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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 30, 1999

MEMORANDUM

SUBJECT: Response to: *Dow AgroSciences' Response to U.S. EPA's Preliminary Risk Assessment for Chlorpyrifos-Methyl, Health Effects Division FQPA Reassessment Chapter Dated July 19, 1999*, PC Code # 059102, DP Barcode 259302, MRID 449069

FROM: Gary Bangs, Risk Assessor
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THROUGH: Steve Knizner, Branch Senior Scientist
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TO: Stephanie Nguyen, Chemical Review Manager
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Responses to the HED Chlorpyrifos-methyl Preliminary Risk Assessment, which was dated July 19, 1999, were received from Dow AgroSciences. Below please find a summation of comments and HED's response prepared by the risk assessment team. This memo is an updated version of the September 23rd memo including clarifications suggested by Special Review and Registration Division.

Executive Summary

Dow AgroSciences has supplied the EPA with responses to the Agency's Preliminary Risk Assessment for Chlorpyrifos-methyl during Phase 1 of the organophosphate pilot process which allows for corrections of errors and inaccuracies. The Dow submission addresses perceived errors and omissions as well as commenting on the Agency's approach to the risk assessment. Minor errors or inaccuracies have been corrected as noted herein with no substantive impact on the conclusions of the risk assessment. Major commentary on Agency policy was included in the response, particularly in Dow's Executive Summary and Appendices. The Dow commentary focused on the following issues:

-the use of human studies for EPA pesticide risk assessments;
-the adequacy of the toxicology database for chlorpyrifos-methyl;
-the impact of the first two points on the FQPA factor;
-and the significance of plasma cholinesterase versus red blood cell (rbc) cholinesterase.

These policy issues fall primarily within the hazard identification portions of the risk assessment. Dow's comments and corrections of EPA's estimate of acute and chronic dietary risk factors were based primarily on the submission of references that contained information on processing or cooking grains. These references are being evaluated by the Agency to determine if additional processing factors beyond those already incorporated in the risk assessment can be used.

Comments by Dow on the non-dietary risk assessment relied upon changes in the policies already mentioned, which might permit the use of a human-subjects-based NOAEL, or lower the FQPA safety factor by using same-species (human) data. No significant changes in the non-dietary risk assessment are indicated until these policy issues are addressed.

Three not-previously-submitted studies on toxicity and 2 references in the published literature on effects of residues on grain from cooking and processing were submitted. These studies are in review. Preliminary reviews indicate that the 3 toxicology studies will not have any impact on the hazard assessment. The 2 studies of food residues may have an impact on the dietary risk assessment. Any changes as a result of the reviews will be reflected in the next revision of the chlorpyrifos-methyl risk assessment.

Introduction

General statements in the Dow response, such as the Executive Summary, the Introduction, and Appendices A-C are not addressed specifically in this document, but the intent is addressed in the Agency's specific responses.

The comments from Dow AgroSciences have been grouped in either Section A: Corrections, or Section B: Comments. The suggested corrections were acted upon if indicated in the HED responses. Several of the corrections and comments were based on decisions of Agency policy, and therefore some of the HED responses may be similar.

A. Corrections from Dow AgroSciences (referred to as DAS in their paper)

Section II A. EPA's Hazard Assessment Section.

DAS: Page 5, line 7. Statement is inaccurate. There is not an in vivo study on dermal absorption, but there is an in vitro study on EC formulation of chlorpyrifos-methyl (Perkins, 1995) that showed the dermal penetration of the undiluted formulation is ca 3% and about 1% for a 1% aqueous dilution of the formulation.

HED Response: Current HED policy does not accept in vitro dermal absorption studies for estimation of dermal absorption/penetration for risk assessment purpose. EPA has no data that show that in vitro data accurately and reliably predict in vivo dermal absorption. Refer to the "Reviewing Dermal Absorption Studies" prepared by R. Zendzian (dated 7/18/97).

DAS: Page 6, line 3. The statement "There were insufficient data on which to base recommendations" is inaccurate and misleading. There were very few reported incidences with chlorpyrifos-methyl, but the absence of an adverse report is also data. Thus, this sentence should read "There were insufficient reported incidences to warrant any recommendations at this time."

HED Response: Both statements may be correct, but the lack of data does not allow the Agency epidemiologists to make any recommendations. Statements regarding the relatively low number of incidents are included in the risk assessment and the incident report review.

EPA's Toxicology Assessment Section

DAS: Page 8, Table 1. Entries for acute inhalation (p 8) and dermal sensitization (p 9) are inaccurate and should read as indicated below because studies for both endpoints exist:

Guideline No.: and Study Type	MRID #	Results	Tox Category
81-3 (870.1300) Acute Inhalation		4 hr LC_{50} >0.67 mg/L highest attainable vapor conc.	II
81-6 (870.2500) Sensitization		Not sensitizing	NA

HED Response: The acute inhalation toxicity study indicated by DAS was conducted with a test material identified as "chlormercaptophen" in HED's files and not as chlorpyrifos methyl. The Pesticide Index was consulted to determine if the stated name is a synonym for chlorpyrifos methyl and this name was not listed. Therefore, results of this study are not appropriate for use. DAS needs to verify that the test material was chlorpyrifos methyl and provide information on purity and lot number and verification that the synthesis method used is the same as for current production lots of chlorpyrifos methyl. For the series 81-6 study, DAS did not provide the appropriate reference number or other identification for a study that

demonstrates that chlorpyrifos methyl is not a sensitizer. The studies in HED's files are with formulations or otherwise not studies considered acceptable with technical grade chlorpyrifos methyl.

DAS: Page 9, lines 2-3. Sentence is inaccurate. There is an acute inhalation study (Hardy and Jackson, 1984, Accession No. 256616) and a dermal sensitization study (Jones, 1985) on the technical. However, because technical chlorpyrifos-methyl is an amorphous solid with a low vapor pressure, DAS does not object to setting the hazard category based on inhalation data with a formulation.

HED Response: Again, the acute inhalation toxicity study indicated by DAS was conducted with a test material identified as "chlormercaptophen" in HED's files and not as chlorpyrifos methyl. Therefore, results of this study are not appropriate for use.

EPA's Carcinogenicity/Chronic Toxicity Section

DAS: Page 10, line 29. Delete "a dose related increase" as treatment-related histopathological lesions of the adrenal gland in males were limited to the top-dose level tested of 50 mg/kg/day. An increased incidence of adrenal vacuolation, graded as slight, was observed in rats given the 1 mg/kg/day dose level relative to control. However, as explained by Browning (1992) (a copy is submitted with this response), the incidence of this adrenal observation in rats given the 1 mg/kg/day dose level was within the control range.

HED Response: The term "dose related" has been corrected to "treatment-related".

DAS: Page 10, line 35. Delete "pathological findings." As noted above, treatment-related histopathological findings were limited to the top-dose level.

HED Response: HED concurs and the term "pathological findings" should not refer to an effect occurring at the LOAEL since the pathological findings were noted only at the highest dose tested and not at the LOAEL. This phrase was not used in the Risk Assessment, only in the HIARC Report, so there was no correction in the Risk Assessment.

EPA's Executive Summary Section (HIARC Report)

DAS: Page 4, lines 29-32. Change "Cholinesterase activity" to "Plasma cholinesterase" as neither RBC nor brain cholinesterase activity was consistently depressed at this dose level. Replace the rest of the sentence following "40-46% at 24 months and" with "... and following the 50 mg/kg/day dose level both plasma (85-94% at 24 months) and brain (37-47%) cholinesterase were depressed versus the controls."

HED Response: The term cholinesterase inhibition is used in a general sense to mean that any one of the three enzyme species was inhibited. Use of this term does not imply that a

specific cholinesterase species was inhibited. It should not be necessary to replace the statement as DAS is suggesting since the species of cholinesterase is clearly defined in the current document.

DAS: Page 5, line 1. Treatment-related histological lesions of the adrenal gland in male rats were limited to the top-dose level tested (50 mg/kg/day). An increased incidence of adrenal vacuolation, graded as slight, was observed in rats given the 1 mg/kg/day dose level relative to control. However, as explained by Browning (1992), the incidence of this adrenal observation in rats given the 1 mg/kg/day dose level was within the control range. Additionally, in all cases the adrenal vacuolation in animals given the 1 mg/kg/day dose level was found only in animals found dead or sacrificed moribund.

HED Response : As stated above, the term dose-related was changed to "treatment-related" in the Risk Assessment document.

EPA's Dermal Absorption Section (HIARC Report)

DAS: Page 5, line 21. This sentence is inaccurate. Data are available on dermal absorption from an *in vitro* study (Perkins, 1995). This study was conducted according to the draft OECD Method (Percutaneous Absorption, *In-vitro* Method, March 1994) in accordance with ECETOC recommendations (Monograph No. 20, Percutaneous Absorption; August 1993) and GLP standards. The results indicate dermal penetration of *ca* 3% with the undiluted EC formulation chlorpyrifos-methyl and 1% for a 1% aqueous dilution of this formulation.

HED Response: Again, current HED policy does not accept in vitro dermal absorption studies for estimation of dermal absorption/penetration for risk assessment purpose. EPA has no data that show that in vitro data accurately and reliably predict in vivo dermal absorption.

EPA's Classification of Carcinogenic Potential Section

DAS: Page 8, line 14 (*this was found on page 10 of the RA Document*). Change "for 24 hours" to "for 24 months."

HED Response: This change was made in the revised Risk Assessment document.

DAS: Page 8, line 16. Change "wright gain" to "weight gain."

HED Response: This misprint in the HIARC Report will be corrected.

DAS: Page 8, line 18. Change "This decrease" to "In males, this decrease."

HED Response: This change was made in the revised Risk assessment. Note, however, that the following sentence clearly indicates that the topic changes to females.

DAS: Page 8, lines 22, 23 (*HIARC Document*). Change "Cholinesterase activity" to "Plasma cholinesterase" as neither RBC or brain cholinesterase activity was consistently depressed at this dose level. Replace the rest of the sentence following "40-46% at 24 months and" with "and following the 50 mg/kg/day dose level both plasma (85-94% at 24 months) and brain (37-47%) cholinesterase were depressed versus the controls."

HED Response: This change is not considered necessary because the term cholinesterase inhibition is used in a general sense to mean that any one of the three enzyme species was inhibited. Use of this term does not imply that a specific cholinesterase species was inhibited.

DAS: Page 8, lines 25-26. Treatment-related histopathological lesions in the adrenal gland of males were limited to the top dose level tested, 50 mg/kg/day. An increased incidence of adrenal vacuolation, graded as slight, was observed in rats given the 1 mg/kg/day dose level relative to control. However, as explained by Browning (1992), the incidence of this adrenal observation in rats given the 1 mg/kg/day dose level was within the control range.

HED Response: HED concurs and the term "pathological findings" should not refer to an effect occurring at the LOAEL since the pathological findings were noted only at the highest dose tested and not at the LOAEL. This phrase was not used in the Risk Assessment, only in the HIARC Report, so there was no correction in the Risk Assessment.

DAS: Page 8, line 30. Qualify this sentence to indicate the increased absolute and relative adrenal weight was observed only at the 50 mg/kg/day dose level.

HED Response: The sentence will be changed to " .....and relative adrenal weight noted at the high dose group" in the HIARC Report.

DAS: Page 8, line 34. Delete "and pathological findings" as no treatment-related histopathological findings were observed at 1 mg/kg/day.

HED Response: The term pathological findings was deleted from the LOAEL expression in the revised Risk Assessment document.

DAS: Page 9, line 7 (*HIARC Report*) Insert "early" before "mortality" as all rats in this study eventually died.

HED Response: This change is not considered necessary.

EPA's FQPA Considerations, Developmental Toxicity Section (HIARC Report)

DAS: Page 11, last line, continuing on page 12. Sentence is incorrect as there were 10 hens examined histologically at 500 ppm dose level. DAS agrees with the reviewer's conclusion "that

the study did not appear to induce histopathological lesions indicative of neurotoxicity in hens."

HED Response: No change is necessary since the HIARC report does not indicate the number of hens actually examined but states that 1 to 4 hens had the axonal degeneration and 1 to 6 hens had the gliosis, thus indicating a total of 10 hens.

EPA's FQPA Considerations, Reproductive Toxicity Section

DAS: Page 13, line 3. Statement is inaccurate. A teratology study has been conducted with chlorpyrifos-methyl in rabbits. This study was conducted prior to issuance of the GLP guidelines. While it may not meet current EPA guidelines, this study followed good scientific procedures and provides data that can be used to assess the relative susceptibility of infants and children versus adults to chlorpyrifos-methyl. This study reported that chlorpyrifos-methyl, when fed in the diet of pregnant rabbits at dosages of up to 16 mg/kg/day on gestation day 6-18, caused a transient decrease in maternal food and water consumption, but had no effects on rabbit embryo or fetal development.

HED Response: Contrary to the registrant's claim that this study is technically valid, the Agency concluded that this study has numerous technical inadequacies, did not follow good scientific procedures, was classified as unacceptable and not ungradable. In addition, the dose levels tested were judged to be inadequate to assess maternal or developmental toxicity. Since no maternal toxicity was demonstrated at the highest dose tested (indicating that the dose selection was inadequate), the results of this study cannot be used to assess the relative susceptibility of infants and children.

EPA's FQPA Considerations, Determination of the Need for a Developmental Neurotoxicity Study Section (HIARC Report)

DAS: Page 13, lines 17-18. Sentence is inaccurate as written. The cited studies are scientifically valid but were classified as unacceptable because they did not meet current EPA guidelines. Additionally, as discussed above, U.S. EPA's current guidelines indicate the acute delayed neurotoxicity study in hens (series 81-7) should be classified as acceptable because the Agency has an acceptable subchronic delayed neurotoxicity study (series 82-6) which they agree is negative.

HED Response: The prenatal developmental toxicity study in rabbits and the three-generation reproduction study in rats are classified as unacceptable for regulatory purposes and are, therefore considered to be data gaps. Contrary to the registrant's claim that these studies are technically valid, the Agency concluded that these studies have numerous technical inadequacies and did not follow good scientific procedures.
In the rabbit study, the dose levels tested were judged to be inadequate to assess

developmental toxicity. Since no maternal toxicity was demonstrated at the highest dose tested (indicating that the dose selection was inadequate), the results of this study cannot be used to assess the relative susceptibility of infants and children.
In the three-generation reproduction study in rats, only two dose levels were selected which does not meet Agency Guideline requirements. Again, the results of this study are inadequate to assess susceptibility of infants and children after pre-/postnatal exposure to chlorpyrifos methyl.
With regard to the neurotoxicity studies in hen, the HIARC will re-evaluate the results of these studies and the need for a repeat for the acute delayed neurotoxicity study in hens. It should be noted that the Agency on August 2, 1999 announced a data-call in program requiring acute and subchronic neurotoxicity and a developmental neurotoxicity study for cholinesterase-inhibiting organophosphates which includes chlorpyrifos methyl

DAS: Page 13, lines 19-20. Sentence is misleading. The U.S. EPA has no requirements for either an acute (series 81-8) or subchronic (series 82-7) neurotoxicity study in mammals.

HED Response: The Agency considers these studies as critical for evaluation of the neurotoxicity and/or neuropathology for the organophosphates. In addition, neurotoxicity studies are required for assessment of neurotoxicity as per the FQPA requirements.

DAS: Page 14, line 7. Insert "observed at much higher dose levels," between "Other systemic effects" and "included ...". The no observed effect level (NOEL) used by the U.S. EPA for chronic risk assessment is 0.1 mg/kg/day, while the other effects cited were observed only in animals given 40 to 50 mg/kg/day.

HED Response: A change in this sentence will be made in the HIARC Report to reflect that the systemic effects occur at dose levels higher than the LOAEL.

Section II C. Chlorpyrifos-methyl Acute and Chronic Dietary Exposure Analyses (EPA Attachment D).

DAS : The major error in the assessment as provided was in the inappropriate use and omission of processing and cooking information for grain fractions.

HED Response: HED agrees that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

DAS: As a matter of science policy, DAS is especially concerned with the lack of statistical rigor in generating 99.9th percentile estimates of acute dietary risk. DAS does not believe that the 99.9th percentile estimates as they are currently derived are reliable or representative. DAS urges

EPA to adopt a policy based on scientifically defensible exposure estimates. A more comprehensive discussion of this issue can be found in Wolt (1999) (a copy is enclosed with DAS's response submission).

HED's Response: The Agency issued a draft policy paper April 1, 1999 for public comment entitled, "Choosing a Percentile of Acute Dietary Exposure as a Threshold of Concern". The docket for public comments closed June 9,1999 to this issue. The Agency will announce their final policy on this after full consideration of all public comments. Until such time, dietary exposure estimates at the 99.9th percentile will continue to be presented.

DAS: The dietary exposure analyses presented by the EPA utilizes residue information from USDA PDP to estimate both acute and chronic dietary exposures to chlorpyrifos-methyl. The use of PDP data is strongly encouraged because of the richness of the database for a wide number of food commodities and pesticide products. It also measures pesticide residues that are closer to the "dinner plate" than are field residues traditionally used to estimate exposures. The major error in the assessment as provided was in the inappropriate use and omission of processing information for grain fractions. In addition to processing data previously submitted to the EPA for inclusion in their risk assessment, key processing information is available from the published literature and is referenced in this response to help the EPA refine their assessment. The processing studies submitted show that chlorpyrifos-methyl residues are substantially reduced by cleaning, milling, polishing, and cooking of treated grains. As Nakamura et al. state in their rice study "...no permeation inside (the treated grain) was observed...." The appropriate application of processing factors reduces the estimated exposures to chlorpyrifos-methyl to a small fraction of the amount estimated by the EPA. The resulting estimate of dietary exposures shows that neither the US population nor any sub-population is exposed to amounts of chlorpyrifos-methyl greater than 0.0008 mg/kg/day at the 99.9th percentile for acute exposures and 0.000043 mg/kg/day for chronic exposures. These exposures are far less than the amounts recognized as safe.

HED's Response: HED agrees that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

1. Specific Errors and Comments - Residue Information

DAS: Page 4. "HED concluded that TCP need not appear in the tolerance expression, and that tolerances are to be expressed in terms of CPM per se (M. Flood, 4/29/91)." Dow AgroSciences agrees it is appropriate to base the tolerances on chlorpyrifos-methyl only.

HED's Response: No Response.

DAS: Page 4. "The PDP residue values should be used in the acute and chronic dietary exposure assessments." Dow AgroSciences agrees with the use of PDP data in place of field residue data as representative of potential residues in stored grain. However, it should be recognized that when the market shares differ between the various commodities, such use may overestimate the exposures from the other commodities.

> **HED's Response:** HED did use the available PDP monitoring data for wheat, and translated these data to other grains. The Agency considers all available information of percent of crop treated in the market. If the registrant has further market share information, then they should submit it to the Agency for evaluation.

DAS: Page 4. "Monitoring data is preferred over field trial data because it is sampled longer after harvest and is therefore more reflective of residues consumed 'at the dinner plate'; PDP data is preferred over FDA data because of the statistical design of the PDP program specific for dietary risk assessment and because the foods are prepared before analysis as they would be at home (i.e. peeling, washing, etc.)." This statement is inaccurate for grains. Grains are not cleaned, milled, or processed prior to analysis by PDP and, therefore, represent the worst case residues. Processing data should be included in the dietary assessment to account for the residues on hulls and other fractions not consumed. See additional comments below.

> **HED's Response**: The above HED quoted statement is a generalization. HED recognizes that in the case of grains, this statement is inaccurate with respect to peeling, washing, etc because grains are not processed when analyzed by PDP. Furthermore, HED acknowledges that residues may decrease over time in transit through commerce and that the majority of residues consumed 'at the dinner plate' would be in the form of processed commodities. Therefore, HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

DAS: Page 4, Table 2 of the Dietary Assessment and Table 4 of the Preliminary Risk Assessment. The data presented in these tables are misleading. The number of samples and the maximum residue concentrations detected in the PDP database are accurate, but the minimum concentration in each year is misleading and should be changed to "not-detected." The data as presented gives the minimum measured residue observed among the detects for each year, not the minimum residue for all samples collected in that year. For example, in 1995 the maximum residue measured was 3.322 ppm out of 325 detects; in the remaining 275 samples, no chlorpyrifos-methyl was detected. The average concentration should include these non-detects and the value in Table 2 should be the same as that used in the chronic assessment. The average number of detections cited in Table 4 of the Preliminary Risk Assessment (DP Barcode D257859) needs clarification.

The value cited (61%) is the average yearly detects, not the percentage of detects for the three

years. We suggest the following summary table and figure to describe the PDP data.

Corrected Table 2 of the Acute and Chronic Dietary Exposure Analyses, and Table 4 of the Preliminary Risk Assessment

Crop	Year	# of Samples Analyzed	# of Detects	% of Detects	Minimum Conc. (ppm)	Maximum Conc. (ppm)	Average Conc. (ppm)	LOD (ppm)
Wheat	1995	600	325	54	ND	3.322	0.057	0.001
Wheat	1996	340	249	73	ND	1.525	0.068	0.001
Wheat grain	1997	622	346	56	ND	1.796	0.059	0.001
Total		1562	920	Avg = 59 %				

ND = not detected

HED's Response: HED acknowledges that the data in Table 2 of the Dietary Assessment and Table 4 of the Preliminary Risk Assessment may be misinterpreted. The columns entitled, "Minimum Concentration (ppm)" should be changed to read, "Minimum Concentration Detected (ppm)" and the columns entitled, "Average Concentration (ppm)" should be changed to read, "Average of Detectable Residues (ppm)". These changes will be implemented after the sixty-day public comment period. However, changing the column headings does not change the outcome of the dietary risk assessments.

DAS: Page 5, Table 4; Page 6, footnote 2. "The acute dietary risk assessment should utilize the entire distribution of monitoring data (PDP) of CPM residue value detections with no further adjustment for % CT;" When PDP data is used as a surrogate for multiple commodities, the data should be adjusted to account for a difference in percentage of crop treated, especially when there are large differences in the %CT. One way to make this adjustment is to create DEEM .rdf files for each commodity that include sufficient zeros to account for the correct proportion of samples not treated. For example, if 30% of one commodity were treated but only 5% for another, then additional zeros should be added to make the data equal 5% of the total samples. Using this method, the magnitude of the residues would not change, but the frequency of detects would be proportional to the amount of the crop treated.

HED's Response: Because commodities such as grain are a widely blended commodity, no further adjustments for percent crop treated are necessary. Furthermore, for Tier 3 assessments of blended commodities, the entire distribution of residue values from (blended commodity) monitoring data should be used (with no correction for percent crop treated since this is already incorporated into the monitoring data), with ½ LOD or LOQ substituted for all non-detects (Draft Policy Paper open for public comment entitled, "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs" dated November 5, 1998. The docket was closed to public comments on January 4, 1999). However, a sensitivity analysis should have been done by HED where zero residues were used for those commodities assuming ½ LOD, in accordance with TRAC policy paper #5.

entitled "Assigning Values to Nondetected/Nonquantified Pesticide Residues in Human Health Dietary Exposure Assessments". Therefore, HED will perform a sensitivity analysis as part of their revised dietary exposure analyses.

DAS: Page 6, footnotes 2, 5, 6, and 8. "Processing factors should be incorporated where appropriate... Data on oat flour are not available; however, the wheat processing study indicates that residues of CPM per se do not concentrate in flour. The available rice processing study indicates that residues of CPM per se do not concentrate in polished rice." References to milling data and cooking data were cited but not utilized in this assessment except to show that residues concentrated in certain fractions (the hulls, bran, germ, red dog, shorts and germ oil). A summary of available processing factors for chlorpyrifos-methyl from both reports submitted by Dow AgroSciences, and from the published literature, is provided in these comments. The use of processing factors greater than one for the concentration of residues in a portion of the grain (e.g., rice hulls 3.6x) must be balanced by factors less than one (e.g., brown rice 0.2, bran 0.45) for residues in the rest of the grain. Application of 6 ppm chlorpyrifos-methyl to intact grain puts most of the residues on the outer hulls with very low or no residues penetrating into the rest of the grain. Nakamura et al. states "no permeation inside was observed" in their processing studies with rice. The Preliminary Assessment document implicitly assumes that, for example, application to rough rice at 6 ppm results in 21.6 ppm in the hulls + 10.8 ppm in the bran + 6 ppm in the polished rice + 6 ppm in the cooked rice, etc., because of the way processing data were selectively applied. Clearly, the concentration of residues in one part of the grain must lead to lesser residues in the rest of the grain. This dilution of residues in various parts of the grain should also be considered in the estimation of anticipated residues in meat and meat byproducts.

HED's Response: HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used. However, because wheat is a widely blended commodity, no further adjustments for percent crop treated are necessary. The percent crop treated data from the Office of Pesticide Program's Biological and Economic Analysis Division (BEAD) showed that approximately 10% of the wheat was treated with chlorpyrifos-methyl. However, the fact that PDP data shows 59% of wheat (sampled from 1995-1997) had residues of chlorpyrifos-methyl indicates that there is mixing of the treated and untreated wheat as it moves through commerce. Ideally, the percent of grain treated in silo's would be useful to refine the dietary analyses. HED notes that if there is a large difference in the percent of silo's treated among wheat and the translated commodities, then HED may be overestimating the residue detections for the translated commodities. However, in the absence of this data, HED translated the PDP wheat data to the other commodities (which is not as conservative as the use of field trial data). If the registrant has further information on the percent of silo's treated with chlorpyrifos methyl, then they should submit it to the Agency for evaluation.

DAS: The consistency between processing factors derived from multiple studies and from multiple crops suggest that such factors can be widely utilized in grains. For example, processing either whole wheat meal or flour into loaf bread and cookies gave processing factors of 0.54 to 0.34 with an average of 0.42. Production of brown rice from rough rice in three studies gave processing factors of 0.2, 0.3, and 0.2 (average = 0.25). Processing the rough grain into finished foods by boiling or baking gave processing factors of 0.04, 0.08, 0.08, and 0.013, for wheat and rice. Nakamura notes "The percentage of organophosphates removed by washing (rice) with water was 61.8% to 99.0%. The remaining were completely removed by steaming twice...no permeation inside was observed." (p 1915) Also, the residues were not increased by re-using the steep water, thus indicating chlorpyrifos-methyl evaporated from the food during the cooking and was not extracted into the water. A similar effect would occur in the elevated temperatures of baking and frying. The processing factors utilized in this document are given in Appendix B as part of the residue data file. In the refined assessments presented in these comments, a processing factor of 0.01 was used for all boiled commodities, based on the measured values for rice. The processing factor for baking was derived from the average bread value of 0.42. Cooked commodities were assumed to be baked, whereas canned commodities were assumed to be boiled. For a food form such as baked wheat bran, the processing factor was equal to the highest baked whole wheat factor (0.39). For cooked rice bran, the bran factor (1.3) was multiplied by the average baking factor (0.42) to give 0.55. Alcohol/fermented/distilled fractions were assumed to equal the beer process study with no detects and was assigned a value of ½ the level of detection (LOD) (LOD = 0.01). [Processing Data and Tables by Registrant Given]

HED's Response: Again, HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

Section II D. Chlorpyrifos-methyl Occupational and Residential Exposure Chapter (EPA Attachment E).

Three typographical errors:

- Page 1, paragraph 4, line 1. ". . .risk for the all of" should read "risk for all of."
- Page 9, Table 2, footnote b, bullet 3. ". . .and-held duster" should read "hand-held duster."
- Page 12, Table 4. Heading under Dermal reads "Macximum." It should read "Maximum."

HED Response: The typographical errors noted for Pages 1, 9, and 12 in the Occupational and Residential Exposure Chapter are acknowledged, and will be corrected.

DAS: Item # 23. Section II D. (EPA Attachment E). "DAS believes the assessment of exposure to chlorpyrifos-methyl should be based on the use of NOELs established from human testing

studies. This would result in a NOEL of 0.1 mg/kg/day..."

HED Response: The NOEL of 0.1 mg/kg recommended by DAS is based on a human study. At present, the Agency is not using human studies for risk assessments.

B. Dow's Comments on Interpretation of Data, etc.

Section II A. 1. EPA's Hazard Assessment Section

DAS: Page 4, lines 3-4. Sentence is inaccurate. There is a scientifically valid study for each of the endpoints needed to make a Food Quality Protection Act (FQPA) reassessment for chlorpyrifos-methyl, although some of these studies may not meet current EPA guidelines.

HED Response: Contrary to the registrant's claim, the critical studies (developmental studies in rabbit and the reproductions study in rats) required for FQPA assessment are not technically valid due to numerous technical inadequacies, and are classified as unacceptable for regulatory purposes. The rabbit study, the dose levels tested were judged to be inadequate to assess developmental toxicity. Since no maternal toxicity was demonstrated at the highest dose tested (indicating that the dose selection was inadequate), the results of this study cannot be used to assess the relative susceptibility of infants and children. In the three-generation reproduction study in rats, only two dose levels were tested. *The purpose of the FQPA reassessment process is to assure that the toxicity data base meets current standards.*

DAS: Page 4, line 11. Sentence is inaccurate. There is a scientifically valid study for each of the endpoints needed to assess the acute toxicity of chlorpyrifos-methyl, although some of these studies may not meet current EPA guidelines.

HED Response: The acute toxicity studies are not scientifically valid and does not meet the Subdivision F Guideline requirements. Also, the purpose of the FQPA tolerance reassessment process is to assure that the toxicity data base meets current standards.

DAS: Page 4, lines 14-16. Sentence is inaccurate. There is a scientifically valid acute inhalation toxicity study (Hardy and Jackson, 1984, Accession No. 256616) and dermal sensitization study (Jones, 1985) with technical chlorpyrifos-methyl. These studies may not meet current guidelines, but are adequate to assess the inhalation toxicity and dermal sensitization potential of chlorpyrifos-methyl.

HED Response: The acute inhalation toxicity study indicated by DAS was conducted with a test material identified as "chlormercaptophen" in HED's files and not as chlorpyrifos methyl. The Pesticide Index was consulted to determine if the stated name is a synonym for chlorpyrifos methyl and this name was not listed. Therefore, results of this study are not

appropriate for use. DAS needs to verify that the test material was chlorpyrifos methyl and provide information on purity and lot number and verification that the synthesis method used is the same as for current production lots of chlorpyrifos methyl.

For the dermal sensitization study, DAS did not provide the appropriate reference number or other identification for a study that demonstrates that chlorpyrifos methyl is not a sensitizer. The studies in HED's files are with formulations or otherwise not studies considered acceptable with technical grade chlorpyrifos methyl.

DAS: Page 4, lines 22-24. Statement is inconsistent with EPA guideline 870.6100. The EPA has an acceptable subchronic hen study with chlorpyrifos-methyl which the Agency agrees is negative. The guideline indicates the subchronic hen study will resolve any uncertainty caused by equivocal results in the acute hen neurotoxicity study.

HED Response: The Agency will re-evaluate the results of these studies and the need for the repeat acute delayed neurotoxicity study.

DAS: Page 4, lines 32-34. Sentences are inaccurate and misleading. There is a three-generation reproductive study (MRID 00030757). In addition, there is a rabbit teratology study not cited in the "Chlorpyrifos-methyl: Toxicology Endpoint Selection: Report of the Hazard Identification Assessment Review Committee" document. These studies may not meet current EPA guidelines, but they are scientifically valid and adequate to show the dam is more sensitive to chlorpyrifos-methyl than the fetus and neonate.

HED Response: The three-generation reproduction study in rats is unacceptable and not upgradable because of several deficiencies which include: lack of purity, stability and homogeneity data; the use of only two dose levels, the lack of rationale for dose selection; and the lack of statistical analyses on reproductive and viability endpoints. The results of this study are inadequate to assess susceptibility of infants and children after pre-/postnatal exposure to chlorpyrifos methyl.

EPA's Determination of Susceptibility Section

DAS: Page 12, line 3 . The statement "the data base is incomplete" is inaccurate. A valid scientific study exists for each of the endpoints required for registration. Thus, the database is complete, although some of these studies may not meet current EPA guidelines.

HED Response: The toxicology data base is not complete. Data gaps exists for the acute and subchronic neurotoxicity studies which are required for all cholinesterase inhibiting chemicals. In the absence of these studies, the evaluation of the neurotoxic potential of chlorpyrifos-methyl could not be made. Additionally, the prenatal developmental toxicity study in rabbits and the three-generation reproduction study in rats are classified as unacceptable for regulatory purposes and are, therefore considered to be data gaps. Contrary

to the registrant's claim that these studies are technically valid, the Agency concluded that these studies have numerous technical inadequacies and did not follow good scientific procedures. FQPA clearly states that "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure be applied to infants and children to take into account pre-and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.." Therefore, under the mandate of FQPA, the toxicology data base is incomplete for chlorpyrifos-methyl.

The Agency makes its tolerance reassessment decisions based on the best data that are available. Where data are incomplete the Agency may compensate by using additional uncertainty factors or making reasonable health protective assumptions. This has long been Agency practice, and is reinforced by FQPA's emphasis on the importance of the use of uncertainty factors where data are incomplete.

DAS: Page 12, lines 4, 6. The term "unacceptable studies" is misleading. There is a scientifically valid study for each of the endpoints identified. Moreover, the request that the acute delayed neurotoxicity study in hens (series 81-7) be repeated (1999 EPA document on endpoint selections) is not consistent with the EPA guideline for conducting these studies. The document on endpoint selection states that "Due to the equivocal nature of the results of the available studies a repeat study with measurement of neurotoxic esterase (NTE) is required." However, the EPA guideline indicates that a subchronic delayed neurotoxicity study in hens is needed to address ambiguities in the acute delayed neurotoxicity study. The EPA has a subchronic delayed neurotoxicity study in hens with chlorpyrifos-methyl, which the EPA considers to be adequate, and which provides no evidence that chlorpyrifos-methyl causes delayed neurotoxicity.

HED Response: The Agency will re-evaluate the results of these studies and the need for the repeat acute delayed neurotoxicity study in hens.

EPA's Determination of Susceptibility Section

DAS: Page 12, lines 7, 8 . The acute (series 81-8) and subchronic (series 82-7) neurotoxicity studies are not required for registration, and DAS has never been given a DCI for these studies.

HED Response: The Agency considers these studies as critical for evaluation of the neurotoxicity and/or neuropathology for the organophosphates. In addition, neurotoxicity studies are required for assessment of neurotoxicity as per the FQPA requirements.

EPA's Toxicology Endpoint Selection Section (HIARC Report)

DAS: Page 13, Table 3. As noted elsewhere, the endpoint for both the acute and chronic reference dose (RfD) should be RBC cholinesterase inhibition in human volunteers. When this is done there is no need for an intraspecies uncertainty factor or an FQPA safety factor since valid

scientific data are available on the critical parameters and show infants and children are not more susceptible to chlorpyrifos-methyl.

HED Response: On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects on human subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be based on human studies until the Agency has in place an approach for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions. During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including chlorpyrifos-methyl, pursuant to the pilot process for public participation in risk assessment and risk management. All risk assessments used only animal endpoints. OPP expects to reevaluate this approach pursuant to the Agency's decisions about how to consider the ethical acceptability of human studies. Also, there are presently on-going efforts at EPA to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

B. Report of the Hazard Identification Assessment Review Committee (EPA Attachment A)

DAS: The two studies in which human volunteers were given chlorpyrifos-methyl need to be included and reviewed in this document (Chmiel et al., 1975, MRID 00030755, 00043239; Coulston et al., 1975, MRID 00030754, 00043238).

HED Response: On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects on human subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be based on human studies until the Agency has in place an approach for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions. During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including chlorpyrifos-methyl, pursuant to the pilot process for public participation in risk assessment and risk management. All risk assessments used only animal endpoints. OPP expects to reevaluate this approach pursuant to the Agency's decisions about how to consider

the ethical acceptability of human studies. Also, there are presently on-going efforts at EPA to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

EPA's Introduction Section

DAS: Page 3, lines 16-17. Document needs to explain why studies considered by the Agency as adequate to assess the RfD for chlorpyrifos-methyl in 1986 were considered inadequate in 1998.

HED Response: The two year dog study (conducted in 1974) used to establish the RfD in 1986 was re-reviewed in 1998. This re-review determined that this study is unacceptable for regulatory purposes because of the problems encountered in the evaluation of the primary toxicological effect (i.e., cholinesterase inhibition).

EPA's Acute Reference Dose Section

DAS: Page 4, lines 9-10. As discussed elsewhere, no interspecies or FQPA uncertainty factor is needed.

HED Response: DAS has implied that no interspecies or FQPA factor is needed since there are data from human studies that available for evaluation of the risk. However, as discussed earlier, human studies are not currently used for risk assessment purposes.

DAS: Page 5, lines 14-15. As discussed elsewhere, no interspecies or FQPA safety factor is needed.

HED Response: Currently human studies are not used for risk assessment purposes by the Agency.

EPA's Short-Term Dermal Section

DAS: Page 6, lines 7–8. Statement is inaccurate. Data are available from an acute dermal toxicity study, a dermal irritation study, and a guinea pig dermal sensitization study.

HED Response: Data from an acute dermal toxicity study are not used by HIARC for a dermal risk assessment because these data result from a single exposure that was designed to determine the LD_{50} for product labeling purposes and the endpoint is not appropriate for risk assessment.

DAS: Page 11, Acute Study (series 81-7, 1979 study). The EPA has sufficient information on chlorpyrifos-methyl to conclude it does not cause delayed neurotoxicity. The acute delayed neurotoxicity study may not meet the current EPA guidelines since it was conducted in 1979;

however, at that time, it was considered adequate for registration. Moreover, guideline 870.6100 for Acute and 28-Day Delayed Neurotoxicity of Organophosphate Substances states: "If the results of the acute study are completely negative, that is, there are no delayed behavioral or histopathological effects, and no significant NTE inhibition, the 28-day study is not required." The document goes on to state that if there are ambiguities in the acute delayed neurotoxicity study a 28-day study may be required to resolve these ambiguities. The Agency has an acceptable subchronic delayed neurotoxicity study for chlorpyrifos-methyl which they agreed indicates chlorpyrifos-methyl did not produce evidence of neurotoxicity. Based on the Agency's own guideline document, the results of the 28-day study should have resolved any uncertainty caused by equivocal results in the acute neurotoxicity study.

HED Response: The Agency will re-evaluate the results of these studies and the need for a repeat for the acute delayed neurotoxicity study in hens.

EPA's FQPA Considerations, Determination of Susceptibility Section

DAS: Page 13, lines 24, 26. Sentence is misleading. Scientifically valid studies exist for each of the endpoints needed to "make a determination of increased susceptibility to infants and children to chlorpyrifos-methyl." These studies addressed all the critical information needed for the endpoint of interest. In spite of the availability of the scientific information, the U.S. EPA classified these studies as "unacceptable" because they did not meet current EPA guidelines, and then did not consider these scientifically valid studies in its assessment.

HED Response: The toxicology data base is not complete. Data gaps exists for the acute and subchronic neurotoxicity studies which are required for all cholinesterase inhibiting chemicals. In the absence of these studies, the evaluation of the neurotoxic potential of chlorpyrifos-methyl could not be made. Additionally, the prenatal developmental toxicity study in rabbits and the three-generation reproduction study in rats are classified as unacceptable for regulatory purposes and are, therefore considered to be data gaps. Contrary to the registrant's claim that these studies are technically valid, the Agency concluded that these studies have numerous technical inadequacies and did not follow good scientific procedures. FQPA clearly states that "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure be applied to infants and children to take into account pre-and post-natal toxicity and <u>completeness of the data with respect to exposure and toxicity</u> to infants and children.." Therefore, under the mandate of FQPA, the toxicology data is incomplete for chlorpyrifos-methyl.

EPA's Hazard Characterization Section

DAS: Page 14, line 5. Sentence is misleading. Sentence needs to specify the U.S. EPA has chosen to base their risk assessment on either plasma and/or RBC cholinesterase inhibition. Most other regulatory bodies specifically state that "plasma cholinesterase is not an appropriate basis for risk assessment" and that "red blood cell cholinesterase inhibition is appropriate only

when the data are taken from human studies."

HED Response: Sentence is not considered misleading since the accompanying table indicates which species of cholinesterase was used for risk assessment determination.

DAS: Page 14, lines 8-10. Sentence is inaccurate. The U.S. EPA guidelines (acute and 28-day delayed neurotoxicity study of organophosphorus compounds, series 870.6100) indicate that negative results in the 28-day delayed neurotoxicity study should resolve any uncertainty caused by equivocal results in an acute neurotoxicity study.

HED Response: The Agency will re-evaluate the results of these studies and the need for a repeat for the acute delayed neurotoxicity study in hens.

DAS: Page 14, lines 14-16 (HIARC Report). Sentence is inaccurate and misleading. Change "Developmental toxicity assessment is considered incomplete because there is only a rat study but no acceptable rabbit (or second species) study and there is no acceptable multi-generation reproduction study" to read "Developmental toxicity assessment is considered incomplete because only the teratology study in the rat study meets current EPA guidelines. There was no teratology study in a second species or a multi-generation reproduction study that meet current EPA guidelines."

HED Response: This change is not needed.

EPA's Data Gaps Section

DAS: Page 14, line 24. Sentence is misleading. Change "there is currently no acceptable study for the listed study type" to read "there is no study which meets current EPA guidelines for the following endpoints."

HED Response: This change is not appropriate because the studies that are available are classified as unacceptable and not upgradable because they can not meet current guidelines and can not be used for regulatory purposes.

EPA's Acute Toxicity Section

DAS: Page 15, Table. Entries for acute inhalation (p 8) and dermal sensitization (p 9) are inaccurate and should read as indicated below because studies for both endpoints exist:

Guideline No.: and Study Type	MRID #	Results	Tox Category
81-3 (870.1300) Acute Inhalation		4 hr LC_{50} >0.67 mg/L highest attainable vapor conc.	II
81-6 (870.2500) Sensitization		Not sensitizing	NA

HED Response: The acute inhalation toxicity study indicated by DAS was conducted with a test material identified as "chlormercaptophen" in HED's files and not as chlorpyrifos methyl. The Pesticide Index was consulted to determine if the stated name is a synonym for chlorpyrifos methyl and this name was not listed. DAS needs to verify that the test material was chlorpyrifos methyl and provide information on purity and lot number and verification that the synthesis method used is the same as for current production lots of chlorpyrifos methyl.

EPA's Summary of Toxicologic Endpoint Selection Section

DAS: Page 16, Table. As noted elsewhere, the endpoint for both the acute and chronic RfD should be RBC cholinesterase inhibition in human volunteers. When this is done there is no need for an interspecies uncertainty factor or an FQPA safety factor since valid scientific data are available on the critical parameters and show infants and children are not more susceptible to chlorpyrifos-methyl. Acute and chronic RfDs listed in Table IX are not consistent with those listed on pages 4 and 5 of this document.

HED Response: As discussed previously, at present the Agency is not using human studies in risk assessments.

C. Chlorpyrifos-methyl Acute and Chronic Dietary Exposure Analyses (EPA Attachment D)

Revised Acute Dietary Exposure Estimates Using Processing Factors and the EPA's Acute Population Adjusted Dose (as Determined by DAS)

DAS: The inclusion of processing factors into the dietary assessment significantly decreased the estimated exposures to all population subgroups. Applying the processing factors broadly across grains and using the EPA's aPAD of 0.001 mg/kg/day gives the following:

Subgroup	95th Percentile Exposure	% aPAD	99th Percentile Exposure	% aPAD	99.9th Percentile Exposure	% aPAD
U.S. pop - all seasons:	0.000050	4.98	0.000142	14.24	0.000441	44.10
Non-nursing infants (<1 yr):	0.000055	5.53	0.000139	13.93	0.000422	42.22
Children (1-6 years):	0.000106	10.64	0.000288	28.79	0.000803	80.26
Females (13-19 yrs/np/nn):	0.000040	3.98	0.000115	11.48	0.000359	35.92
Males (13-19 years):	0.000050	5.05	0.000142	14.18	0.000411	41.08

No sub-population exceeded the aPAD at the upper percentiles when milling and cooking were considered. The inclusion of processing data reduced the estimated (acute) exposures to approximately 1/10 the estimate provided by the EPA.

HED's Response: Again, HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

3. Revised Acute Dietary Exposure Estimates Using Processing Factors and the RfD that Dow AgroSciences Considers Appropriate

DAS: Dow AgroSciences does not agree with the aPAD of 0.001. Adequate toxicological data exists to support a PAD of 0.01 mg/kg/day based on the equivalency of the human and animal data and a NOEL of 0.1 mg/kg/day. Use of the processing data and the reference dose Dow AgroSciences considers valid and the most appropriate results in the following acute dietary risk assessment:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
US population - all seasons	0.000063	0.63	0.000177	1.77	0.000441	4.41
Non-nursing infants (<1yr)	0.000086	0.86	0.000235	2.35	0.000422	4.22
Children (1-6 years)	0.000147	1.47	0.000384	3.84	0.000803	8.03
Females (13-19 y/np/nn	0.00005	0.5	0.000138	1.38	0.000359	3.59
Males (13-19 years)	0.000049	0.49	0.000133	1.33	0.000411	4.11

The most sensitive sub-population was children ages 1-6 years. Their estimated exposures of chlorpyrifos-methyl through food items was 0.000803 mg/kg/day, or approximately 8% of the reference dose.

HED's Response: Again, HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used. The aPAD for the Agency's Risk Assessment is based on the animal NOAEL.

4. Revised Chronic Dietary Exposure Estimates Using Processing Factors

DAS: Processing factors should also be applied to the chronic assessments, using averaged residue values from PDP. The estimates provided by the EPA and a chronic Population Adjusted Dose (cPAD) of 0.0001 mg/kg/day and the inappropriate use of processing data were:

Table 6. Chronic Dietary Exposure Results for Chlorpyrifos-methyl (as determined by the EPA)

Subgroups	**Chronic Total Exposure (mg/kg/day)**	**Chronic Risk (% cPAD)**
U.S. Population	0.000124	124%
Non-nursing infants (<1 year old)	0.000148	149%
Children (1-6 years old)	0.000288	288%
Females (13-19 years old/not pregnant/not nursing)	0.000108	108%
Males (13-19 years old)	0.000126	126%

Inclusion of processing factors into the EPA's assessment (cPAD = 0.0001 mg/kg/day) gave the following exposure estimates:

	Total Exposure	
Population Subgroup	**mg/kg /day**	**% of cPAD**
U.S. Population (total)	0.000017	16.7
Non-nursing infants	0.000017	17.4
Children 1-6 yrs	0.000043	43.0
Females 13-19(not preg or nursing)	0.000014	14.2
Males 13-19 yrs	0.000018	17.8

Once again the most sensitive sub-population was children ages 1-6 years; their maximum estimated exposure of 0.000043 mg/kg/day was below the cPAD proposed by the EPA.

HED's Response: Again, HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

DAS: Inclusion of processing factors and the reference dose Dow AgroSciences considers the most appropriate (RfD = 0.01 mg/kg/day) gave the following results:

	Total Exposure	
Population Subgroup	**mg/kg /day**	**% of cRfD**
U.S. Population (total)	0.000020	0.2%
Non-nursing infants	0.000025	0.2%
Children 1-6 yrs	0.000052	0.4%
Females 13-19(not preg or nursing)	0.000016	0.1%
Males 13-19 yrs	0.000020	0.2%

No sub-population had an estimated exposure of greater than 0.4% of the reference dose supported by Dow AgroSciences data.

HED's Response: HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for

those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used.

DAS: Page 7, last paragraph. "*...with the proposed uses of chlorethoxyfos are..*" should be changed to chlorpyrifos-methyl.

HED's Response: Dietary chapter, Page 7, last paragraph will be changed to read as, "with the proposed uses of chlorpyrifos-methyl are..".

DAS: In summary, the inclusion of processing factors as suggested in the EPA's own dietary risk assessment substantially decreases the estimated exposure to chlorpyrifos-methyl. The use of processing factors is justified by the demonstrated loss of residues as grain products are processed into refined food forms and further reduced by cooking.

HED's Response: HED acknowledges that residues of chlorpyrifos-methyl may be reduced when treated grains are processed. HED will evaluate the previously submitted processing studies as well as open literature studies to determine if additional processing factors (for those processed commodities listed in Table 1 of OPPTS 860.1000) beyond those already incorporated into HED's analyses can be used. Furthermore, HED will conduct a sensitivity analysis assuming zero residues for those commodities where ½ LOD was used (in accordance with TRAC policy paper #5, entitled "Assigning Values to Nondetected/Nonquantified Pesticide Residues in Human Health Dietary Exposure Assessments."