. It should also be noted that the toxicological endpoint associated with the reference value used by Dr Kim is decreased foetal weight, which is of questionable relevance to the most sensitive exposed individuals in a methamphetamine-contaminated property (infants).

Figure 1. Illustrative figure showing various toxicological points of departure in relation to a hypothetical dose-response curve



Human exposure to methamphetamine due to surface contamination

Dr Kim uses the exposure assessment carried out by Hammon and Griffin (2007), to determine human exposure resulting from different levels of surface methamphetamine contamination, as the basis for his conclusions. The approach taken in the study of Hammon and Griffin appears to be satisfactory and determines that exposure will be predominantly by oral exposure resulting from surface to hand to mouth transmission. Dermal absorption was assessed to contribute a lesser amount to methamphetamine exposure. Hammon and Griffin calculated exposure as an 'internal dose' assuming 100% absorption of oral doses and 10% absorption of dermal doses. The highest estimated exposures were for infants and ranged from 0.019 μg/kg bw per day at a surface contamination of 0.05 μg/100 cm^2 to 0.19 μg/kg bw per day at a surface contamination of 0.5 μg/100 cm^2 (the current New Zealand guideline level).

The exposure model used by Hammon and Griffin has a linear relationship between surface methamphetamine contamination and human exposure. Dr Kim used the linearity of this relationship to determine that exposure equivalent to the lowest Hammon and Griffin reference value (5 μg/kg bw per day) would result from a surface methamphetamine contamination of 12.5 μg/100 cm^2. It should be noted that, by the same reasoning, the OEHHA RfD exposure level would equate to a surface methamphetamine contamination of 0.8 μg/100 cm^2. While the RfD was derived from an external (administered) dose and the exposure estimates of Hammon and Griffin are internal doses, the assumption of 100% oral absorption of methamphetamine used by Hammon and Griffin means there is no conflict between the bases used for the exposure dose and RfD.

Use of the term 'contaminated'

Dr Kim argues that surface methamphetamine concentrations of less than 12 μg/100 cm^2 should not be referred to as 'contamination', as this level is unlikely to be hazardous. Dr Kim contends that 'contaminated' should only apply in situation where the substance is present at concentrations sufficient to result in harm.

In my opinion, methamphetamine can reasonably be considered to be a contaminant, rather than a normal component, of the domestic environment. Normal dictionary definitions of contamination refer to the presence of something undesirable, rather than its presence at a level high enough to cause harm. Methamphetamine's presence, at any concentration, is likely to be unwanted and undesirable. Therefore, if methamphetamine is a contaminant, then any measurable concentration of methamphetamine in a house could lead to the house being described as contaminated with methamphetamine.

Indeed, in some cases a normal component of a medium may still be referred to as a contaminant. For example, the heavy metal mercury may be naturally present at appreciable concentrations in fish. Mercury is conventionally referred to as a contaminant in this context, even when present at low concentrations.

References

Chapman JD. (1961). Control of weight gain in pregnancy, utilizing methamphetamine. Journal of the American Osteopathic Association; 60: 993-997.

Hammon TL, Griffin S. (2007). Support for selection of a methamphetamine cleanup standard in Colorado. Regulatory Toxicology and Pharmacology; 48(1): 102-114.

Salocks C. (2009). Development of a Reference Dose (RfD) for Methamphetamine. California Environmental Protection Agency. Office of Environmental Health Hazard Assessment. Integrated Risk Assessment Branch.