P8510 committee meeting 25 July 2016

ESR (Dr Jeff Fowler) comments on Dr Nick Kim's paper

- Both the Californian and Colorado derived health risk based MA values are based on different studies and came to different values. However their derivation (based on dermal contact) is applicable to 'homes that were formerly used as laboratories or inhabited by MA users'. (my underling -last line 2nd para)
- Human data is preferable to experimental animal data. For MA, rats elimination of half-life is up to 15 times quicker than for humans (1 hour verses 10-15 hours) and the effective doses for onset of toxicity for MA vary by a factor of 50 fold with humans being far more sensitive. Using the rat dosage information is therefore 'problematic'.
- Human data exists (related to pregnant women) as used by the Californian EPA. It is unclear why Dr Kim dismissed this data as it was statistically significant and in Jeff Fowles view an indication of plausible biological response.
- The Californian exposure assessment is however based on infants/toddlers who would have higher exposure (than pregnant women). Given the lack of sensitivity of the rat model to MA, Dr Fowles view is that the human data should be preferred and that pregnant women should be considered the most exposed population. Recent studies have shown Neurodevelopmental effects from pre-natal exposure are of significant concern (see 2) but scientists do not completely understand the dose response relationship of small doses of MA to unborn foetuses and the uncertainty factor of 3 employed by California EPA is, in Dr Fowles view, completely justified
- the difference in point of departure between rat and human studies could account for a substantial difference in guidance value outcome
- a detailed re-evaluation of the various toxicological considerations including recent human data and detailed inputs to exposure models is currently being carried out (under MoH contract). However the analysis in Dr Kims paper, by itself is not a convincingly improved alternative to the current standard or that from California
- There are now 6 US States which have adopted the Californian Standard

As well as the dot points above, Jeff's earlier email with his three main concerns with the Kim paper are relevant:

Although I agree with much of what Nick has written in terms of him setting the background to the issues, there are at least three areas that I will need to disagree on

1) his decision to use the older Colorado reference dose based in rodents when a more recent RfD based on human data exists. There is clear evidence that the kinetics of meth are radically different in humans compared with rats.

2) The recent published data showing long term neurodevelopmental effects in kids from in utero or infant exposure, and,

3) the notion that any risk based value should be considered a level above which you automatically start seeing clinical effects. His dismissal of the public health importance of maintaining uncertainty factors is of concern.

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