Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Linda S. Adams
Secretary of Environmental Protection

Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

Sue Edmiston, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, California 94612

DATE: May 10, 2010

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT CHLOROTHALONIL.

Attached please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) comments for the active ingredient chlorothalonil. The comments were prepared in response to the Department of Pesticide Regulation's (DPR) draft document: "Chlorothalonil, Risk Characterization Document, Volume I and Volume II" dated September, 2008.

OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, 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.

Thank you for providing the draft risk characterization document (RCD) for our review. Comments are provided in two attachments. Attachment 1 addresses the draft RCD, Volume I, Health Risk Assessment. Attachment 2 addresses the draft RCD, Volume II, Exposure Assessment. If you have any questions regarding OEHHA's comments, please contact Dr. David Ting or Dr. Anna Fan at (510) 622-3160.

Attachment

cc: Allan Hirsch
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment

David Ting, Ph.D., Chief
Pesticide and Food Toxicology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Charles Salocks, Ph.D., Chief
Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Martha Sandy, Ph.D., Chief
Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment

John Faust, Ph.D.
Staff Toxicologist
Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment

Elaine Khan, Ph.D.
Staff Toxicologist
Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

ATTACHMENT 1

BACKGROUND INFORMATION

The draft Risk Characterization Document (RCD) assessed the occupational, residential/bystander, and aggregate exposures to chlorothalonil under the mandate of the Birth Defect Prevention Act (SB 950) and included a consideration for potential listing under the Toxic Air Contaminant Act (AB 1807). The risk assessment for dietary exposure of chlorothalonil, conducted under the mandate of AB 2161 (also known as the Food Safety Act), was finalized in 2006.

According to the draft RCD, the routes of exposure were dermal and inhalation for workers, and inhalation for residents and bystanders. The critical toxicity endpoints were derived from laboratory animals: skin irritation, respiratory tract irritation, clinical signs (e.g., soft stools, decreased motor activity, discharges from the eyes, nose, and urogenital area), and kidney effects, including tumors. The draft RCD concluded that estimated risks were considered unacceptable for a number of receptors. For handlers, the dermal and inhalation Margins of Exposure (MOEs), and lifetime cancer risks for many work tasks were unacceptable. The main concern for field workers was dermal exposure and lifetime exposure. The aggregate exposure, limited to combined dietary and dermal exposures, was also of concern because of the high dermal exposure levels for workers. There was insufficient data in the inhalation toxicology database to include inhalation route in the aggregate exposure assessment. For bystanders and residents, the exposures from the ambient air was acceptable, but not from the air near treated fields. The cancer risk from the latter scenario met the criteria for listing under AB 1807 as a toxic air contaminant.

On three separate occasions, the Office of Environmental Health Hazard Assessment (OEHHA) reviewed and commented on risk assessments of chlorothalonil prepared by the Department of Pesticide Regulation (DPR). These comments incorporate our health-based recommendations regarding chlorothalonil. The three OEHHA memoranda are listed below:

- "Comments on the Department of Pesticide Regulation's draft risk characterization document for the active ingredient chlorothalonil," dated June 10, 1999.
- "Comments on the draft dietary risk characterization document for the active ingredient chlorothalonil prepared by the Department of Pesticide Regulation," dated December 2, 2004.

- "Final dietary risk characterization document for chlorothalonil," dated April 23, 2007.

As part of our review of the draft RCD, we also revisited other DPR chlorothalonil risk assessments for background and context. Our comments, however, focus primarily on issues identified in the draft RCD dated September, 2008.

In Attachment 1, OEHHA provides major and minor comments on the draft RCD, Volume I, Health Risk Assessment, of the active ingredient, Chlorothalonil. In Attachment 2, OEHHA addresses issues identified in the draft RCD, Volume II, Exposure Assessment.

Major comments on the draft RCD, Volume I

OEHHA comments are separated into two groups: those addressing the non-cancer health effects and those addressing cancer health effects.

(A) Comments on the evaluation of non-cancer health effects

1. Not all of the studies cited for critical No Observed Effect Levels (NOELs), as presented in Summary Table 1 (page x), can be considered as "acceptable according to FIFRA study guidelines." For instance, the study cited for the critical NOEL for short-term local effect of dermal exposure (Shults et al., 1986) is a range-finding study in which 2 animals/sex/group were exposed. The study cited for systemic effects of dermal exposure (Mizens, 1996) is considered by DPR to be an acceptable ancillary study. DPR should provide reasoning or justification for using these studies in selecting critical NOELs.

2. On page 107, under the heading of "IV.A.2.e. Subchronic Inhalation Toxicity," DPR states, "For systemic effects, route-to-route extrapolation was used and the critical oral NOEL was 1.5 mg/kg/day (absorbed dose of 0.51 mg/kg/day) for kidney effects (inclusion bodies, increased labeling indices, and increased organ weight) in rats (Wilson *et al.*, 1983a, and Hironaka, 1996)." OEHHA suggests that DPR describe the uncertainty involved in this route-to-route extrapolation, considering the following factors:

    - Chlorothalonil exists in particulate or aerosol forms in the air.

- There is no data showing kidney is the target organ through the inhalation route.
- According to acute inhalation studies, the target organ is the lung.

3. On page 108, under the heading of "IV.A.2.h. Chronic Inhalation Toxicity," DPR states, "Critical chronic NOEL for inhalation exposure for local effect was not established for the same reason as for subchronic exposure (see IV.A.2.e. Subchronic Inhalation Toxicity). The critical chronic NOEL for systemic effect was 1.8 mg/kg/day (absorbed dose of 0.61 mg/kg/day) for kidney lesions in rats after dietary exposure (Wilson and Killeen, 1989)." OEHHA suggests that DPR describe the uncertainty involved in this route-to-route extrapolation, for the same reasons listed in comment #2 above.

4. On page 128, DPR states, "For local irritation effect from either dermal or inhalation exposure, the DPR benchmark MOE is 10 to account for intra-individual differences." And "For irritation effects from inhalation exposure, species difference in the uptake was accounted for by breathing rate adjustment to the NOEL." OEHHA has concerns with the way health effects of acute inhalation were evaluated and characterized. The lowest nose-only acute inhalation Lowest Observed Adverse Effect Level (LOAEL) identified in animals was 7 µg/L (see page x, page 35, and c1 in Appendix C). It was based on abnormal respiratory noise and signs of respiratory tract irritation observed in rats exposed for 4-hr (Rattray, 2002). However, a similar nose-only acute inhalation exposure study reported by Warren and Halliburton (1996) indicated that the lethal concentrations (LC_{50}s) for male and female rats were 31µg/L and 67µg/L, respectively. Furthermore, a whole-body acute (4 hr) inhalation study using chlorothalonil powder showed that the LC_{50}s for rats were 32 µg/L and 13 µg/L for males and females, respectively (Holbert, 1993). In other similar studies described on pages 28-32 (Lundberg et al., 1980; Moore, 2000; Wnorowski, 1999), death was observed in rats at doses as low as 40 µg/L or 56 µg/L. Lung appears to be the target organ in these studies. Given the critical LOAEL of 7 µg/L is less than 10-fold lower than some of the reported lethal concentrations, OEHHA recommends a MOE of at least 100.

   Additionally, the summary of the study by Rattray (2002, discussed on page 35 of the RCD) indicates, "Abnormal respiratory noise was noted on the first day after exposure for 4/5 males and 2/5 females. This was considered as a sign of respiratory tract irritation..." Given the size of the respirable particles (mass median aerodynamic diameter, or MMAD, 2.33 µm), deep lung deposition of these particles is possible. OEHHA believes that the observed abnormal respiratory noise may be a much more serious sign of inflammation and edema in the lung as

opposed to the seemingly milder assessment of respiratory tract irritation. This further supports a MOE of at least 100 for acute inhalation exposure.

5. On page 128, DPR states, "For local irritation effect from either dermal or inhalation exposure, the DPR benchmark Margin of Exposure (MOE) is 10 to account for intra-individual differences. The 10-fold interspecies extrapolation factor was not needed for dermal irritation since the rabbit is the most sensitive species, with human generally less or equal in sensitivity than laboratory animal species." DPR should provide scientific data to support this determination.

6. On page 137, DPR states, "In the absence of sufficient data to evaluate skin sensitization, the evaluation of skin irritation only might not protect against this concern if a lower dose could elicit a sensitization response." OEHHA agrees that skin sensitization is a concern and recommends that DPR include an additional uncertainty factor for the dermal exposure MOE, for both local and systemic effects:

- The acute toxicity database reviewed and presented by DPR in Table 3 showed that chlorothalonil caused skin sensitization in guinea pigs.
- Allergic contact dermatitis has been reported in humans exposed to chlorothalonil-containing products (page 94 of RCD).
- Dannaker, et al. (1993) reported that a 49-year-old woman experienced contact urticaria and anaphylaxis after exposure to pesticides used in a redwood plant nursery. It was later confirmed that her symptoms were caused by chlorothalonil exposure when she had a large wheal and flare reaction to Daconil 2787 (75 percent chlorothalonil) in a 0.01 percent aqueous solution. This was followed by facial flushing, eyelid edema, and difficulty in swallowing and breathing within 10 minutes of exposure. According to Bashir and Maibach (2009), immunologic contact urticaria is a Type 1 hypersensitivity reaction mediated by IgE antibodies specific to the eliciting agent, which indicates prior immune sensitization is required for this type of reaction. Sensitization can be at the cutaneous level, but it may also be via the mucous membranes, such as the respiratory or gastrointestinal tract. In more severe cases, contact immunologic urticaria may lead to anaphylactic shock (Bashir and Maibach, 2009).

7. OEHHA recommends that an additional uncertainty factor of at least 3 should be applied to the MOE for local irritation to account for the lack of sufficient data to evaluate skin sensitization and in an effort to prevent hypersensitization from occurring. Anaphylaxis due to immunologic contact urticaria may be considered systemic in nature. Therefore, OEHHA believes an additional uncertainty factor

of 3 should be applied to the MOE for systemic effect as well, in order to protect those workers who may already be sensitized to chlorothalonil. On page 9, section II.G.6 Plant Residues/Metabolism, the second paragraph states, "Samples with zero residues were assigned a value of 0.05 ppm, which was the lowest detected level. There were seven field trials with soybean; the highest residue was 0.08 ppm, and the mean residue level was 0.037 ppm." There seems to be a mistake. A discussion is needed to explain why the mean residue level is lower than the lowest detected level when the non-detects are not assumed to be zero.

8. On page 38, section III.B.5 Dermal – Rabbit, the last sentence of the last paragraph states, "DPR considered the study unacceptable according to FIFRA study guidelines because inadequate number of animals (3 instead of 5) was tested." However, the first three studies described in this section (Kuhn, 1992a; Shults et al, 1991; and Johnson, 2000) were considered acceptable according to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) study guidelines despite also using 3 animals instead of 5. DPR should explain the apparent inconsistency in rating these toxicity studies. In addition the study reported by Kuhn (1992a) was considered acceptable according to the FIFRA guidelines though the purity of chlorothalonil was not stated and the true treatment concentration of chlorothalonil was not known. DPR should explain why this study was considered acceptable despite the deficiencies.

9. On page 54, DPR should specify that chlorothalonil technical was used in this study and state percent purity. The animals in this study were fed chlorothalonil in the diet for a maximum of 28 days and DPR cited this study in its determination of the critical NOEL for systemic effect from subchronic oral exposure.

10. The last paragraph on page 57 states, "For subchronic systemic effects, the NOEL was 60 mg/kg/day for increased incidence of clinical signs and relative kidney weights at 100 mg/kg/day." However, Table 17 on page 58 shows statistically significant increases in both kidney/body weight ratio (9 percent) and kidney/brain weight ratio (8 percent) at 60 mg/kg/day. DPR should provide the rationale for selecting 60 mg/kg/day as the NOEL since statistically significant treatment-related effects were seen at this dose.

11. On page 86, "The developmental NOEL was 1500 ppm (67.5-178.3 mg/kg/day) based on the reduction of pup weights...USEPA established the developmental NOEL at 1500 ppm (115 mg/kg/day) for lowered neonatal body weight by day 21 at 3000 ppm (234 mg/kg/day)." However, the F1b pups (Table 29 on page 88)

showed a statistically significant 8 percent decrease in body weight at 1500 ppm and the F2b pups had a statistically significant 8 percent decrease in body weight at 500 ppm compared to control. According to DPR's Guidance for Benchmark Dose (BMD) Approach – Continuous Data (DPR, 2004), "A 5% BMR also appears reasonable for endpoints such as body weight changes, since a 10% reduction is considered a marker of toxicity, an indication that the Maximum Tolerated Dose (MTD) has been reached." DPR needs to provide justification why 1500 ppm is identified as the NOEL when it appears that the Lowest Observed Effect Level (LOEL) could reasonably be 500 ppm based on the F2b data.

12. In its risk assessment, DPR uses default breathing rates according to the joint policy memorandum issued by the Worker Health and Safety and Medical Toxicology branches (Andrews and Patterson, 2000). OEHHA disagrees with the use of these default values for the following reasons:

- According to the policy memorandum (*Interim Guidance for Selecting Default Inhalation Rates for Children and Adults*; Andrews and Patterson, 2000), "These rates are interim values until more detailed analyses are conducted to determine the appropriate rates for different age groups, gender, and duration of exposure (*i.e.*, acute and chronic exposures)...This Guidance Document is subject to revisions for the incorporation of new data and approaches." The values listed in Andrews and Patterson (2000) were based on the method of Layton (Layton, 1993), which utilized food-energy intake values from the 1977-1978 Nationwide Food Consumption Survey (NFCS). OEHHA believes that there are sufficient new data and improvements in methodologies for estimating inhalation rates that warrant a revision of the policy memorandum. See below.
- OEHHA urges DPR to adopt the recommended inhalation rates in the Child-Specific Exposure Factors Handbook (U.S. EPA, 2008) because they are based on four studies published in 2006 and 2007, representing more current exposure conditions and improvements upon the approach used by Layton (1993). OEHHA believes that the inhalation rates in the 2008 Handbook are the most health-protective for young children. For example, the recommended long-term exposure inhalation rate for a child aged 1 to <2 years provided in Table 6-1 of the Child-Specific Exposure Factors Handbook is 8.0 m^3/day (mean) whereas the value provided by Andrews and Patterson (2000) for a child 1-2 years of age is 6.8 m^3/day. When calculating the absorbed daily dose, the difference of 0.05 m^3/hr (50 L/hr) could significantly impact the exposure for young children, whose rapidly developing systems may be more susceptible to the effects of toxic air contaminants.

- Layton (1993) used outdated food-energy intake values. For example, in the 1977-1978 National Food Consumption Survey (NFCS), fat comprised 41 percent of the average daily caloric intake and carbohydrates 42 percent (Layton, 1993); in the 1994-1995 Continuing Survey of Food Intake by Individuals (CSFII), fat fell to 32 percent for women, 34 percent for men, and carbohydrates rose to 52 percent for women, 49 percent for men (Enns, 1997). Another limitation of Layton's approach for calculating inhalation rates is its dependence on a ventilatory equivalent. The ventilatory equivalent value of 27 applied by Layton, which relies on an individual's fitness and energy expenditure levels, may be appropriate for adults but not necessarily for children (U.S. EPA, 2009). The four studies cited in the Child-Specific Exposure Factors Handbook (U.S. EPA, 2008) employ three different methodologies for estimating inhalation rates (i.e., doubly labeled water, food-energy consumption, and metabolic derivation), which have different strengths and limitations, yet they complement each other in providing useful information for this purpose (U.S. EPA, 2009).

13. On page 37, the rat dermal study by Longobardi (2001b) indicated "There was body weight gain for all animals." It did not specify whether the weight gain was normal or a result of treatment. Was there any explanation for body weight gain after only 24 hours of dermal exposure? Furthermore, the rats were exposed to liquid Nuocide 2010, which consists of 19.31 percent chlorothalonil and 9.52 percent 3-iodo-2-propylnyl butylcarbamate. Did the study rule out effects from the 3-iodo-2-propylnyl butylcarbamate? OEHHA has the same questions regarding the second rat dermal study described on page 37 (Longobardi, 2001g).

14. On page 40, the rabbit dermal study (Kuhn, 1992b) is considered acceptable according to FIFRA study guidelines. However, the reporting of the study is limited as the purity of chlorothalonil was not stated and it is not possible to accurately estimate the exposure concentrations.

15. On page 42, Table 9, why were the data provided only for the first four days of exposure in a 21-day study?

(B) Comments on the evaluation of cancer health effects

1. OEHHA agrees with DPR's determination that chlorothalonil is a carcinogen. The chemical increased the incidence of kidney and forestomach tumors in rats of both

sexes and in male mice after more than one year of exposure in the diet (Wilson et al., 1985; Wilson and Killeen, 1989; Wilson et al., 1983). It is listed as a carcinogen under Proposition 65. Chlorothalonil is also identified as "likely" to be a human carcinogen by the U.S. EPA (1999) and as a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer (IARC, 1999).

2. There have been suggestions of cell proliferation as the mechanism for the kidney tumors observed in the exposed animals. After consideration of the database as well as the conclusions of the Scientific Advisory Panel and U.S. EPA, DPR determined that available data were insufficient to support a threshold mechanism. As a result, a linearized multi-stage model was used to calculate the cancer potency of chlorothalonil. OEHHA supports this decision in characterizing the dose-response relationship of the chemical.

3. DPR used the combined kidney tumor data in male rats from two dietary cancer studies (Wilson et al., 1985; Wilson and Killeen, 1989) to calculate the cancer potency of chlorothalonil. DPR estimated that the 95% upper confidence limit (q_1^*) on the cancer potency in the male rat is 0.0029 $(mg/kg\text{-}day)^{-1}$. Assuming an interspecies dose equivalence factor based on the body weight to the ¾ power, a male rat body weight of 0.35 kg, and an oral absorption factor of 0.34, DPR calculated a cancer potency of 0.031 $(mg/kg\text{-}day)^{-1}$ for humans. DPR did not use the forestomach tumor data in calculating cancer potency, citing concerns about the human relevance of forestomach tumors. DPR characterized the rat forestomach as a holding compartment, and noted there is no similar anatomical part in humans. OEHHA considers the induction of forestomach tumors by dietary administration of chlorothalonil in the rat to be relevant to human cancer risk, and disagrees with DPR's decision to not include the forestomach tumor data in the cancer potency calculation. In 1999 the IARC reviewed the issue of rodent forestomach tumors, and determined that these tumors should be considered in human health risk assessment:

> "While humans do not have a forestomach, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. Thus, in principle, carcinogens targeting the forestomach squamous epithelium in rodents are relevant for humans. Also, the target tissues for carcinogens may differ between experimental animals and humans and a forestomach carcinogen in rodents may target a different tissue in humans. Furthemore, tumorigenic effects in the forestomach are usually accompanied by similar effects in other tissues, indicating that there may be either general or multiple modes of action." (International Agency for Research on Cancer, 2003. *Predictive Value of*

Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risk to Humans [Views and Expert Opinions of an IARC Working Group, Lyon, 29 November -1 December 1999]. Technical Publication No. 39).

OEHHA estimated the animal cancer potency for chlorothalonil using the kidney and forestomach tumor data from the cancer studies conducted in male and female rats reported by Wilson et al. (1985). Because chlorothalonil induced tumors at multiple sites in male and female rats, a combined 'multisite' potency distribution was estimated from the site-specific potency distributions for each experiment. This was done using a Monte Carlo procedure to statistically sum across the site-specific potency distributions. The tumors at different sites are assumed to be independent. The result of this procedure is an estimate of cancer potency for the total treatment-related cancer burden observed in each study. The upper 95% confidence bound on the summed distribution is taken as the multisite animal cancer potency estimate. The upper 95 percent confidence bound for individual tumor sites as well as the multisite cancer potencies for male and female rats are shown in Table 1. Based on both the individual site and the multisite potency estimates, female rats appear to be more sensitive to the carcinogenic effects of chlorothalonil. For this reason, OEHHA recommends the multisite potency estimate of 0.0036 $(mg/kg\text{-}day)^{-1}$ for female rats be selected to estimate the human cancer potency.

Table 1. Estimated cancer potencies, based on kidney and forestomach tumor data in male and female rats. Based on data reported by Wilson et al. (1985).

	Animal Cancer Potency $[(mg/kg\text{-}day)^{-1}]$	
Tumor site	**Male Rats**	**Female Rats**
Kidney	0.0027	0.0031
Forestomach	0.00055	0.00091
Multisite	0.0031	**0.0036**

5. On page xv, 4th paragraph, DPR states, "The MOEs for short-term or acute exposure of golfers to chlorothalonil treated courses were greater than the MOE

benchmarks, with the oncogenic risks of 1.7×10^{-5} and 2.2×10^{-5}, close to the negligible risk level of 1×10^{-5}." It would be helpful if DPR can provide an explanation why 1×10^{-5} is being considered a negligible risk level in this situation.

Minor Comments on the draft RCD, Volume I

1. In Summary Table 1 (page x), under "Inhalation exposure, Systemic effect: All durations," DPR indicates "use NOELs for oral exposure" for both "NOEL or ENEL (estimated no-effect level)" and "Human eq. NOEL." This is misleading. OEHHA suggests restricting the phrase to "Human eq. NOEL."

2. Page x, Summary Table 1: the 8* and 9* in the "Ref." column are not defined.

3. Page 3, second paragraph, last sentence: *processing* should be process.

4. Page 6, third paragraph, last sentence: *resulting* should be thereby.
   Page 6, last paragraph, line 5: *residues at inlet* should be residues at the inlet; line 7: *most of airborne* should be most airborne.

5. Page 7, line 6: *only few* should be only a few.

6. Page 8, line 1: *2-6 folds* should be 2-6 fold.

7. Page 9, third paragraph of section II.G.6, line 4: *interval ranged* should be interval ranging.

8. Page 64, Table 20: the asterisk is not defined and footnote b is defined but is not indicated in the table.

9. Page 69, line 2 of new paragraph: *slides was* should be slides were.

10. On page 74, "The NOEL was <750 ppm (<127 mg/kg/day) for kidney and stomach lesions...USEPA established the NOEL at <750 ppm (113 mg/kg/day)..." Please explain the differences in the conversion from ppm to mg/kg/day, given that the "calculated average doses for both sexes were: 0, 127, 265, 551 mg/kg/day."

11. Page 87, Table 29: asterisks are not defined.

12. Page 89, second paragraph, line 1: *previous study 3-generation study* should be previous 3-generation study.

13. Page 92, first paragraph, line 3: *20 mg/kg/day was reduced* should be 20 mg/kg/day group was reduced; line 16: *at the Bio/dynamics* should be at Bio/dynamics.

14. Page 93, second paragraph, line 5: *percentage cells* should be percentage of cells.

15. On page 94, the last paragraph needs some re-phrasing. The study being described was published in 1992, but the wording in the description (e.g., "his first asthma attack was 10 years ago...second attack was 2 years ago...further episodes last year") implies that the episodes occurred relative to the present time.

16. Page 94, third paragraph, line 3: *chlorothalonil containing wood-preservatives* should be chlorothalonil-containing wood preservatives.

17. Page 95, second paragraph, line 1: *(2006)* should be (2003); last paragraph, line 2: *itchy and scaling* should be itching and scaling; line 7: *allergic origin* should be allergic in origin.

18. Page 96, first paragraph, lines 3-4: *oral LD50* should be oral LD50 values and *was* should be were.

19. Page 98, Table 31: footnote "a" is not defined.

20. Page 102, first paragraph, line 6: *ethnical* should be ethical; fourth paragraph, line 8: *Such retention* should be Such a retention.

21. Page 103, line 1: *details* should be detail.

22. Page 105, second paragraph, line 3: *mean* should be means; last sentence of third paragraph doesn't make sense: "However, this NOEL was not used in this risk assessment because human inhalation exposure, likely only mixers of powder formulation, to solid aerosols was not determined."

23. Page 106, first paragraph of section IV.A.2.c., line 2: *before applied* should be before being applied.

24. Page 108, last paragraph, line 6: *Prolong cell* proliferation should be Prolonged cell proliferation.

25. Page 109: *Step 1. Chlorothalonil is convert* should be Step 1. Chlorothalonil is converted.

26. Page 110, line 5: *alkene* should be alkenes; line 9: Step 5. *Thiols induces cytotoxicity, cell* should be Step 5. Thiols induce cytotoxicity and cell.; line 19: *forestomach in form* should be forestomach in the form.

27. Page 111, line 2: *the an oncogenic* should be the oncogenic.

28. Page 116, first paragraph, line 3: *use of oral* should be use of the oral.

29. Page 118, first paragraph, line 13: *40 year* should be 40 years; numbered points 4 and 6: *emulsifible* should be emulsifiable.

30. Page 119, numbered point 2: add period at the end of the sentence.

31. Page 121, table legend: *Emulsifible* should be Emulsifiable.

32. Page 126, first paragraph, line 5: *in effort* should be in an effort.

33. Page 129, second paragraph, line 4: *emulsifible* should be emulsifiable; last paragraph, line 5: *mean* should be means (used twice in sentence).

34. Page 139, last sentence of V.C.2: *large* should be larger; last sentence of first paragraph of V.C.3 should be rephrased.

35. Page 140, line 4: *Particular* should be Particulate; last paragraph, line 2: *sensitivity young animals* should be sensitivity in young animals.

References

Andrews, C and Patterson, G (2000). Interim guidance for selecting default inhalation rates for children and adults. Memorandum from Chuck Andrews and Gary Patterson to Worker Health and Safety Branch staff and Medical Toxicology Branch staff, December 1, 2000. Worker Health and Safety Branch and Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Bashir, S and Maibach, HI (2009). Urticaria, Contact Syndrome. eMedicine online article accessed at: http://emedicine.medscape.com/article/1050166-overview on 10/7/2009.

Dannaker, CJ, Maibach, HI, and O'Malley, M (1993). Contact urticaria and anaphylaxis to the fungicide chlorothalonil. Cutis 52: 312-315.

DPR (2004). Guidance for Benchmark Dose (BMD) Approach – Continuous Data. DPR MT-2. Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Enns, CW, Goldman, JD, and Cook, A (1997). Trends in food and nutrient intakes by adults: NFCS 1977-1978, CSFII 1989-1991, and CSFII 1994-1995. Family Economics and Nutrition Review, 10: 2-15.

Holbert, MS (1993). Acute inhalation toxicity study in rats. Stillmeadow, Inc., Laboratory Study number 9686-92. Sostram Corporation. DPR Vol. 275-190 #132847.

IARC (1999). International Agency for Research on Cancer (IARC) – Summaries and Evaluations. Chlorothalonil. Vol. 73, pp. 183-193. Web address: http://www.inchem.org/documents/iarc/vol73/73-06.html

Johnson, IR (2000). Chlorothalonil technical: Skin irritation study in rabbits. Central Toxicology Laboratory Report ID CTL/EB4891. GB Biosciences Corporation. DPR Vol. 275-391 #186265.

Kuhn, JO (1992a). Primary dermal irritation study in rabbits. Stillmeadow, Inc., Laboratory study number 9377-92. Sostram Corporation. DPR Vol. 275-190 #132849.

Kuhn, JO (1992b). Acute dermal toxicity study in rabbits. Laboratory study number 9375-92. Sostram Corporation. DPR Vol. 275-190 #149456.

Layton, DW (1993). Metabolically consistent breathing rates for use in dose assessments. Health Phys 64: 23-36.

Longobardi, C (2001). Nuocide 2010: Acute dermal toxicity in the rat. Research Toxicology Centre S.p.A. RTC study no. 8046-006. International Specialty Products. DPR Vol. 275-428 #215525.

Lundberg, D, Killeen, JC, and Heilman, RD (1980). An acute inhalation toxicity study in albino rats with Nopcocide N-96. Document number 103-5TX-79-0137-002. Diamond Shamrock Corporation. DPR Vol. 275-014 #941825 (also in Vol. 275-168 #88770).

Mizens, M (1996). A 21-day repeated dose dermal toxicity study in rats with technical chlorothalonil. Ricerca, Inc. document number 6859-96-01130TX-002. DPR Vol. 275-297 #150595 (also in Vol. 275-325 #161759).

Moore, GE (2000). Acute inhalation toxicity study in rats. Product Safety Labs laboratory project identification number 8138. Farmsaver.com LLC. DPR Vol. 275-410 #207602.

Rattray, NJ (2002). Chlorothalonil Bravo 720 SC Formulation (WF2728) spray strength dilution (13.54 ml/l): 4-hour acute inhalation toxicity study in rats. Contract Lab Study Number HR2397 Syngenta Number 2707-01. Syngenta Crop Protection, Inc. DPR Vol. 275-409#204445.

Shults, SK, Wilson, NH, Killeen, JC, and Ignatoski, JA (1986). Range-finding studies for the 21-day repeated dose dermal toxicity study in albino rabbits with technical chlorothalonil. SDS Biotech Corporation. DPR Vol. 275-138 #54951.

Shults, SK, Brock, AW, and Killeen, JC (1991). Primary dermal irritation study in albino rabbits with ASC-66518-0101-1203. Document number 3780-91-0033-TX-001. ISK Biotech Corporation. DPR Vol. 275-180 #125630.

U.S. EPA (1996). Soil Screening Guidance: Technical Background Document. Appendix B: Route-to-Route Extrapolation of Inhalation Benchmarks. EPA Doc. No. EPA/540/R-95/128, May 1996. Office of Solid Waste and Emergency Response, United States Environmental Protection Agency, Washington, D.C.

U.S. EPA (1999). Reregistration Eligibility Decision, Chlorothalonil. United States Environmental Protection Agency. Prevention, Pesticides and Toxic Substances. Washington D.C. EPA 738-R-99-004. April 1999.

U.S. EPA (2008). Child-Specific Exposure Factors Handbook. U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-06/096F.

U.S. EPA (2009). Metabolically derived human ventilation rates: a revised approach based upon oxygen consumption rates. National Center for Environmental Assessment, Washington, D.C., EPA/600/R-06/129F.

Wilson, NH and Killeen, JC (1989). A tumorigenicity study of technical chlorothalonil in rats. Document number 1102-84-0103-TX-007. Ricerca, Inc. DPR Vol. 275-164 #74770.

Wilson, NH, Killeen, JC, and Ignatoski, JA (1983). A chronic dietary study in mice with technical chlorothalonil. Diamond Shamrock Corporation. DPR Vol. 275-70, and 77-82 #941871, #941877-941882.

Wilson, NH, Killeen, JC, and Ignatoski, JA (1985). A tumorigenicity study of technical chlorothalonil in rats. SDS Biotech Corporation. Document number 099-5TX-80-0234-008. DPR Vol. 275-100 to 104 #34366 and #34367, #34348-34352, and #34372.

Warren, DL and Halliburton, AT (1996). Acute four-hour inhalation toxicity study with HGB 2205 668 F in rats. Study #96-042-IX, Report No. 107472. Bayer Corporation. DPR Vol. 51951-202.

Wilson, NH and Killeen, JC (1989). A tumorigenicity study of technical chlorothalonil in rats. Document number 1102-84-0103-TX-007. Ricerca, Inc. DPR Vol. 275-164 #74770.

Wnorowski, G (1999). Acute inhalation toxicity study in rats. Product Safety Labs Laboratory. Project Identification Number 8118. DPR Vol. 275-348 #173371.

ATTACHMENT 2

In Attachment 2, the Office of Environmental Health Hazard Assessment (OEHHA) provides major and minor comments on the draft Risk Characterization Document (RCD), Volume II, Exposure Assessment, of the active ingredient, Chlorothalonil.

Major comments on the draft RCD, Volume II

1. Description of the physical and chemical properties of chlorothalonil

The chemical and physical properties of a chemical provide a means of predicting the fate and transport of the chemical in the environment. Page 9 of the Department of Pesticide Regulation (DPR) report reviews several of these properties. However, several important parameters are missing. Most notably, the octanol:water partition coefficient (K_{OW}), the organic carbon partition coefficient (K_{OC}) and the Henry's Law constant were not provided. These should be added to the report.

This section of the report also discusses the rates of photolysis in water, photolysis in soil, and hydrolysis. These environmental fate processes should probably be discussed in a separate section, not under the heading, "Physical and Chemical Properties." Similarly, synonyms and trade names for chlorothalonil should be listed under a separate heading.

2. Estimation of transdermal absorption of chlorothalonil

Given that chlorothalonil has an exceedingly low vapor pressure, it is not surprising that exposure via inhalation represents a small fraction of total exposure to the pesticide. For example, inhalation accounted for less that 1 percent of mixer/loader exposure estimated to occur during ground and aerial applications (p. 48). In the same scenario, dermal exposure accounted for more than 99 percent of total exposure. Similar results were obtained for all the handler and fieldworker exposure scenarios evaluated in this report.

Given the predominance of the dermal pathway in all occupational exposure scenarios, determination of the absorption of chlorothalonil across the skin is a critical parameter in assessing absorbed dose. Pages 20-26 of the DPR report summarize the results of a number of studies that were conducted to assess transdermal absorption, including

whole animal studies using rats and monkeys, and in vitro studies conducted with human skin samples.

In analyzing data from studies of dermal absorption in animals, the authors identified a rat study conducted by Andre et al. (1991) as the critical study. In this study, radiolabeled chlorothalonil in a Bravo® 720 formulation base was applied to a 10 cm^2 area of skin that had been clipped free of hair and washed with acetone. Three doses, equivalent to 2.2, 11.0 and 110 µg chlorothalonil per cm^2 of skin surface, were evaluated. After dosing, the treated area was covered with a non-occlusive patch. Transdermal absorption was determined 1, 2, 4, 10, 24, 48, 72, 96 and 120 hours after dosing from the percent of the applied dose recovered in the carcass, urine, feces, cage wash, blood, kidney and liver. "Skin residue" – the amount of radioactivity recovered from the treated area of skin after the residual remaining on the surface had been removed by washing – was determined at the same time points. Total dermal absorption was determined by adding the absorbed radioactivity to the radioactivity detected in the skin. DPR identified the amount absorbed 10 hours after dosing as most representative of a typical 8-hour workday, including traveling time or waiting time before taking a shower. At the 2.2 µg/cm^2 dose, the residual radioactivity remaining in the skin appeared anomalously low, and total transdermal absorption at the highest dose (110 µg/$cm^{2)}$ was generally much less than absorption observed and the low and middle doses. As a result, the 10-hour absorption data from the 11 µg/cm^2 dose (27.5 percent) was used to calculate human dermal absorbed doses in all the handler and fieldworker scenarios evaluated in this report.

Two in vitro studies of the dermal absorption of chlorothalonil [Fermenta ASC Corporation (1991) and Cage (2004)] were cited and briefly discussed. In both studies, absorption across human skin samples was very low, amounting to less than 1 percent of the applied dose 24 hours after dosing. The results of these studies were discounted by the authors of the DPR report because "results from in vitro dermal absorption studies...are not considered reliable predictors of in vivo dermal absorption." Further, "DPR does not use results from in vitro dermal absorption studies...because there were inadequate validation studies concerning the test method, including receptor fluids, preparation of membranes, and types of diffusion cells."

We have several concerns with DPR's analysis of the available dermal absorption data for chlorothalonil:

i. Rats are not a particularly good animal model for estimating dermal absorption of chemicals across human skin because the high density of hair follicles in rat skin leads to relatively greater absorption of dermally applied chemicals (U.S. EPA, 1992). Therefore, data from the Andre et al. (1991) study likely

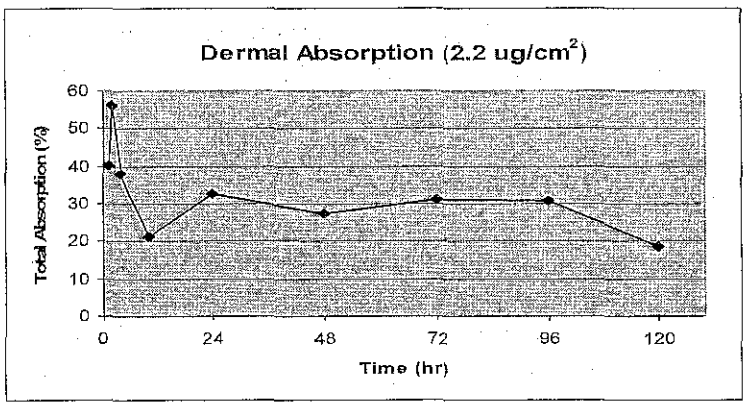
overestimate the rate of transdermal absorption of chlorothalonil across human skin.

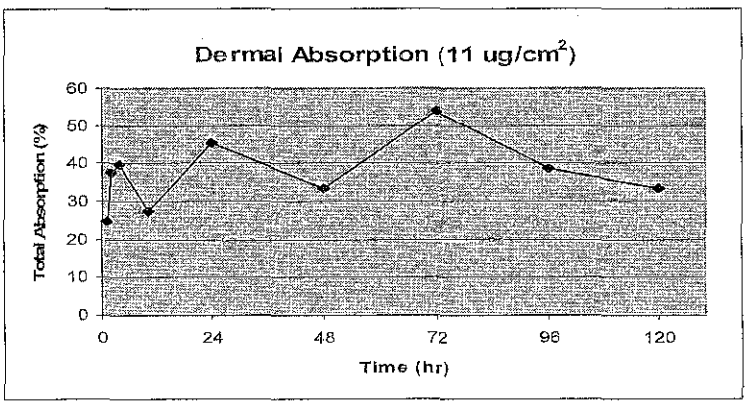
ii. In our opinion, the data from the study conducted by Andre et al. (1991) do not provide a clear basis for quantifying the kinetics of chlorothalonil absorption across the skin of rats. In Figure 1, total absorbed dose was determined by adding the absorbed radioactivity and the "skin residue" radioactivity. One would expect to observe a steadily increasing absorbed dose with increasing duration of exposure. Nevertheless, a clear relationship between the duration of exposure and transdermal absorption was not apparent at the two lowest doses, and only became apparent at the highest dose after 24 hours.

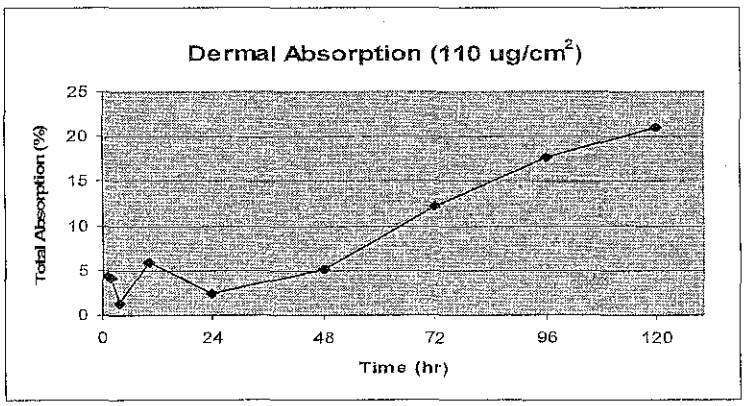
iii. In our opinion, identification of the 10-hour time point as most representative of an occupational exposure scenario does not appear to be justified. This decision might be justified if all dermal loading occurred at the beginning of the workday, but this does not happen. Assuming that exposure occurs continuously in the course of an 8-hour workday, which would be reasonable for the fieldworker scenario, the average residence time for pesticide residues on the skin should be 4 hours. If the 4-hour time point had been selected as most representative of an occupational exposure scenario, the transdermal absorption of chlorothalonil would have been 39 percent - half again higher than the value that DPR identified - based on data from the low and middle doses.

iv. According to a review by Van de Sandt et al. (2007), results from in vitro studies of dermal absorption continue to find wider use in risk assessment of pesticides, cosmetic ingredients and industrial chemicals. This review cites two evaluations of the robustness of in vitro methodology, and notes that the *Guidance Document on Dermal Absorption* (European Commission, 2004) explicitly allows for use of in vitro studies as a standalone methodology to obtain dermal absorption data. Based on these newer evaluations, we believe there is adequate justification for DPR to re-visit its decision not to use results from in vitro studies as a basis for estimating dermal absorption of chemicals across human skin.

v. Figure 1. Transdermal Absorption of Chlorothalonil in rats (data from Andre *et al.*, 1991).







3. Relevance of activity-specific studies

To estimate exposure to cherry harvesters and thinners/pruners (pages 65-66 of the DPR report), the report cited a study of chlorothalonil dislodgeable foliar residues (DFRs) on five sour cherry trees conducted in Ohio by Ricerca, Inc. in 1993. In California, cherries are typically harvested in June, and June weather in California differs significantly from the early summer weather pattern in Ohio. Specifically, most regions of Ohio typically receive 3-4 inches of rainfall in June and July while California generally receives little or none. The persistence of pesticide residues on foliar surfaces would be expected to be reduced by rainfall-induced wash-off, suggesting that data collected from a study of DFRs in Ohio would not be a good representation of what would likely occur in California. Why wasn't precipitation taken into consideration when data from this study was selected as a basis for estimating exposure for this class of fieldworkers? What results would have been obtained if the DFR had been estimated using the default approach that was used to assess exposure for activities lacking activity-specific data (e.g., the methodology described for Christmas tree harvesters and thinners)?

4. Estimation of DFRs from field applications rates

To estimate the exposure of Christmas tree harvesters and thinners (pages 66-67), the report notes that a field exposure study of exposures resulting from this activity has not been conducted. Therefore, "An estimated initial DFR value was determined by assuming that it is equal to 20% of the maximum application rate of 4.2 AI/A for Christmas trees (i.e., 20% of 4.2 lbs AI/A was converted to $\mu g/cm^2$ and used as the initial DFR value). This is the current practice at the WHS Branch, DPR." This approach is justified on the basis that it is consistent with the approach taken in field DFR studies of more than a dozen pesticides. In our opinion, adopting an approach simply because it was used in previous exposure assessments does not constitute adequate justification for continuing to use it. The important issue is, has this approach been validated by comparing the DFRs predicted using this methodology with actual DFRs determined by analysis of field samples? Furthermore, the report does not include a description of the equations and assumptions that were required to estimate a DFR, expressed in units of µg of pesticide per square centimeter of leaf surface area, from the field application rate, expressed in units of pounds of active ingredient applied per acre. This would appear to be particularly problematic when the crop under consideration has needles, and estimating the total surface area of the needles on a Christmas tree (which we presume is a necessary parameter in this calculation) would appear to be challenging.

5. Evaluation of the potential for chlorothalonil to cause contact dermatitis

Dermal sensitization to chlorothalonil is discussed on page 18 of the DPR report, and a statement at the top of page 98 notes that chlorothalonil may cause dermal irritation in animals. We believe the latter statement is somewhat misleading insofar as it understates the severity of consequences that may result from dermal contact with the pesticide. In studies of field workers, farmers and individuals exposed occupationally during manufacture or packaging of the pesticide, dermal exposure to chlorothalonil has been shown to cause irritant contact dermatitis and allergic contact dermatitis. In a case study discussed on page 18, exposure of a sensitized patient to a 0.01 percent solution of the pesticide caused an anaphylactoid reaction.

Furthermore, the DPR report notes that

> *Exposure of body parts (e.g., chest, back, forearms, head) of workers or volunteers to chlorothalonil…varies tremendously. For example, one worker may experience a high exposure level on the chest area, but another worker participating in the same study may not.*

Symptoms of allergic and non-allergic contact dermatitis (erythema, indurations, vesiculation and scaling) can occur on areas of the skin that are in direct contact with the chemical agent. Despite these well-documented observations noted above, the dermal exposure analysis presented in Section F (pages 98-99) calculates μg of chlorothalonil per cm^2 of skin surface area as the average or 95th percentile estimate of total dermal exposure (in units of mg/person-day) divide by an average *total body* surface area. Given that contact dermatitis is most likely to occur on portions of the skin that receive the highest exposure, this approach is likely to underestimate the potential of chlorothalonil to produce this adverse effect. (According to Cohen and Rice (2001), the occurrence of contact dermatitis is also influenced by skin pH, temperature, duration and repetitiveness of contact, and occlusion.)

Despite these well-documented observations, the dermal exposure analysis presented in Section F (pages 98-99) calculates μg of chlorothalonil per cm^2 of skin surface area as the average or 95th percentile estimate of total dermal exposure (in units of mg/person-day) divided by an average *total body* surface area. Given that contact dermatitis is most likely to occur on portions of the skin that receive the highest exposure, this approach is likely to underestimate the potential of chlorothalonil to produce this adverse effect.

In our opinion, these exposure estimates should be based on data derived from field studies of actual dermal skin loading. For example, the total amount of chlorothalonil

analyzed in a hand washing study would be divided by the surface area of the hands to obtain a dermal loading estimate in units of μg of chlorothalonil per cm^2 of skin surface. The amount of pesticide detected in wipe samples collected from the most heavily contaminated portions of the body could also be used for this purpose.

Minor Comments on the draft RCD, Volume II

1. In Table 5, the far left cell in the next to last row should read "Total *for 8* years," not "Total/6years."

2. The last column of Table 22 (page 61) lists "corrected" DFRs to account for the fact that the experimental data reflect an application rate of 2 pounds active ingredient per acre (AI/A), while the maximum application rate is 2.25 pounds AI/A. Therefore, the correction factor should be 2.25/2, or 12.5 percent. However, the values presented in the last column are simply the experimental data from the second column rounded off from three significant figures to two. The corrected DFRs for post-application days 1, 3, and 7 should be 4.28, 4.22, and 3.42 $\mu g/cm^2$, respectively.

3. On the first line of page 62, a default body surface area of 16.9 m^2 is indicated. This should be 1.69 m^2.

4. On page 77, data from a 1999 study conducted by Honeycutt were used to estimate exposure of sweet corn harvesters. Exposure parameters and observation data are presented within the text of the report, reducing the clarity of the discussion and making it very difficult for a reviewer to validate the analysis of the data. This is particularly difficult because the DFRs and transfer coefficients (TCs) do not vary in a time-dependent fashion. For clarity, the authors should consider inserting the following table in this section of the report.

Post-Application Day	DFR	TC	Dermal exposure (mg/8-hr workday)
9	1.390		
14	0.803	14900	95.72
21	0.543		
22	0.217	11600	20.14
23	0.405	21400	69.34
24	0.630		

Data from Honeycutt (1999)

References

European Commission (2004). Guidance Document on Dermal Absorption. European Commission, Sanco/222/2000 rev. 7.

U.S. EPA, Office of Research and Development (1992). Dermal Exposure Assessment: Principles and Applications. Interim Report. EPA/600/8-91/011B.

Van de Sandt, JJM, Dellarco, M, and Van Hemmen, JJ (2007). From dermal exposure to internal dose. Journal of Exposure Science and Environmental Epidemiology 17 (Suppl. 1): S38-S47.