Appendix 3

Afternoon notes from the January 25 methyl iodide meeting of the SRC and DPR

Afternoon Session

Tasks agreed upon by the SRC and DPR based on the morning discussion:

1. Comments in balloons now will be put into text where appropriate.
2. There are four areas of exposure modeling/assessment which the value as used could be systematically underestimated. The four values shouldn't be changed in principle finding but an alternative value will be presented for the point of discussion as to what the impact would be on a different approach (numeric value). These four areas are the 50% respiratory protection factor, some level of skin exposure, an increased breathing rate (the SRC suggests using the OSHA rate), and a 10-hour work day. These aren't necessarily the final values put forward by DPR but are alternative calculations that may yield different numbers and are warranted by scientific argument.
3. DPR will discuss in the text whether or not temperature will be a driving factor in the model.
4. DPR doesn't have the science to quantitate the effect of temperature on emission. Therefore they will mention that temperature has an effect but it cannot be quantified. DPR couldn't detect a reasonable pattern with temperature. Soil temperature is a major factor and there is a smaller temp variation. They will add a narrative to cover these points.
5. Small points to address panel comments on Vol. I to the extent that is appropriate.
6. Add a factor of 10 for database uncertainty since the acute neurotoxicity study did not adequately examine neurotoxicity, and there is no neurotoxicity study for repeated exposures. Human exposure showed neurotoxicity after repeated exposures.
7. Regarding Table 6 in Vol. I, currently it is not clear why there are two rows for "Lifetime"/"Thyroid Tumors in rats" and what each row represents. There was also an agreement that these two rows would be reversed in order and that each would have a titled added (something like): Genotoxic MOA (non-threshold) and Antithyroid MOA (threshold).
8. Include comments about the absence of any data on developmental neurotoxicity (as distinct from chronic exposure neurotoxicity in the adult and the high likelihood that MeI would prove to be a developmental neurotoxicant.
9. Genotoxic MOA will be added before thyroid perturbation MOA. Reverse text in all places including tables.
10. Add a paragraph on the genotoxicity that will be stronger and evoke the correlary among the other methylating agents that act at the same site as MeI. Add electrophilic chemistry as appropriate, specifically mention MMU and MMS. (MNU--a methylating agents like MeI--is an established thyroid mutagen. Furthermore, MeI is an S_N2 electrophile, like

MNU and MMS, and all three form the same kind of mutagenic adduct (m6G), where MNU and MMS are both 2A carcinogens according to IARC. This kind of information, along with references, can be found in the Appendix that Dr. Loechler submitted back in November 2009).

11. Take out "reject the PBPK model" sentence and revise. Include DPR rationale for dropping model and using default model.
12. Include inadequacy of the protocol for 18 mo study.
13. When the point of departure is based on BMDL, take out the statements that indicate the use of NOEL for that endpoint for hazard identification.
14. Take out acceptability statement regarding Wagner and Dakoulas (2001) as to emphasize DPR's concerns about the study in agreement with USEPA which called in a "No-test".
15. Linear projection of low-dose extrapolation deserves first mention because the most likely mode of action is direct reaction of MeI with DNA.