Comments on: Background notes relating to the nature and health significance and persistence of trace of methamphetamine on indoor surfaces. Author**:** Dr. Nick Kim, Senior Lecturer, School of Public Health, Massey University, Wellington.

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The background provides a useful summary of several key issues for consideration in the development of a health-based surface standard or guideline for methamphetamine (MA) in reoccupied dwellings. The delineation of health-based vs instrument-based standards is importantly emphasized, and some cautions about the potential for over-interpretation of the health implications of risk assessment values are provided.

There are two independent health risk based MA values derived by the State of Colorado and California that are discussed, each based on completely different toxicological studies and with different sets of exposure assessment modelling and associated uncertainties. These two authorities (and the Australian and New Zealand guidelines that currently align with the Colorado value) subsequently have 2 different surface guideline levels (0.5 and 1.5 µg/100 cm^2). This illustrates, as discussed by Dr Kim, the degree to which the variability and uncertainty inherent in these calculations can result in variations in outcome and interpretation of health risk from a given guideline level. There are however, in my view, some technical issues that warrant further consideration when deriving or adopting a health-based guidance value for MA from homes that were formerly used as laboratories or inhabited by MA users.

1) As a general principle, <u>human data are preferable</u> to experimental animal data in risk assessment, if appropriate and sensitive endpoints exist for both. This is particularly true in cases where toxicokinetics or toxicodynamic differences between humans and the studied non-human species are large. In this case, the elimination half-life of MA is roughly an order of magnitude faster in the rat (about 1 hour) (Riviere et al., 2000) than in humans (around 10-15 hours) (Mendelson et al., 2006). While toxicokinetic differences often occur between humans and experimental animals, in this case, the effective doses for onset of toxicity are reported to vary by a factor of about 50-fold, with humans being far more sensitive (OEHHA, 2011; Salocks, 2016). Thus, unless dosimetric adjustments were made to a given rat study, extrapolation of experimental doses in rats to those in an environmental exposure situation, or in a human risk assessment context, could be problematic. Given that human data (although dated), from pregnant women exist, as summarized in the California EPA (OEHHA) assessment, it is unclear why these data have been dismissed as the point of departure for the risk assessment calculation presented in the Background Paper. The use of

decreased body weight gain as a toxicological endpoint in the study on pregnant women is questionably adverse and may be a reversible effect, however the effect was statistically significant and is consistent with reduced appetite with amphetamine users. Thus it is an indication of a plausible biological response, and in my view it is prudent to err on the conservative side to consider it adverse. There is also ample precedent in experimental animal studies in regulatory settings for considering decreased weight gain to be an adverse effect.

The receptor in the California exposure assessment, however, is not pregnant women, but rather infants and toddlers, who would have much higher exposures. Thus the exposed population for risk assessment and the toxicological study subjects are not aligned. On balance, although the human toxicological data used by OEHHA are marginal, given the lack of sensitivity of the rat model to MA toxicity, my view is that the human data should receive preference for use. The exposure assessment should consider pregnant women as the most relevant exposed population.

The Background Paper employs the rodent toxicological data used by the State of Colorado, and a benchmark dose (BMD) calculation, with new exposure estimates as the basis for an alternative risk value for MA. While the rodent data can be informative and a BMD approach is generally preferred over a NOAEL approach, I do not agree that the rat is the best choice of a toxicological starting point for the risk assessment, and the difference in point of departure between the rat and human studies could account for a substantial difference in guidance value outcome.

2) Several recent studies, including the IDEAL study conducted in New Zealand, point to lasting neurodevelopmental effects in children stemming from pre-natal exposures (Smith et al., 2015; Wouldes et al., 2014; LaGasse et al., 2011). While the doses received by the fetuses in these studies were only categorized and presumably are higher in magnitude than in the dermal exposure scenario presently under consideration, thresholds for toxicity were not established and these subtle and latent effects may indicate that fetal or early post-natal exposures are of significant concern. Profound neurodevelopmental effects are also found in neonatal rats exposed to therapeutic doses (McDonnell-Dowling et al., 2014; NTP 2005). These relatively new findings indicate that scientists do not yet completely understand the dose-response relationship of small doses of MA to unborn fetuses or early neonates. The database uncertainty factor of 3 employed by the California EPA was incorporated explicitly to acknowledge this data gap, and is, in my view, completely justified.

Given the problems with the available data sets, the different approaches taken by different authorities, and the recent findings in human studies, ideally an updated literature review should be undertaken with a full

accounting of all available human and rodent data, with a current benchmark dose modelling approach, if possible, to arrive at a reference dose for the human neurodevelopmental effects of MA. To my knowledge, no authority is undertaking this task.

3) In apparent contrast to the conclusions reached in the Background Paper, a recent publication by Van Dyke and colleagues (Van Dyke et al., 2014) examined experimental and modeled dermal exposures to MA and concluded that 1.5 µg/100 cm^2 may not provide adequate protection against the California reference dose in all instances. This group used cotton gloves which they acknowledge are likely to overestimate the transfer of surface residues as compared with human skin. Furthermore, the direct application of their data [particularly transfer efficiency] in regard to their conclusion that a "clean" value of 1.5 µg /100 cm^2 can still lead to excessive exposure, i.e., an exceedance of the RfD, is likely exaggerated. This is because transfer efficiency from a surface cleaned to 1.5 µg/100 cm^2 is likely to be different. For example, it is noted by Martyny (2008) that once a surface has been cleaned with a solvent such as "simple green" very little material remains readily dislodgeable. These authors noted that additional washings were not particularly effective in removing more material. Thus, once cleaned, the efficiency of transfer from surface-to-dermis is going to be significantly different than assessed by Van Dyke who measured efficiency using cotton gloves on a freshly contaminated surface. It is my view that the study by Van Dyke does not provide cause for concern about the health protective nature of the California guidance value, but does illustrate the widely varying results one can generate using artificial experimental exposures and modelling assumptions.

Dr Kim correctly points out that, given the many conservative assumptions that are employed in the risk assessment process, small excursions above a reference dose do not automatically translate into the onset of adverse clinical effects. Indeed, a goal of risk assessment is to help ensure that such effects never come into play. The use of uncertainty factors is thus inherently subjective and involves a degree of conservatism. However, I do not find that the use of uncertainty factors such as those used in the California and Colorado calculations to be inappropriately conservative particularly in light of point 2 above.

It may well be that a surface concentration could be different (higher or lower) than the current 0.5 µg /100cm^2 NZ Guideline value based on a detailed re-evaluation of the various toxicological considerations including recent human data, and detailed consideration of inputs to exposure models, and we are currently in the process of exploring those possibilities. The analysis presented by Dr Kim in the background paper by itself is, however, not a convincingly improved alternative to the current standard or that from California.

It is worth noting that, since California implemented its standard, there are now 5 additional US States that have adopted this including: Minnesota, Wyoming, Washington, Virginia, and Kansas.

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