Office of Environmental Health Hazard Assessment

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Linda S. Adams
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MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: July 16, 2009

SUBJECT: ADDITIONAL COMMENTS ON DRAFT RISK CHARACTERIZATION DOCUMENT (Vol. I, Appendix A, PBPK modeling) FOR INHALATION EXPOSURE OF METHYL IODIDE (IODOMETHANE)

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) expanded comments on the Department of Pesticide Regulation's (DPR) Draft Risk

Characterization Document, dated March 2009, Vol. I, Appendix A, for the active ingredient methyl iodide. A request for an additional review of Vol. I, Appendix A, Review of Physiologically Based Pharmacokinetic Model for Human Equivalent Concentration, was sent to us on June 25, 2009 by Dr. Marylou Verder-Carlos. Dr. Joseph Brown has provided additional comments which we are sending in the enclosed memorandum.

Under the general authority of the Health and Safety Code, Section 59004, and the Food and Agricultural Code (FAC), Section 13129, OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticides. Pursuant to FAC Sections 14022 and 14023, OEHHA provides consultation and technical assistance to DPR on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings.

Should you have any questions regarding these comments, please contact Dr. Joseph Brown at (510) 622-3163. You may also contact Dr. Anna M. Fan at (510) 622-3165, Dr. Melanie Marty at (510) 622-3154, or Dr. David Ting at (510) 622-3226.

Enclosure

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FROM: Joseph P. Brown, Ph.D.
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C. J. Salmon for J. P. Brown 7/21/09

DATE: July 16, 2009

SUBJECT: COMMENTS ON APPENDIX A: REVIEW OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR HUMAN EQUIVALENT CONCENTRATION, IN APPENDICES TO VOLUME I: HEALTH RISK ASSESSMENT OF METHYL IODIDE. (Draft report from the Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency).

This memo constitutes additional comments by the Office of Environmental Health Hazard Assessment (OEHHA) on a Department of Pesticide Regulation (DPR) review of a Physiologically Based Pharmacokinetic (PBPK) model used in a health risk assessment of methyl iodide. This memo is not an assessment of the model itself. There are several outstanding questions and uncertainties which could be resolved by augmenting the subject report appendix. We list specific details that could be supplied, and could improve the report, in our comments below.

A. Fetal Death in Rabbits

Comment 1. Page A4, Line 8. It is stated that "the same basic model structure is used for all three endpoints" except that the rat has an enhanced nose compartment. It would be helpful to provide a model diagram of the rat PBPK model.

Comment 2. Page A4, Line 42. "This section provides only a very brief description of the model." In our view this is a major deficiency of this report. The appendix on PBPK contains few details of the subject model variants; more details should be added as shown below.

Comment 3. Page A-5, Line 1. "Comparison of model output to the experimentally measured values is used to adjust input variables for model fit." How was the model validated? Were there different data sets used for model calibration and validation?

Comment 4. Page A5, Lines 5-8. This brief discussion of the origins of key model parameters is difficult to follow. It would help the reader if you could insert a table of model parameters actually used in the model and expand on their individual origin (i.e., Morris, Mileson, Sloter, or other).

Comment 5. Page A6, Fig A-1. It is not clear what the difference is between A-1a and A-1b. Figure legends should be specific as to exposure conditions and there are some misspellings that need correction.

Comment 6. Page A-7, Lines 2-3, 9-11, Table A-1. This text and table describe two ventilation rates and a table for modeled and measured results for one (12L/kg^0.75). This is confusing. The second table is not presented and should be included so the reader does not need to go to Section II C to get the comparison.

Comment 7. Page A-8, Lines 32-40, Table A-2. It would help to add the NaI data to Table A-2 even though the doses are different. The rabbit simulations seem consistent in over-predicting F/M ratios. Why wasn't this taken into account in setting the fetal influx and efflux rates in the model? The values given (some of the very few) show a rate ratio of 4.7-fold in favor of fetal uptake. This ratio is probably too high. In the human model this ratio is only 1.25.

Comment 8. Page A-11 lines 19-21. How well does the model predict fetal exposures at anticipated human exposure levels? Are there data in humans other than cord blood iodide?

Comment 9. Page A13, Lines 18-21, Fig A-3. This text and figure report model predictions of up to 513-fold fetal to maternal iodide concentration ratio in rabbit thyroid follicles following a 6 hr exposure to MeI. Were other concentrations or ventilation rates simulated? A diagram of the rabbit PBPK model would be helpful.

Comment 10. Page A15, Lines 8-9, Page A-16 Lines 1-9. The text reports predicted values of 1800-fold for fetal/maternal follicle iodide and raises concern with respect to model validation and the lack of tissue data. Gargas et al. 2005 is cited in support of the prediction but this is not published work in the available literature. Can a table be added to provide the key Gargas results "fit to human fetal thyroid iodide levels" that support the "likelihood of reality"?

Comment 11. Page A16, Lines 11-13. "The need to further investigate this issue ...." We agree that there is a need to thoroughly evaluate model parameters and structure to assure that the model predictions are reliable.

Comment 12. Page A-16, Lines 24-26. "61.1 kg and a fetal weight of 0.27 kg (i.e. a single fetus at maternal weight fraction 'VFETC' of 0.0044). The model targets the stage of fetal ontogeny...." Does the model include parameters for fetal, placental, uterine, mammary and fat growth during gestation? It seems to us that such a narrowly focused model is more likely to give erratic predictions than one covering a larger portion of the gestation period.

Comment 13. Page A-20, Lines 36-39. Notwithstanding the sharp temporality of the fetal death response during GD23-26, it makes more sense to us to adopt a not-to-exceed value at ANY point during gestation. Using a single day model metric to base the HEC may be too narrow.

Comment 14. Page A-21, Lines7-8. "Significant GSH depletion in fetal blood was detected as early as after one 6 hour 20 ppm exposure." This is unclear. Was the significant depletion seen at 6 hour or at some point after the 6 hour exposure? Please indicate the kinetics of GSH depletion (i.e., a graph).

Comment 15. Page A-21, Lines 19-21. "In summary, with insufficient support for a single MOA within the time frame of 30 or less hours, it is prudent to model the HEC at the 2 ppm NOEL based on a single day exposure for both rabbits and humans." In our view, a sound rationale for adopting a single day exposure in humans has not been established. It seems more likely that, in humans, the period of fetal vulnerability would extend well beyond a single day.

Comment 16. Page A-21, Lines 41-43. "However, the range of human F/M ratio is wide, and there are nine sets of values above 2 (range 2.08-5.4) which exceed the average F/M ratios in rabbits." This is not evident from Tables A-1 and A-2 where human F/M values are generally lower than measured or modeled rabbit values. Is there something missing from the nine sets?

Comment 17. Page A-22, Lines37-38. "In conclusion, the overall evidence presented in this and previous sections indicates that maternal iodide dose metric is most reliable for reflecting the maternal MeI exposure status on which the rabbit NOEL was based." Which maternal iodide metric is being referenced in this sentence, Cmax, C steady state, or AUC?

Comment 18. Page A-23, Lines 23-25. The discussion of rabbit and human AUCs is not clear. Generally AUCs are in units of concentration × time and usually averaged per day, e.g., mg hr/L d. Here the report is apparently equating ppm × 24 hr in rabbit with ppm × 96 hr in humans. Were regressions between ppm external and AUC established for rabbit and human exposures? This would seem to be a more rational process for extrapolating AUC rabbit to AUC human and then to HEC (i.e. ppm external for human).

Comment 19. Page A-24, Table A-4. In view of comment 18 above, it would help to show a sample calculation for AUC-derived HECs in the table. Are there any further comments on the HECs presented in the table that cover a 17-fold range? Which ones seem more reliable? Or did you pick the lowest?

Comment 20. Page A-25, Figure A-7. This figure is difficult to read. Does the inset represent the human or the main graph? The inset exposure concentrations can't be read and should be specified in the legend.

Comment 21. Page A-27, Figure 8. Is a two-day simulation sufficient to assess occupational exposure? Normally you would expect a 5 day occupational plus 2 day population exposure (168 hr). The peak concentration with 0.35 ppm × 8 hr/d has clearly not been reached. If DPR has simulations predicting a steady state Cmax, then the report should show it. Again, these are predictions subject to sufficient model validation.

B. Nasal Olfactory Epithelial Degeneration in Rats

Comment 22. Page A-28, Lines 5-6. "This section provides only a very brief description of the the Arysta mei3 model…" As noted above, a model diagram and list of parameters would greatly assist review of DPR's use of the model.

Comment 23. Page A-29, Figure A-9. Figure A-9a shows that the model overestimates the reduction in olfactory GSH concentration. ppm should be added to the inset legend. Figure A-9b shows two model simulations. What is the difference between them?

Comment 24. Page A-30, Lines 5-6. "DPR agrees with USEPA that GSH depletion at the dorsal olfactory epithelium can be the dose metric for modeling the nasal effect HECs." In view of model overestimation of this metric, which appears to increase with exposure concentration, have other model metrics been adequately evaluated? For example, the model can predict Cmax's, AUCs, and fluxes in nasal epithelium.

Comment 25. Page A-31, Figure A-10. This figure is clear and understandable. A 6 hr exposure to rats results in about a 35% reduction in GSH in the dorsal meatus region, which serves as DPR's basis for estimating an HEC.

Comment 26. Page 30, Lines 31-33. We agree that 50% GSH reduction is not a suitable benchmark for a no-effects level. Since tissues vary in GSH concentration, a single benchmark may be a flawed concept. DPR's use of 25% in relation to a nasal tissue GSH reduction threshold seems a reasonable place to start but more tissue specific data are needed to confirm this.

Comment 27. Page A-34, Lines 23-26. "Repeated exposure may result in a greater severity of cellular damage from which an HEC based on a single day exposure at 25% GSH depletion may not be adequate to protect." Agreed. That is why simulations estimating an HEC for human occupational exposure should be run for at least a week (5 × 8 hr/d plus weekend).

Comment 28. Page A-35, Lines 3-4. "The rat model uses mei3.csl and mei3cmd files submitted to DPR by Arysta (2007). Three sets of HEC simulation runs were conducted by Arysta in 2008." Does this mean that DPR didn't run any simulations with the model to confirm proposed HECs?

Comment 29. Page A-35, Lines 17-19. "..applying input parameters for children of various age (i.e., 3 month-old infants, children at 1, 5, 10, and 15 years old) did not result in different HECs than for adults." It would be useful if the report could expand on this. For example, what body weights and ventilation rates were used for infants and children?

Comment 30. Page A-35, Lines 23-29, Figure A-11. These graphs are difficult to read. Presumably they proceed from inside to outside, top to bottom. Please indicate the outermost layer in the text, gsdoe11 "The time to a less than 0.5% change in GSH level is not reached until hour 14 of exposure." What does this mean? It is not clear how this relates to the other text or Fig. A-11.

Comment 31. Page A-38 Lines 2-3, Figure A-12. "DPR's 8-hour HEC is 2.8 ppm based on DPR's default breathing rate of 833 L/hr..." It is not clear what the basis of the HEC is? Is it the average depletion of GSH in the olfactory epithelium? Please indicate clearly in the text and legend. Again the graph is difficult to read and some additional labeling would help.

C. Neurotoxicity

Comment 32. Page A-40, Lines 14-18. "...the concerns remain about the use of blood or brain MeI concentration instead of its AUC for the HEC dose metric." It seems to us that the brain AUC is the most reasonable metric for the analysis.

Comment 33. Page A-43, Lines 13-15. "Since this 8-hour HEC does not take into account the additional 16-hour exposure after work, it is realistic to set the 8-hour HEC at 3.4 ppm, the same

level for the 24-hour HEC." Is this realistic? The rationale is not clear. Why not a time weighted average, e.g., 5.5 ppm? It just seems odd that a rationale for an 8-hour value was developed and then discarded.

Comment 34. Overall the neurotoxicity section is better presented than the other endpoints.