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DATE: August 28, 2006

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT DIETARY RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENTS *ORTHO*-PHENYLPHENOL AND SODIUM *ORTHO*-PHENYLPHENATE

Thank you for the opportunity to review the Risk Characterization Document (RCD) for dietary exposures to ortho-phenylphenol and sodium ortho-phenylphenate, dated June 6, 2006. These fungicides are used in the post-harvest treatment of a variety of fruits and vegetables. This document quantifies the exposures to these chemicals through the food supply, and compares the exposures to toxicologic screening levels determined in animal studies.

The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by the Department of Pesticide Regulation (DPR) under the general authority of the Health and Safety Code, section 59004, and also under the Food and Agricultural Code, section 13129, which gives OEHHA the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

The document is comprehensive, well reasoned and clear. We appreciate and concur with the conclusions and the detailed description of the data indicating that ortho-phenylphenol is a genotoxic carcinogen, warranting calculation of its slope factor in humans via a linear low-dose extrapolation model (slope factor = 2.2×10^{-3} [mg/kg/day OPP]$^{-1}$). Our comments are presented

below, divided into a few general comments followed by a longer list of additional comments. Please feel free to contact us if you have any questions.

General Comments

1) In the chronic feeding study by Wahle and Christenson (1996), female rats exhibited cardiomyopathy at the low (49 mg/kg/day) and mid (248 mg/kg/day) dose levels (both $p<0.05$). It is clear from effects in hearts, kidneys and bladders that male and female rats react differently to OPP. Female mice also reacted differently than male mice, exhibiting increased absolute heart weights in a chronic feeding study (Ito, 1983). Thus, it is unjustified to assume that since male rats exhibited no cardiomyopathy at 39 mg/kg/day (Wahle and Christenson, 1996) the same would be true for female rats. However, selection of the male NOEL of 39 mg/kg/day as the study NOEL makes this assumption. We recommend using the NOEL of 39 mg/kg/day for quantifying the risk to the male human population, and a NOEL of 5.0 mg/kg/day (49 mg/kg/day divided by an uncertainty factor of 10 for LOEL to NOEL extrapolation of a serious toxic effect) for quantifying the risk to the female human population. It should be noted that the DPR toxicology summary of Wahle and Christenson (1996) concluded that 39 mg/kg/day in male rats was a LOEL (Appendix A). We recommend that this discrepancy be addressed.

2) In Tables 51 and 53, and at various places in the text, the 95^{th}, 97.5^{th} and 99^{th} percentile groups for dietary exposure are presented. If we understand the data correctly, the groups are based on three different levels of food consumption, with the same OPP residue level used for all three. We recommend making this clear. Also with regard to these levels of food consumption, it is not clear why these high ends of the food consumption spectrum were taken into account only in the acute exposure assessment. A range of low to high food eaters would also be expected over the long term. We recommend discussing why these high percentile food consumers were not used to calculate dietary exposures for the chronic exposure assessment and also for calculating the lifetime cancer risk.

3) There are a number of tables (17, 19, 24, 31) where incidences of different tumors or different nonneoplastic lesions were combined. It appears that the different tumors or different nonneoplastic lesions never occurred in the same animal. For example, in Table 17 at the mid dose level, the papilloma incidence was 3/24, the carcinoma incidence was 20/24, and the combined tumor incidence was 23/24. This was probably an intentional assumption made by either the study authors or DPR in calculating the combined incidences. If so, this should be stated in the legend of each table.

4) We recommend something be said about the conversion of SOPP to OPP. Does this risk assessment consider that all SOPP becomes converted to OPP following ingestion, and what about following application to the various fruits and vegetables?

Additional Comments

Page 23, Absorption. We recommend stating how the radioactive OPP and SOPP were administered.

Page 23, "the oral absorptions of OPP and SOPP from the gastrointestinal tract." This phrase does not make sense. We recommend correcting.

Page 23 and various places in the Metabolism section. When discussing in vivo studies, recommend including by what route and method the animals were dosed (in food, water, gavage, injection, etc.).

Page 27 and various places in the Absorption section. The phrase "oral absorption" is unclear. We recommend explaining what is meant.

Table 6. We recommend indicating in the table that these measurements were made at the completion of the 13 week period.

Table 7. We recommend stating in the footnote what P/N means.

Table 8. The weeks in footnote [a] do not match the weeks in the table. We recommend correcting.

Page 50, "Although bromodeoxyuridine (BrdU)-labeling index, an indicator of cell proliferation, appeared to decrease after 4 weeks, the index increased ($p<0.05$) with dose at both weeks 4 and 13 (Table 8)." The index increased with dose at week 4, but not at week 13, where only the high dose exceeded the control. We recommend correcting.

Tables 9 and 11. It is not clear why some values for numbers of animals (all 10) have asterisks. We recommend explaining.

Page 50, "At the end of the 4-week recovery period, 684 mg/kg/day group still exhibited some urinary-tract effects: one animal exhibited renal tubular proliferation, two animals had renal tubular dilation, and one animal had mild hyperplasia in the bladder (Table 7)." Table 7 does not show renal tubular proliferation or renal tubular dilation. We recommend correcting the text. It would be helpful to the reader if "(data not shown)" were used where appropriate.

Table 10. In footnote [b], we recommend changing protein to creatinine.

Page 54, "(Table 10); correspondingly, there were reductions in urinary specific gravity and creatinine concentrations." Table 10 shows osmolality, which is not the same as specific gravity. We recommend correcting the text.

Table 12. We recommend adding when these animals were sacrificed.

Table 13. We recommend correcting 10,000 ppm in the table.

Page 57, "The observation that the high-dose males exhibited no bladder tumors but nephritis …" Table 12 shows that 1/10 high dose males exhibited a urinary bladder transitional carcinoma. We recommend correcting the text.

Page 61, "as the nephritis progressed, it disturbed the acid-base balance of the urine, which in turn affected the transformation and proliferation of the bladder epithelium." We recommend being more specific and stating that as the nephritis progressed, the urine became more acidic, thereby inhibiting both transformation and proliferation of the bladder epithelium.

Page 63, "TBZ appeared to synergize the increase in papillomas and carcinomas." Using the data in Table 15, it is not possible to determine whether there is a true synergistic interaction between SOPP and TBZ. We recommend dropping the word "synergize" and instead stating that TBZ appeared to increase papillomas and carcinomas.

Table 15. According to the data, no males had both papillomas and carcinomas. We recommend checking to be sure this is correct.

Table 16. We recommend adding when the measurements were made.

Table 17. The data indicate that no animal had both pyelonephritis and interstitial nephritis. The data also indicate that no animal had both papillomas and carcinomas. We recommend checking to be sure this is correct.

Table 18. A few of the standard errors are 0. We recommend checking to be sure they are correct.

Table 18. The controls exhibited six to ten-fold increases in the protein concentration of their urine during the course of the study. OPP had the opposite effect on urine protein concentration, presumably due to increased water intake. We recommend discussing the possible reason(s) for the increases in the controls.

Table 19, footnote [6]. We recommend adding that the 0.49% value refers to "historical" controls.

Table 19. The data indicate that in the high dose group, no animal had both carcinomas and papillomas. We recommend checking to be sure this is correct.

Page 74, third paragraph. For the eye alterations, we recommend stating when the examinations were performed and adding the incidences in the controls.

Page 87, "transitional cell carcinomas of the kidneys are rare spontaneous neoplasms in male F344 rats." We recommend providing a historical control value if available.

Tables 24 and 25. We recommend indicating when the animals were sacrificed, perhaps in a footnote.

Table 24, 56 week recovery study. Two animals had papillomas and 21 had carcinomas. Twenty-three animals had "combined tumors." This implies that of the animals with carcinomas (21/25), none had any papillomas. We recommend checking to be sure this is correct.

Page 93, "but the reverse is true for the kidney effects (neoplastic lesions only)." We recommend changing neoplastic to nonneoplastic.

Page 95, last paragraph, "For the animals whose exposure was extended to 52 weeks (therefore, a recovery period of 68 weeks)." However, Table 27 shows that the 52 week exposure period was followed by a 62 week recovery period. We recommend correcting.

Page 97, top paragraph. The data are consistent with the conclusions of the first sentence, but they do not prove them. No data were presented concerning DNA changes. We recommend modifying the paragraph accordingly.

Page 97, second paragraph. We recommend adding in what tissue alkaline phosphatase was measured.

Page 97, "However, DPR considered that the occurrence of hepatic hemangiomas in each of the SOPP-exposed male groups was treatment-related because of their rare spontaneous occurrence in this strain of mice. For example, Haseman et al. (1999) reported that in the NTP database of feeding studies, only 3 hemangiomas occurred among 1350 livers from untreated male B6C3F1 mice (0.2% incidence)." We recommend dropping the reference to the low historical control value since the concurrent control gave an incidence of 2%. Thus, it may be necessary to reconsider the argument that the hemangiomas in livers of dosed males were treatment-related.

Page 99, third paragraph. Should read SOPP rather than OPP.

Page 103, first paragraph. As mentioned above, recommend not using the word "synergistic" since the data in Table 31 do not allow this conclusion.

Bottom of page 141. No reproductive NOEL is given, while parental and pup NOELs are listed. We recommend including the reproductive NOEL or the specific reason(s) why not.

Page 143, last paragraph. We recommend checking whether the definition of fertility index is correct.

Page 144, second paragraph, "In each of these periods, the increased incidence of lactation day-21 weanlings with stunted growth occurred at 500 mg/kg/day (Table 42)." We recommend qualifying this statement by adding that these were the only statistically significant ($p<0.05$) increases in pup stunting (smaller increases occurred at 100 mg/kg/day).

Table 43. We recommend adding that the units are grams. Also recommend adding the litter incidences of resorptions and whether they were significantly elevated compared to control.

Table 46 and text. We recommend checking whether the dates in the study citations are correct.

Page 158, "Second, there is no reason to expect that if OPP and/or SOPP were developmental toxicants, they would induce a type of malformation that does not occur "spontaneously" in fetuses from control animals." We fully agree. By their argument, most if not all chemically-induced malformations would be disregarded since most if not all malformations induced by chemicals also occur spontaneously in untreated animals.

Page 160, "Reduced body-weight gain could be the basis for the maternal LOEL." We recommend stating the maternal LOEL.

Page 160, "In conclusion, this study documented that SOPP affected the fetuses and that the increased toxicity of fetuses occurred at the same or lower doses as those causing parental toxicity." We recommend showing the maternal body-weight gain data (if need be, read the data from the graph) and discussing whether the decreased maternal body-weight gain is of sufficient magnitude to cause malformations in mice, and cleft palate in particular.

Page 163. Specific gravity is not the same as osmolality. We recommend correcting.

Page 163, section IV.A.3. We recommend adding the citations when specific studies are discussed.

Pages 162-3. Polydipsia and dilution of urinary constituents are discussed as possible toxicological endpoints. These occurred at some quite low dose levels in the subchronic rat studies (54 mg/kg/day in Christenson et al., 1996a). We recommend checking to determine whether any of these changes occurred in the first week of the subchronic study. If so, they could be used to set the critical acute NOEL by the same reasoning used to select the maternal NOEL from the developmental rat study (Kaneda et al., 1978) as the NOEL for assessing acute risks to the general population.

Page 168, third paragraph. We recommend correcting the citation to read 1996b instead of 1996a.

Page 174, PDP section. For the fruit rinds, such as for oranges and lemons, we recommend that DPR clarify whether the residue samples came from only the edible part of the fruit or whether rind samples were included.

Page 174, PDP section, "For OPP- and SOPP-treated commodities, PDP reported only residue of OPP." Is it assumed that all SOPP was converted to OPP prior to sampling and analysis? We recommend discussing this and the data, if any, that show this to be true.

Page 174, PDP section. If the residue data have geographical locations associated with them, recommend reviewing them to determine whether California samples are significantly different from the average values. If the California values are significantly higher, recommend using the California-specific residue data together with the Western Region food consumption data, to calculate California-specific exposures.

Table 50. We recommend checking the "detected residues" range for nectarines to be sure the values are correct.

Page 180, "Based on the classification of related raw agricultural commodities into crop groups (as established in 40 CFR 180.40) and the agricultural practice specified in the product labels, suitable surrogate for tangerine, lime, lemon, kumquat, and citrus citron was orange (all belong to Citrus Fruit Group 10) and surrogate for plum was peach (both belong to Stone Fruit Group 12)." We recommend explaining how the surrogate data were used to do this. It is not obvious.

Page 180, discussion of adjustment factors. In Table 50, the acute point estimate residue values do not appear to be influenced at all by the adjustment factors. We recommend explaining this. Also recommend discussing how these factors affected the chronic residue values.

Page 178, discussion of Table 51. We recommend stating that the different percentile categories shown in Tables 51 and 53 are based on different RAC consumption estimates, not different residue concentrations.

Page 181, last paragraph. We recommend stating what assumption was made regarding the amount of each RAC consumed each day. In other words, for the exposures in Table 52, were the average daily consumptions of each RAC used?

Bottom of page 183 to top of page 185, discussion of Table 53, "Since the lowest MOEs were $\geq$ 10-fold greater than the acceptable MOE (i.e., 100)." This is not true, since 893 is less than 1000.

Page 185, third paragraph. Does this paragraph mean that KOPP is not used for post-harvest application to foods, has no established tolerances, or some other possibility? We recommend explaining.

Page 191, fifth paragraph, "Nevertheless, this analysis produced MOEs ranged from 10^3-10^4 at the 95th, 97.5th and 99th percentiles." The MOE was 893 for females 13-49 years (Table 53). We recommend correcting.

Page 192, last paragraph. Given that this RCD identified a developmental NOEL in a rabbit study that was lower than the maternal NOEL, we recommend presenting justification in this section for not including an additional FQPA safety factor in the calculations of risks to fetuses and children.

Table 56. We recommend adding the units for the Tolerance column.

Page 196, "Table 56 summarizes the ranges of the exposure and MOE values at the 95th percentile for each of the evaluated commodity at its tolerance level in the background of the chronic dietary exposure." We recommend stating in the text what the 95th percentile represents, and also adding this information to the table.

Page 198. Should read 10^{-6} rather than 10^6.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. Charles Vidair at (510) 622-2070 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

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