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DATE: March 1, 2007

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR ENDOSULFAN

Thank you for the opportunity to review the Draft Risk Characterization Document (RCD) for endosulfan, dated December 5, 2006. Endosulfan is an insecticide used to control a large number of different insects on a variety of different crops. The RCD quantifies exposures to endosulfan via the oral, dermal and inhalation routes, both for workers applying the chemical and for members of the general public. The exposures are then compared to toxicological screening levels determined in animal studies, to estimate the risk of health effects to exposed humans.

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

We appreciate the hard work that went into both the toxicology and exposure assessment parts of the document. Our comments and recommendations are presented below, divided into three major comments, followed by a longer list of minor comments. Please feel free to contact us if you have any questions.

Major Comments

1) OEHHA disagrees with the RCD's use of oral studies to evaluate inhalation exposures. In Tables 35-38, margins of exposure (MOEs) are calculated for persons exposed to endosulfan via the inhalation route. The inhalation MOEs are calculated using no-observed-effects-levels (NOELs) from studies in which the animals were exposed to endosulfan via the oral/dietary route. However, Table 11 shows that rats exposed subchronically to endosulfan were significantly more sensitive via the inhalation route compared to the dietary route: 10-fold more sensitive comparing the subchronic inhalation NOEL to the subchronic dietary NOEL, and 6-fold more sensitive comparing the subchronic inhalation NOEL to the week 24 parental NOEL determined in the two-generation dietary study. For both of these comparisons, the inhalation lowest-observed-effects-level (LOEL) was lower than the corresponding oral NOEL (Table 11), demonstrating that differences in dose selection were not responsible for the apparently greater sensitivity of the inhalation route. Therefore, OEHHA recommends using the subchronic inhalation study in the rat (Hollander et al., 1984) to evaluate subchronic/seasonal inhalation exposures to endosulfan. This study conformed to Federal Insecticide, Fungicide, and Rodenticide Act guidelines, and was designated "acceptable" by reviewers from both U.S. EPA and DPR.

Since an "acceptable" subchronic inhalation study is available, OEHHA recommends it be used to calculate all subchronic inhalation MOEs. The draft RCD calculates subchronic inhalation MOEs for members of the general public in Table 38 using this inhalation study. However, an oral study is used for calculating subchronic inhalation MOEs for workers (Tables 35, 36 and 37). Unless justification can be provided, OEHHA recommends that this apparent inconsistency be corrected by applying the same subchronic inhalation study by Hollander et al. (1984) to subchronic inhalation MOE calculations for both workers and members of the general public.

Since no acceptable acute or chronic inhalation studies are available, a decision is required as to what study should be used to calculate inhalation MOEs for those exposure periods. Looking at the oral NOELs from the rat studies presented in Tables 10-12 of the RCD, they were 2.0, 1.18 and 0.6 mg/kg-day for the developmental (acute), subchronic and chronic studies, respectively. This is a relatively narrow range for acute through chronic dosing in the same species via the oral route. A similar narrow range may exist for exposures via the inhalation

route. Therefore, OEHHA recommends using the subchronic inhalation NOEL, possibly with an adjustment factor, for calculating all (acute, subchronic/seasonal and chronic) inhalation MOEs.

2) OEHHA recommends using the most recent pesticide residue and food consumption data sets to estimate dietary exposures to endosulfan. Some raw agricultural commodities (RACs) measured in the more recent residue monitoring program (United States Department of Agriculture Pesticide Data Program, 1994 for broccoli only and 1997-2004 annual summaries) exhibited increased endosulfan residue concentrations (Table 24) compared to the older residue data used in the RCD's exposure assessment (DPR 1993-1995 market basket program). In addition, the per person consumption rates of some RACs treated with endosulfan were higher in the more recent Continuing Survey of Food Intake by Individuals (1994-98 CSFII) compared to the older food consumption data set used in the RCD's dietary exposure assessment (1989-92 CSFII). Thus, it is possible that some dietary exposures to endosulfan, calculated using the newer data sets, would be higher than the exposures calculated in the RCD. Therefore, OEHHA recommends doing the dietary exposure assessment with the two more recent data sets. Given some of the low acute dietary margins of exposure (MOEs) for some of the population subgroups shown in Table 40, this seems the prudent thing to do.

3) On pages 47-48 the RCD discusses endocrine effects of endosulfan in young rats. Two studies detected effects on male reproductive endpoints at low dose levels: decreased spermatid counts, decreased sperm counts and sperm abnormalities at 2.5 mg/kg-day in 3 week-old animals (Sinha et al., 1997), as well as decreased weight of testes, epididymis, ventral prostate and seminal vesicle at 1.0 mg/kg-day in 6 week-old animals (Chitra et al., 1999). The latter value of 1.0 mg/kg-day is lower than the LOELs of all critical studies selected for calculating oral MOEs (Tables 10-12). OEHHA recommends discussing the reasons these effects on male reproductive organs/function were not chosen as the critical effects for risk assessment.

Minor Comments

Page two, third paragraph. Recommend explaining what a "centrally acting agent" is.

Page four, second paragraph. "Of the 55 illnesses resulting from exposure to endosulfan in combination with other pesticides, 42 occurred as the result of exposure to residue, …" Recommend clarifying whether these were field residues, or some other type of residue.

Page four, last paragraph. If available, recommend stating the length of exposure rather than "prolonged."

Page nine, last paragraph. Where it is stated that, "no endosulfan residues have been detected in drinking water in California in the past three years for which data are available," recommend adding the approximate (or exact) number of samples upon which this statement is based.

Page 11, second paragraph. "In California, endosulfan has been monitored and detected in 34/39 or 23/39 samples by 8 hours after application for the alpha- and beta-isomers, respectively." Recommend adding where this air sampling was performed. For example, were these samples taken in the fields, or in towns miles away from the fields?

Page 12, last paragraph. Recommend explaining what is meant by endosulfan being bioconcentrated 5.2 times but having a bioconcentration factor of 37.5 (for example).

Page 16, third paragraph. It is not clear why the percent total absorption (47.3 percent) was calculated using the percent absorption at the two lowest dose levels, rather than just the percent absorption at the lowest dose level (the lowest dose level showed the greatest absorption at 24 hours). Since the value of 47.3 percent is used by the Worker Health and Safety Branch to calculate occupational exposures, we recommend this be explained.

For Table 3, recommend specifying whether the values are means.

On page 31 is a discussion of a rat subchronic dietary study. The text's characterization of the data in Table 3 contains a number of inaccuracies. Recommend correcting. In addition, there were decreases in red blood cells (RBCs) and hemoglobin at 1.92 mg/kg-day, and microscopic alterations to the kidneys at 0.64 and 1.92 mg/kg-day, which might be used to argue for a lower NOEL than that designated in the draft RCD for this study (1.92 mg/kg-day). Thus, the absence of these effects in the rat chronic dietary study (Table 5) is noteworthy. OEHHA recommends noting this in the discussion of the subchronic study.

Page 33, bottom paragraph. It is mentioned that the animals exhibited hyperexcitability, tremor, dyspnea and salivation at all dose levels. However, the mid-dose level was chosen as the NOEL in both cases (male and female). Recommend explaining why the clinical signs at the lowest dose level were not used to set the LOEL.

Page 35, second paragraph. The systemic NOEL was based on cholinesterase (ChE) activity. Thus, it is not clear why it is different from the ChE NOEL. Recommend clarifying.

Page 35, second and third paragraphs. In a dermal study reported by Ebert et al. (1985b) brain ChE activity of male Wistar rats was not significantly decreased at 12 and 48 mg/kg-day. However, significant reduction in brain ChE activity was reported in male Wistar rats in a similar

study at doses as low as 3 mg/kg-day (Ebert et al., 1985a). Recommend discussing the possible reason(s) for this discrepancy.

Page 36, first paragraph. It is stated that at 80 mg/kg/day, the females exhibited both a 28 percent decrease in serum ChE and a 24 percent decrease. Recommend correcting since both cannot be true.

Page 38, last paragraph. "There was a non-dose related increase in glomerulonephritis in males at $\geq$ 0.4 mg/kg/day." This dose level does not correspond to any of the male dose levels listed in the text at the top of the paragraph or listed in Table 5. Recommend correcting.

Table 5. The female dose level of 0.5 mg/kg/day does not correspond to any dose level discussed in the text. Recommend correcting.

Table 5. Glomerulonephrosis is mentioned under footnote [d], cited in the blood vessel section of the table. It is not clear why it is mentioned here rather than under a footnote linked to the kidney section of the table. Also, recommend showing in the table the incidences of glomerulonephrosis at the different dose levels.

Page 40, second paragraph. "The chronic NOEL was 0.84 (males) and 0.98 (females) mg/kg/day, based on increased mortality in the main group of females at 2.8 mg/kg/day." The publication in Food and Chemical Toxicology states that the male NOEL of 0.84 was based on decreased bodyweights in males at the next highest dose level. Recommend checking to be sure the RCD is correct.

Page 44, second paragraph. Recommend stating the values for the increased chromosomal aberrations and abnormal metaphases in spermatocytes from dosed animals.

Page 44, fourth paragraph. Recommend providing values for the increases in chromosomal aberrations reported in these two studies.

Page 44, last paragraph. "human lymphoid cells of the LAZ-007 cell line were incubated with 10-4, 10-5 and 10-6M endosulfan technical (0.41, 4.1, 41 ug/ml), respectively." The orders are reversed, recommend correcting.

Page 45, second and last paragraphs. Recommend providing values to indicate quantitatively the magnitudes of increases in these endpoints due to the test article.

Page 53, last paragraph. According to the data presented in Table 7, the maternal NOEL was 0.66 mg/kg/day (based on decreased corrected bodyweight change), not 2 mg/kg/day as stated in

the text and in Table 10. Recommend correcting. Also, the skeletal anomalies supporting the developmental NOEL of 2.0 mg/kg/day occurred at > 2 mg/kg/day, not $\geq$ 2 mg/kg/day as stated in the text. Recommend correcting.

Page 66, Table 10. The inhalation LOEL should be corrected to read 0.567 rather than 0.0036.

Page 66, second paragraph. Here the decision is made to use the NOEL from the developmental study in rabbits (0.7 mg/kg/day) to "calculate margins of exposure for potential acute single-day human exposures to endosulfan." OEHHA agrees that this NOEL should be used for oral exposures in the human, but disagrees with using it for short-term inhalation exposures, since the inhalation route is much more sensitive than the oral route (see Table 11). Rather, OEHHA recommends using the subchronic inhalation study in the rat (NOEL = 0.194 mg/kg/day) for short-term human exposures via inhalation.

Page 67, fourth paragraph. "There were no FIFRA Guideline acceptable studies for subchronic dermal exposure." Recommend correcting, since two such studies are available (discussed on pages 35-36 of the RCD). Since most worker exposure is via the dermal route, this also raises the issue of why Seasonal Average Daily Dosage (SADD) MOEs (Tables 35-37) were calculated using a subchronic oral NOEL, rather than a NOEL from one of these subchronic dermal studies. Recommend providing justification for using a NOEL from an oral study to calculate the dermal MOEs.

Table 12. The table and text on page 68 indicate that the dogs were dosed via capsule, but the text on page 41 and the "Summary of Toxicology Data" in the Appendix indicate that the test article was fed in the diet. Recommend correcting.

Page 69, top paragraph. Here the choice is made to use the chronic dog feeding study NOEL of 0.57 mg/kg/day in calculating the non-occupational, chronic inhalation risk. However, the inhalation route is clearly more sensitive than the oral route, as illustrated by the 6- to 10-fold lower subchronic NOEL for rats dosed via inhalation compared to via the diet (Table 11). Thus, as discussed above, OEHHA recommends using the subchronic rat inhalation study to estimate chronic inhalation risks to bystanders (including "ambient") and workers.

Page 75, third paragraph. Recommend adding PPE to the Abbreviations list.

Table 18. Recommend adding footnote [g].

Table 19. Recommend adding footnote [f].

Page 82, second paragraph. Recommend adding REI and PHI to the abbreviations list.

Page 87, second paragraph. The U.S. EPA draft 2002 Reregistration Eligibility Decision (RED) for endosulfan calculated acceptable MOEs for acute and chronic dietary exposures. Since the draft RCD used a similar methodology for dietary exposure assessment, this is cited as justification for not performing a dietary exposure assessment using more recent pesticide residue and food consumption databases. However, the U.S. EPA selected a higher critical acute NOEL (1.5 mg/kg-day, Table 42). Were the U.S. EPA to use the lower acute NOEL selected in the draft RCD (0.7 mg/kg-day), some MOEs might be unacceptable. In addition, the U.S. EPA draft 2002 RED for endosulfan used the 1989-92 CSFII food consumption database, not the most recent 1994-98 CSFII database. Therefore, OEHHA recommends not citing the U.S. EPA draft 2002 RED for endosulfan as support for the sufficiency of the RCD's dietary exposure assessment.

Page 87, second paragraph. Should read Appendix C rather than Appendix D.

Page 87, third paragraph. It is stated that endosulfan use data from 1998 were the most recent. However, at the end of the paragraph it is stated that endosulfan use remained stable from 1992-2001. Recommend harmonizing these apparently contradictory statements.

Table 23. Recommend explaining what "ac=high#" means. Also recommend explaining what is meant by footnote [e].

Page 90, third paragraph. Recommend explaining what is meant by a "non-systemic pesticide."

Page 91, top paragraph. Should read Table 23 instead of Table 24.

Table 24 compares maximum endosulfan residue values in the older DPR monitoring program to those collected by the more recent Pesticide Data Program (PDP) monitoring program. Since average pesticide residue values are used by DPR for chronic dietary exposure assessments, recommend that a similar comparison also be made in Table 24 for the average endosulfan residue values. Also recommend adding apple, potato and tomato since these are the crops treated with the highest levels of endosulfan. (page 101).

Page 94. The last paragraph is repeated.

Page 101, first paragraph. "The differences between the 2 surveys' consumption rates ranged from a 63% decrease in tomato consumption by nursing infants from the 1989-92 group levels to a 71% increase in potato consumption by non-nursing infants relative to the 1989-92 rates." On the following page the increase is given as 77 percent. Recommend correcting.

Page 102, paragraph 5. "The percent user day rate is the ratio of actual consumers divided by per capita consumption for each community." This definition is unclear. Recommend using the

definition given in Table 25 in footnote [1]. However, that footnote should be corrected to read A Percent User Day Rate.

Pages 101 and 102, apple, pear, potato, tomato. Recommend showing the data for mean consumption rates in a table. Also recommend adding the 95th percentile consumption rates. Also recommend stating which values are based on users only and which values are based on all members of each population subgroup (users + nonusers).

Page 103, top paragraph. "The Exposure-1™ program estimates the annualized average exposure for all members of a designated population subgroup (TAS, 1996b)." Recommend discussing why the chronic dietary analysis is based on the entire population of each subgroup while the acute analysis is based only on the users in each population subgroup.

Page 104, last sentence in paragraph two. Table 27 should be corrected to read Table 26.

Table 26. Recommend adding the proper units to the table: µg/kg/day.

Table 27. In footnote [c] the term "24-hour TWA" is used while in the table under "Air concentration" the term "Short-term" is used. In footnote [d] the term "3-day TWA" is used while in the table under "Air concentration" the term "Long-term" is used. Recommend being consistent in the use of the terminology in order to make this table more easily understood.

Page 106, second paragraph. States that the data in Table 28 were for the period 1990 to 2000. However, Table 28 states that sampling was through July 1996. Recommend correcting.

Page 110, first paragraph. 40/89 does not equal 55%. Also, it is not obvious to this reviewer where the values 51%, 41%, 22% and 60%, 30%, 80% come from. Recommend discussing.

Table 39. Recommend using the rat two generation dietary study (with a NOEL of 1.18 mg/kg/day) rather than the subchronic rat inhalation study (NOEL = 0.194 mg/kg/day) for calculating the non-dietary MOEs in this table. This is because the non-dietary exposures are via the oral route, not the inhalation route.

Page 118, second paragraph. This paragraph discusses subchronic dietary MOEs but no subchronic MOEs are in Table 40. Recommend adding the subchronic MOEs to the table.

Page 118, last paragraph. "There were no percent crop treated (%CT) adjustments used in these calculations." Footnote [d] in Table 40 contradicts this statement. Recommend correcting.

Page 119. Regarding the formula for calculating combined margins of exposure, recommend presenting the rationale for combining exposure dosages from the oral and inhalation routes given the lower NOEL associated with the inhalation route. Lacking a rationale for doing this, OEHHA recommends calculating separate MOEs for the two routes, and then combining the results as performed in the DPR document "Methyl Bromide RCD Volume III Aggregate Exposure" dated October 24, 2002.

Table 40. The acute child MOE of 212 and the acute infant MOE of 220 are relatively close to 100. This suggests that re-analysis using the more recent pesticide residue data and food consumption data is warranted. Same comment for Bystander Infants with a combined MOE of 158 in Table 38.

Page 122, second paragraph. As discussed above, OEHHA recommends using the rat subchronic inhalation study for inhalation exposures, including acute. Given that the rat subchronic inhalation LOEL was 10-fold lower than the rat subchronic oral LOEL (0.3873 versus 3.85), we believe the use of an acute oral NOEL for acute inhalation exposures would underestimate the risk. The more health-protective approach is to use the subchronic inhalation NOEL.

Page 141, last paragraph. It is not clear from this paragraph whether the dietary risk discussed here is based on a dietary assessment as shown in Table 40, or a tolerance assessment as shown in Table 43. Recommend clarifying.

Page 148, second paragraph. "The resulting equivalent acute human inhalation NOEL was 0.7 mg/kg assuming a default respiratory rate of 0.59 m^3/kg/day for children." Should be corrected to read 1.2 mg/kg rather than 0.7 mg/kg.

Pages 148-149. As stated above, OEHHA recommends using the subchronic rat inhalation study result for calculating all inhalation MOEs, including acute, subchronic and chronic.

Page 148, second paragraph. Should be corrected to read rabbit developmental study rather than rabbit reproduction study.

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 draft RCD, please contact Dr. Charles Vidair at 510-622-2070 (primary reviewer), Dr. David Ting at 510-622-3226, or me at 510-622-3165.

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