dpr Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

June 27, 2007

Tracy Perry, Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Mail Code: 7508P
Washington, DC 20460

Dear Dr. Perry:

Thank you for providing comments (January 31, 2007) to the Department's draft endosulfan risk characterization document (December 5, 2006). I have attached our responses to those comments. If you have any questions, please contact Dr. Joyce Gee at (916) 324-3465.

Sincerely,

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

CC: Joyce Gee, Senior Toxicologist
Tobi Jones, Assistant Director w/attachments
William Hazel, Branch Chief, US EPA w/attachments

APPENDIX F.

Endosulfan. Department of Pesticide Regulation Response to USEPA's Review of California' s Endosulfan Risk Characterization Document

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

DATE: May 25, 2007

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

FROM: Marilyn Silva, Ph.D., D.A.B.T., Toxicologist
Medical Toxicology Branch,
Department of Pesticide Regulation,
California Environmental Protection Agency

VIA: Joyce Gee, PhD., Senior Toxicologist,
Medical Toxicology Branch,
Department of Pesticide Regulation,
California Environmental Protection Agency

SUBJECT: **Endosulfan.** Department of Pesticide Regulation Response to USEPA's Review of California's Endosulfan Risk Characterization Document

This document "*Department of Pesticide Regulation Response to USEPA's Review of California' s Endosulfan Risk Characterization Document*" was generated to respond to the January 31, 2007 comments by USEPA on the draft risk assessment document of December 5, 2006.

Toxicology:

USEPA COMMENT: A comparison of the risk assessments produced by CDPR in 2006 and the Agency in 2002 and currently in 2007 reveals two major differences in hazard assessment. The first difference is the lack of the use of the DNT study (Gilmore, 2006; MRID 46968301) in risk assessment by CDPR. The Agency is currently planning to use the DNT study for the dermal short- and intermediate-term scenarios.

DPR RESPONSE: USEPA selected a dermal NOEL of 1.2 mg/kg/day for short term (1-30 days) and intermediate term (1-6 months) from "co-critical studies"; the rat reproduction study, based on decreased body weight (NOEL = 1.18 mg/kg/day, Edwards et al., 1984) and the DNT study, based on decreased pup weight (LOAEL = 3.74 mg/kg/day—no NOEL established according to their review; Gilmore, 2006). This information, obtained from Table 1 in the USEPA MEMORANDUM, was added to the DPR RCD. In contrast, DPR did not establish a subchronic dermal endpoint, since there were no FIFRA Guideline acceptable studies. Instead

DPR used the subchronic oral NOEL from the rat reproduction study (1.18 mg/kg/day; dermal penetration factor of 47.3%), since this was a lower NOEL than DPR identified for the DNT study and it was also an acceptable FIFRA Guideline study.

USEPA COMMENT: Furthermore, the established endpoints of the DNT study by CDPR differ from the identified endpoints by the Agency and are described briefly below.
DNT- (Gilmore et al., 2006; MRID 46968301)
The Agency recently received a developmental neurotoxicity study with endosulfan in Wistar rats in December 2006. The study was reviewed and the findings then presented to the Developmental Neurotoxicity Committee on January 10, 2007. Based on the review of the study by the DNT Committee, the Committee concluded that there was no NOAEL for pups. The LOAEL of 3.74 mg/kg/day was the lowest dose tested (LDT), based on decreased pup weight [PND 11] and weight gain [PND 4-11], with delayed preputial separation in males receiving the MDT. For dams, the NOAEL is 3.74 mg/kg/day. The LOAEL for dams is 10.8 mg/kg/day, based on decreased body weight, food consumption and food efficiency. This study is acceptable/guideline. The data evaluation record (DER) is currently being revised to reflect changes requested by the DNT Committee.

DPR RESPONSE: The maternal NOEL was less than 3.74 mg/kg/day, based upon lower mean body weights (5 - 6%) and lower food consumption (12%) at 3.74 mg/kg/day. While these decreases are marginal, the trend is dose-related and therefore DPR chose to note it as a treatment-related effect. The developmental NOEL was less than 3.74 mg/kg/day based upon the lower mean body weights (8% on post-partum day 11 only) of the offspring at 50 ppm. USEPA pointed out that there was also a decreased body weight gain in pups that was noted on post-partum day 11 only. It was therefore considered by DPR to be a transitional effect, but it will be noted in the DPR RCD

USEPA COMMENT: The second difference among the risk assessments is the critical study identified for the acute dietary assessment. CDPR used the developmental rabbit study (MRID 00094837) NOEL of 0.7 mg/kg/day, based on convulsions that were considered acute effects by CDPR. The Agency, however, established the salivation, convulsions, rapid breathing, and hyperactivity observed at 1.8 mg/kg/day to only occur on day 10 of gestation (not gestation day 6 as indicated by CDPR). Therefore the Agency relied on the acute neurotoxicity study (MRID 44403101) NOAEL of 1.5 mg/kg/day since convulsions were observed 8 hours after a single oral dose, thus making the endpoint more appropriate for the acute dietary assessment.

DPR RESPONSE: The acute oral effects observed in a developmental toxicity study performed in the rabbit, included maternal signs within the first day of treatment (in the absence of fetal effects). Various clinical signs were observed in dams/does, including abortions, phonation, coughing, cyanosis, convulsions/ thrashing, noisy/rapid breathing, hyperactivity, salivation, and nasal discharge and death (Nye, 1981). Clinical signs began on gestation day 6 (day 1 of treatment) at 1.8 mg/kg/day. In particular, hyperactivity was observed only at 1.8 mg/kg/day (no convulsions; thrashing, phonation, coughing, and cyanotic only; page 14 of the report by Nye, 1981). The NOEL for this study was 0.7 mg/kg/day. Similar effects were observed in 2 rangefinding studies also performed in pregnant New Zealand rabbits (Fung, 1981a, b). In these studies the LOELs were 1.0 mg/kg/day, based on neurotoxicity and deaths beginning day 8 of

gestation (treatment day 2). There were no major deficiencies in the rabbit developmental study and it provided the lowest acute oral NOEL. The other studies described above, showed that female rats are more sensitive to acute oral endosulfan treatment than are males and that pregnant female rabbits are more sensitive to endosulfan than are both non-pregnant and pregnant rats. Although the rabbit developmental study involved multiple dosing, rather than a single acute oral dose of endosulfan, the neurotoxic effects were seen on the first day of treatment and were therefore acute oral effects. Therefore, this study, with a critical NOEL of 0.7 mg/kg, was selected as the definitive study for evaluating acute dietary exposure and to calculate the MOE for potential acute single-day (non-inhalation) human exposures to endosulfan.

The changes by USEPA included in Table 1 of the MEMORANDUM: Comparison of Toxicological Data for Endosulfan, were incorporated into the revised DPR RCD for Endosulfan (see Table 1, below).

Table 1. Comparison of critical no-observed-effect levels (NOELs) and endpoints for risk characterization between the Department of Pesticide Regulation and U.S. Environmental Protection Agency

DPR NOELs and Endpoints for Risk Characterization		
Exposure/ Species	**NOEL**	**Endpoint**
Developmental, rabbit[a] Acute Oral	0.7 mg/kg/day UF = 100[a] FQPA SF = 10[b]	LOEL = 1.8 mg/kg; Abortions, death, convulsions, neurotoxic signs immediately after dosing, GD6 (Fung, 1981 a & b) RfD = 0.007 mg/kg/d[c]; aPAD = 0.0007 mg/kg/d[a]
21 day Inhalation, rat[b] For Acute Inhalation	0.194 mg/kg UF Interspecies= 10 UF Intraspecies= 10	Decreased body weight gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day (LOAEL)(Hollander et al., 1984) RfC = 0.0033 mg/m^3 (0.0002 ppm)[d]
Reproduction, rat[b] Subchronic Study	1.18 mg/kg/day UF Intra/Interspecies= 100	Increased kidney and liver weights; decreased food consumption and body weights (Edwards et al., 1984)
21 day Inhalation, rat[b] Short (1-30 d); Intermediate (1-6 mo)	0.194 mg/kg/day UF Interspecies= 10 UF Intraspecies= 10	Decreased body weight gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day (LOAEL)(Hollander et al., 1984) RfC = 0.0033 mg/m^3 (0.0002 ppm)[d]
1 year dog[c] Chronic dietary Study (all populations)	0.57 mg/kg/day UF = 100 FQPA SF = 10	LOEL = 2.09 mg/kg/d; Premature deaths, neurotoxicity; dec bw gain & food consumption (Brunk, 1989);RfD = 0.0057; cPAD = 0.00057 mg/kg/d
21 day Inhalation, rat[b] For Chronic Inhal[e]	0.0194 mg/kg/day UF Inter/Intraspecies= 100 UF Subchron - Chronic=10[e]	Dec body wt gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day (LOAEL)(Hollander et al., 1984) RfC = 0.00033 mg/m^3 (0.00002 ppm)[d] cPAD = 0.000033 mg/m^3
USEPA NOELs and Endpoints for Risk Characterization[g]		
Acute Neurotoxicity, rat[a] (Gen Pop + Infants/children)	1.5 mg/kg/day UF = 100 FQPA = N/A, under review	LOAEL = 3 mg/kg/day; Increased convulsions in females within 8 hrs after dosing (Bury, 1997) Acute RfD = 0.015 mg/kg/day; a PAD = N/A, currently under review
Dermal Short (1-30d) & Intermed (1-6 mo) Co-critical studies: 2-Gen Repro, rat[b] & DNT, rat	NOAEL = 1.2 mg/kg/day, 45% Dermal absorption Occup LOC[f] MOE = 100	2-Gen repro LOAEL = 6.2 mgkg/d (dec bwt; Edwards et al., 1984) DNT LOAEL = 3.74 (dec pup weights); NOAEL not established (Gilmore et al., 2006)
21d Dermal rat; Dermal Long Term (> 6 mos)	NOAEL = 12 mg/kg/d 45% Dermal absorption Occup LOC[f] MOE = 100	LOAEL = 27 mg/kg/day (Increased mortality in females); Ebert et al., 1985
21 day Inhalation, rat[b, g] Short (1-30 d); Intermediate (1-6 mos)	0.2 mg/kg/d (0.001 mg/L) MOE = 100 (100% absorption)	LOAEL = 0.002 mg/L (0.4 mg/kg/day);Decreased body weight gain & lymphocyte counts (M); increased creatinine (F) (Hollander et al., 1984)
104 week rat[c, g] Chronic (all populations)	0.6 mg/kg/day UF = 100 FQPA = N/A, under review	Decreased body weight gain, enlarged kidneys, increased progressive glomerulonephrosis; blood vessel aneurysms (Ruckman et al., 1989). Chronic RfD = 0.006 mg/kg/day; cPAD = N/A, currently under review

a - Acute RfD = acute NOEL ÷ UF 10x (interspecies) x UF 10x (intraspecies); Population Adjusted Dose (aPAD = RfD ÷10x FQPA safety factor)

b - Subchronic, seasonal (intermediate/short-term) exposure RfD= Subchronic NOEL ÷ UF (10 interspecies x 10 intraspecies)

c - Chronic RfD = Chronic NOEL ÷(UF 10 interspecies) x (UF 10 intraspecies)); Population Adjusted Dose (cPAD = RfD) 10xFQPA safety factor)

d - Human inhalation NOEL (mg/m^3) = animal inhalation NOEL (mg/kg/day) ÷ respiratory rate$_{human}$ (m^3/kg) NOTE: The respiratory rate used for humans was for children (0.59 m^3/kg) who are considered to be the highest risk group; RfC (mg/m^3) = human inhalation NOEL (mg/m^3) ÷(UF 10 interspecies x UF 10 intraspecies); RfC (ppm) = RfC (mg/m^3) x (M. Vol (@ 25°C) ÷(M.Wt. (406.9g)); Population Adjusted Dose (cPAD = RfD) 10x FQPA safety factor)

e - A 10x UF is added to the subchronic inhalation NOEL to extrapolate to obtain a chronic inhalation NOEL.

f – Occupational LOC = Level of Concern; MOE = Margin of Exposure

g – The USEPA considers endosulfan to be a Group E (evidence of non-carcinogenicity for humans) and they have not selected a chronic (long-term > 6 months) inhalation NOEL (USEPA, 2007)

Dietary Assessment

USEPA CONCERNS AND COMMENTS: HED has the following comments on the dietary portion of the CDPR endosulfan characterization document. It is important to note that the original CDPR dietary assessment is from 1998. There is an addendum dated September 2006 that addresses the need for a complete revision of the 1998 dietary assessment. A complete reassessment was not conducted. Comparisons will be made between the 1998 CDPR assessment (and addendum) and the 2002 HED dietary assessment. The 2002 HED dietary assessment is likely to change in the near future based upon review of additional submitted data.

HED does not usually present screening level assessments if a more refined assessment has been done. HED only presents the more refined assessment. The CDPR assessment includes data that has been refined (with percent crop treated and PDP monitoring data) as well as a general screening assessment assuming 100% crop treated and tolerance level residues.

Neither assessment included consumption data for drinking water.

The CDPR assessment discusses populations upon which HED does not normally base regulatory decisions on.

The CDPR assessment discusses acute exposures at the 95th percentile. HED typically bases regulatory decisions on the 99.9th percentile.

The CDPR dietary assessment from 1998 used the TAS, Inc EX™ acute and chronic dietary exposure software (TAS, 1996). The 2002 HED dietary exposure assessment used the DEEM™ dietary exposure model. The dietary modeling software program is important to determine if the recipes and age groupings are the same as those used by HED. In other words, an assessment done with a program other than DEEM cannot be directly compared to an assessment done with DEEM. The results could vary based upon this fact. Both HED and CDPR now use the DEEM-FCID™ modeling software. Also, the DEEM™ food recipe libraries may well differ from those used by the TAS, Inc EX™ software.

The TAS, Inc EX™ acute and chronic dietary exposure software analyzes acute exposure, seasonal exposure for California workers, chronic exposure (1 year), and lifetime exposure (oncogenic). Since DPR had no oncogenic exposure factor for endosulfan, a lifetime dietary exposure was not performed. HED conducts acute and chronic (lifetime - age 0 to 85 years) dietary exposure assessments.

The CDPR assessment and the most recent HED risk assessment completed (Endosulfan RED, 2002) both used the same Continuing Survey of Food Intake by Individuals (CSFII) consumption database from 1989-1992. There is a newer database that is currently in use by both HED and DPR (CSFII 1994-1996 and 1998). This newer consumption database will be used in the event the upcoming HED endosulfan risk assessment conducts quantitative dietary risk calculations.

The CDPR assessment used residue data from the following sources: DPR monitoring program (1993-1995), registrant field residue trials, USDA 1994 or 1996 PDP monitoring program, or

USDA 1995 FSIS residue monitoring program. A US EPA tolerance level was only used as the exposure value for sugarcane and its processed commodities. The 2002 HED assessment used a combination of data from PDP, FDA, and registrant field trials. HED typically uses the most recent 5 years of monitoring data and the assessments are supposed to be updated using anticipated residues every 5 years.

For the reasons listed in the draft document, HED agrees with the CDPR conclusion regarding the 2006 dietary addendum being sufficient when combined with the prior 1998 DPR dietary exposure assessment. With the nine tolerances canceled or proposed for cancellation by the registrant and 5 tolerances revoked by the Agency (72 uses decreased to 58), decreased maximum application rates for a number of commodities, along with the fact that the FQPA safety factor is likely to be reduced, it is highly unlikely that dietary risks will exceed the Agency's level of concern. This same rationale will likely be used in conducting the forthcoming 2007 HED dietary risk assessment.

DPR RESPONSE: The USEPA dietary exposure comments are part of the memo from Dr. D. Wilbur et al. to Dr. T. Perry dated January 31, 2007 (USEPA, 2007).

The memo did not contain any comments that require a DPR response. The dietary exposure section of the DPR draft endosulfan RCD is addressed on page 9 of the 16 page USEPA memo. Specifically, the memo agrees with the conclusion of the DPR RCD that the DPR dietary exposure addendum (dated September 29, 2006) combined with the 1998 DPR assessment are sufficient to address dietary exposure concerns. Therefore, an updated DPR dietary exposure assessment is unnecessary. DPR concurs with the U.S. EPA statement.

USEPA COMMENT: HED used an acute endpoint of 1.5 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10) and a chronic endpoint of 0.6 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10). CDPR used an acute endpoint of 0.7 mg/kg/day and a 0.57 mg/kg/day chronic endpoint. There is also mention of a NOEL of 0.25 mg/kg/day used as a chronic endpoint. This is referred to in Appendix A (original 1996 dietary assessment). [page 8 of 16 of Memorandum]

DPR RESPONSE: The NOEL for the chronic dog study mentioned in the Appendix A (original 1998 dietary assessment) was an error and was corrected to 0.57.

NOTE: A response to the comments on Occupational/Residential Assessment is being prepared by the Worker Health and Safety Branch as a separate document.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 31 January 2007

SUBJECT: **Endosulfan.** The Health Effects Division's Review of California's Endosulfan Risk Characterization Draft Document (dated 12/05/2006)

DP Number:	D335812	*MRID:* None	
PC Code:	079401		
40 CFR:	180.182	*Chemical Class:*	Organochlorine insecticide

FROM: Donald Wilbur, Chemist
Elissa Reaves, Ph.D., Toxicologist
Shanna Recore, Industrial Hygienist
Reregistration Branch II
Health Effects Division (7509P)

THRU: Al Nielsen, Branch Senior Scientist
William Hazel, Ph.D., Branch Chief
Reregistration Branch II
Health Effects Division (7509P)

TO: Tracy Perry, Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division (7508P)

The attached document entitled "*The Health Effects Division's Review of California's Endosulfan Risk Characterization Draft Document*" was generated to address the December 5, 2006 California Department of Pesticide Regulation (CDPR) endosulfan risk characterization document. The main focus of this memo is to discuss the differences between California's risk characterization draft document and the Agency's risk assessments for endosulfan (including the Reregistration Eligibility Decision (RED) which was completed in November of 2002 and the forthcoming 2007 risk assessment).

Health Effects Division's Review of California's Endosulfan Risk Characterization Document

I. Introduction

The following is HED's review of California's endosulfan risk characterization draft document dated December 5, 2006. The main focus of this review is to discuss the differences between California's risk characterization draft document and the EPA's 2002 RED and pending 2007 risk assessment. The major reason for the Agency's 2007 revision to the 2002 risk assessment is the completion and subsequent review by HED of a developmental neurotoxicity (DNT) study. Differences in the toxicological, dietary, and occupational portions of the risk assessments are discussed below.

II. Toxicology

Table 1 below highlights the studies and endpoints used in the CDPR 2006 risk assessment as compared to the Agency's 2002 and current 2007 assessment. It is noted that the Agency's endosulfan assessment is currently under revision and changes after this memorandum are possible. A comparison of the risk assessments produced by CDPR in 2006 and the Agency in 2002 and currently in 2007 reveals two major differences in hazard assessment. The first difference is the lack of the use of the DNT study (Gilmore, 2006; MRID 46968301) in risk assessment by CDPR. The Agency is currently planning to use the DNT study for the dermal short- and intermediate-term scenarios. Furthermore, the established endpoints of the DNT study by CDPR differ from the identified endpoints by the Agency and are described briefly below. The second difference among the risk assessments is the critical study identified for the acute dietary assessment. CDPR used the developmental rabbit study (MRID 00094837) NOEL of 0.7 mg/kg/day, based on convulsions which were considered acute effects by CDPR. The Agency, however, established the salivation, convulsions, rapid breathing, and hyperactivity observed at 1.8 mg/kg/day to only occur on day 10 of gestation (not gestation day 6 as indicated by CDPR). Therefore the Agency relied on the acute neurotoxicity study (MRID 44403101) NOAEL of 1.5 mg/kg/day since convulsions were observed 8 hours after a single oral dose, thus making the endpoint more appropriate for the acute dietary assessment.

DNT- (Gilmore et al., 2006; MRID 46968301)

The Agency recently received a developmental neurotoxicity study with endosulfan in wistar rats in December 2006. The study was reviewed and the findings then presented to the Developmental Neurotoxicity Committee on January 10, 2007. Based on the review of the study by the DNT Committee, the Committee concluded that there was no NOAEL for pups. The LOAEL of 3.74 mg/kg/day was the lowest dose tested (LDT), based on decreased pup weight [PND 11] and weight gain [PND 4-11], with delayed preputial separation in males receiving the MDT. For dams, the NOAEL is 3.74 mg/kg/day. The LOAEL for dams is 10.8 mg/kg/day, based on decreased body weight, food consumption

and food efficiency. This study is acceptable/guideline. The data evaluation record (DER) is currently being revised to reflect changes requested by the DNT Committee.

The 2006 assessment by CDPR indicated the DNT study (Gilmore et al., 2006) was reviewed and determined that there was no increase in neurotoxicity in rats receiving endosulfan treatment in diets during pre- and post-natal development. The maternal NOEL is < 3.74 mg/kg/day, based on lower mean body weights (5-6%) and lower food consumption (12%) at 3.74 mg/kg/day. The developmental NOEL is <3.74 mg/kg/day, based on lower mean body weights (8% on post-partum day 11 of offspring). The developmental neurotoxicity NOEL is 29.8 mg/kg/day, based on the lack of a neurologically-related effect noted in the offspring at the highest dose tested.

Table 1. Comparison of Toxicological Data for Endosulfan

Exposure Scenario		CDPR 2006	EPA 2002	EPA 2007
Acute Dietary *(general population including infants and children)*	*PoD, UF*	NOEL = 0.7 mg/kg/day UF = 100 FQPA=10	NOAEL = 1.5 mg/kg/day UF = 100 FQPA = 10x	NOAEL = 1.5 mg/kg/day UF = 100 FQPA = N/A, currently under review
	Level of Concern for Risk Assessment with UFs	**aRfD = 0.007** mg/kg/day **aPAD = 0.0007** mg/kg/day	**aRfD = 0.015** mg/kg/day **aPAD = 0.0015** mg/kg/day	**aRfD = 0.015** mg/kg/day **aPAD = N/A** mg/kg/day
	Critical Study and Endpoints	Developmental- Rabbit LOEL= 1.8 mg/kg/day, based on abortions, death, convulsions, neurotoxicity; signs began on GD6	Acute Neurotoxicity-rats LOAEL= 3 mg/kg/day; based on increased incidence of convulsions seen in female rats within 8 hours after dosing.	Acute Neurotoxicity-rats LOAEL= 3 mg/kg/day; based on increased incidence of convulsions seen in female rats within 8 hours after dosing.
	Reference	Nye, 1981	MRID 44403101	MRID 44403101
Chronic Dietary *(all populations)*	*PoD, UF*	NOAEL = 0.57 mg/kg/day UF = 100 FQPA = 10	NOAEL = 0.6 mg/kg/day UF = 100 FQPA = 10x	NOAEL = 0.6 mg/kg/day UF = 100 FQPA = N/A, currently under review

Exposure Scenario		CDPR 2006	EPA 2002	EPA 2007
	Level of Concern for Risk Assessment with UFs	**cRfD = 0.0057** mg/kg/day **cPAD = 0.00057** mg/kg/day	**cRfD = 0.006** mg/kg/day **cPAD = 0.0006** mg/kg/day	**cRfD = 0.006** mg/kg/day **cPAD = N/A** mg/kg/day
	Critical Study and Endpoints	Chronic dog (capsule)- LOEL= 2.09 mg/kg/day, based on premature termination, neurotoxic effects, decreased body weight gain and food consumption	Chronic/Cancer rats- LOAEL = 2.9 mg/kg/day, based on reduced body weight gain, increased incidences of marked progressive glomerulonephrosis & blood vessel aneurysms in male rats.	Chronic/Cancer rats- LOAEL = 2.9 mg/kg/day, based on reduced body weight gain, increased incidences of marked progressive glomerulonephrosis & blood vessel aneurysms in male rats.
	Reference	Brunk, 1989	MRID 41099502	MRID 41099502
Dermal *Short (1-30 days) and Intermediate-term (1-6 mos)*	*PoD, UF*	Seasonal (1 week to 1 year) 45% dermal absorption (Craine, 1988)	NOAEL = 12 mg/kg/day 45% absorption	NOAEL = 1.2 mg/kg/day 45% dermal absorption
	Level of Concern (LOC) and Margins of Exposure (MOE)		Occupational LOC MOE = 100	Occupational LOC MOE = 100

Exposure Scenario		CDPR 2006	EPA 2002	EPA 2007
	Critical Study and Endpoints		*21-Day Dermal-Rat LOAEL= 27 mg/kg/day, based on mortality in females*	*Co-critical studies: 2-Gen Reproductive toxicity – rat LOAEL = 6.2, based on decreased body weight DNT- rat: LOAEL = 3.74, based on decreased pup weight; NOAEL not established.*
	Reference		MRID 00146841/00147744 MRID 00146841	MRID 00148264 MRID 46968301
Dermal *Long-term (> 6 months)*	*PoD, UF*		NOAEL = 12 mg/kg/day 45% absorption	NOAEL = 12 mg/kg/day 45% absorption
	Level of Concern (LOC) and absorption rate		Occupational LOC MOE = 100	Occupational LOC MOE = 100
	Critical Study and Endpoints		21-Day Dermal-Rat LOAEL= 27 mg/kg/day, based on mortality in females	21-Day Dermal-Rat LOAEL= 27 mg/kg/day, based on mortality in females
	Reference		MRID 00146841/00147744 MRID 00146841	MRID 00146841/00147744 MRID 00146841
Inhalation *Short (1-30 days) and*	*PoD, UF*		NOAEL = 0.2 (0.001 mg/L)	NOAEL = 0.2 (0.001 mg/L)

Exposure Scenario		CDPR 2006	EPA 2002	EPA 2007
Intermediate term (1 – 6 months)	*Level of Concern (LOC) and absorption rate*		MOE = 100 100% absorption	MOE = 100 100% absorption
	Critical Study and Endpoints		21-Day inhalation –rats LOAEL= 0.002 mg/L, based on ↓ body weight gains, ↓ leukocyte counts (M), and ↑ creatinine values (F); 0.4 mg/kg/day	21-Day inhalation –rats LOAEL= 0.002 mg/L, based on ↓ body weight gains, ↓ leukocyte counts (M), and ↑ creatinine values (F); 0.4 mg/kg/day
	Reference		MRID 00147183 MRID 41667501	MRID 00147183 MRID 41667501
Inhalation *Long-term (> 6 months)*	*PoD, UF*		None Established	None Established
	Level of Concern (LOC) and absorption rate			
	Critical Study and Endpoints			
	Reference			
Cancer	*Classification*	Not oncogenic Not genotoxic	Group E- Evidence of non-carcinogenicity for humans	Group E- Evidence of non-carcinogenicity for humans
	Statistical Analysis	none	Q1* not calculated	Q1* not calculated

III. Dietary Assessment

HED has the following comments on the dietary portion of the CDPR endosulfan characterization document. It is important to note that the original CDPR dietary assessment is from 1998. There is an addendum dated September 2006 that addresses the need for a complete revision of the 1998 dietary assessment. A complete reassessment was not conducted. Comparisons will be made between the 1998 CDPR assessment (and addendum) and the 2002 HED dietary assessment. The 2002 HED dietary assessment is likely to change in the near future based upon review of additional submitted data.

- HED does not usually present screening level assessments if a more refined assessment has been done. HED only presents the more refined assessment. The CDPR assessment includes data that has been refined (with percent crop treated and PDP monitoring data) as well as a general screening assessment assuming 100% crop treated and tolerance level residues.

- HED used an acute endpoint of 1.5 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10) and a chronic endpoint of 0.6 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10). CDPR used an acute endpoint of 0.7 mg/kg/day and a 0.57 mg/kg/day chronic endpoint. There is also mention of a NOEL of 0.25 mg/kg/day used as a chronic endpoint. This is referred to in Appendix A (original 1996 dietary assessment).

- Neither assessment included consumption data for drinking water.

- The CDPR assessment discusses populations upon which HED does not normally base regulatory decisions on.

- The CDPR assessment discusses acute exposures at the 95th percentile. HED typically bases regulatory decisions on the 99.9th percentile.

- The CDPR dietary assessment from 1998 used the TAS, Inc EX™ acute and chronic dietary exposure software (TAS, 1996). The 2002 HED dietary exposure assessment used the DEEM™ dietary exposure model. The dietary modeling software program is important to determine if the recipes and age groupings are the same as those used by HED. In other words, an assessment done with a program other than DEEM cannot be directly compared to an assessment done with DEEM. The results could vary based upon this fact. Both HED and CDPR now use the DEEM-FCID™ modeling software. Also, the DEEM™ food recipe libraries may well differ from those used by the TAS, Inc EX™ software.

- The TAS, Inc EX™ acute and chronic dietary exposure software analyzes acute exposure, seasonal exposure for California workers, chronic exposure (1 year), and lifetime exposure (oncogenic). Since DPR had no oncogenic exposure factor for endosulfan, a lifetime dietary exposure was not performed. HED conducts acute and chronic (lifetime - age 0 to 85 years) dietary exposure assessments.

- The CDPR assessment and the most recent HED risk assessment completed (Endosulfan RED, 2002) both used the same Continuing Survey of Food Intake by Individuals (CSFII) consumption database from 1989-1992. There is a newer database that is currently in use by both HED and DPR (CSFII 1994-1996 and 1998). This newer consumption database will be used in the event the upcoming HED endosulfan risk assessment conducts quantitative dietary risk calculations.

- The CDPR assessment used residue data from the following sources: DPR monitoring program (1993-1995), registrant field residue trials, USDA 1994 or 1996 PDP monitoring program, or USDA 1995 FSIS residue monitoring program. A US EPA tolerance level was only used as the exposure value for sugarcane and its processed commodities. The 2002 HED assessment used a combination of data from PDP, FDA, and registrant field trials. HED typically uses the most recent 5 years of monitoring data and the assessments are supposed to be updated using anticipated residues every 5 years.

- For the reasons listed in the draft document, HED agrees with the CDPR conclusion regarding the 2006 dietary addendum being sufficient when combined with the prior 1998 DPR dietary exposure assessment. With the nine tolerances canceled or proposed for cancellation by the registrant and 5 tolerances revoked by the Agency (72 uses decreased to 58), decreased maximum application rates for a number of commodities, along with the fact that the FQPA safety factor is likely to be reduced, it is highly unlikely that dietary risks will exceed the Agency's level of concern. This same rationale will likely be used in conducting the forthcoming 2007 HED dietary risk assessment.

IV. Occupational/Residential Assessment

HED has the following comments on the Occupational and Residential endosulfan characterization document. Tables 2 and 3 below highlight the differences in occupational handler exposure parameters and occupational postapplication exposure parameters, respectively, used in the CDPR 2006 risk assessment as compared to the Agency's 2007 forthcoming risk assessment. Some differences include:

- The duration measured- CDPR measured short-term (1-7 days), seasonal (1 week to 1 year), and annual. HED measured short-term (1-30 days), and intermediate-term (1-6 months);
- CDPR uses PHED, but adjusts the values. For short-term exposure, CDPR applies an upper confidence limit factor on the 95th percentile. The UCL multiplier is 5 for replicates of ≥20 and is 4 for replicates <20. For seasonal and annual exposure, CDPR applies an upper confidence limit factor to the arithmetic mean. The UCL multiplier is 1 if the replicates are >15. HED uses central tendency estimates and does not adjust PHED values;
- CDPR assessed the worse-case (highest transfer coefficient) for major crop groupings and HED assessed all crops and all transfer coefficients applicable to each crop;
- CDPR assessed public exposure to ambient air and to bystanders estimating the concentration of endosulfan in the air and uptake of endosulfan from the air. HED typically does not assess this exposure scenario unless specifically triggered by physical properties, use pattern, and/or incident data; and
- CDPR assessed swimmer exposure using the Swimmodel. HED does not assess this exposure scenario unless a pesticide is directly applied to a body of water or swimming pool.

Table 2. Comparison of Occupational Handler Data for Endosulfan

OCCUPATONAL HANDLER EXPOSURE DATA	CDPR ASSESSMENT – 2006	HED ASSESSMENT
Dermal absorption	47.3%	45%
Body Weight	70 kg	60 kg for dermal; 70 kg for inhalation
Duration Assessed	Short-term, Seasonal, Annual	Short- and Intermediate-Term
Unit Exposure Value Source	PHED, except: • Carbaryl handler study for airblast application • Rags-E for dermal and Swimodel for inhalation for dip application	PHED plus: • ORETF for handgun, and low-pressure handwand scenarios • Carbaryl for airblast application • Malathion for closed system mixing/loading to support aerial application
PHED Unit Exposure Value Adjustments	Adjusts PHED values: • Short-term applies an upper confidence limit factor on the 95th percentile – the UCL multiplier is 5 for replicates ≥20 and the UCL is 4 for replicates < 20 • Seasonal and Annual applies an upper confidence limit factor to the arithmetic mean – the multiplier is 1 if the replicates are > 15	Does not adjust PHED values – uses central tendency estimates
Airblast (Carbaryl) Unit Exposure Value Adjustments	Adjusts carbaryl airblast unit exposures as described for PHED adjustments above	Uses geometric mean unit exposure values from the carbaryl airblast study
Mixing/Loading Liquids	Assumes closed system (CA requirement) plus baseline attire, chemical-resistant gloves, chemical-resistant apron, and respirator	Assesses baseline attire through engineering controls. As per the WPS, assumes baseline attire, chemical-resistant gloves, and chemical-resistant apron (but no respirator) when closed mix/load systems are used
Mixing/Loading Wettable Powder	Assesses both wettable powder and water-soluble packaging scenarios plus baseline attire, chemical-resistant gloves, chemical-resistant apron, and respirator	Assesses wettable powder withbaseline attire and the addition of PPE, including gloves, double layer, and respirator. As per the WPS, applicators using wettable powders in water-soluble packaging are assessed with baseline attire, chemical-resistant gloves, and chemical-resistant apron (but no respirator).

OCCUPATONAL HANDLER EXPOSURE DATA	CDPR ASSESSMENT 2006	HED ASSESSMENT
Aerial Application	Assesses open cockpit with baseline attire plus respirator	Only assesses enclosed cockpit with baseline attire.
Groundboom Application	Assesses open cab with baseline attire plus gloves plus respirator	Assesses open and enclosed cab and assesses baseline attire and addition of PPE, including gloves, double layer, and respirator. As per the WPS, applicators using enclosed cabs are assessed with baseline attire.
Airblast Application	Uses carbaryl-specific data for open cab with baseline attire, gloves, chemical-resistant headgear, and respirator	Uses PHED and carbaryl-specific data. For PHED: assesses open and enclosed cab and assesses baseline attire and addition of PPE, including gloves, double layer, and respirator. As per the WPS, applicators using enclosed cabs are assessed with baseline attire. For carbaryl, assumes same attire as CDPR.
Flaggers	Assumes baseline attire plus gloves	Assesses open and enclosed cab and assesses baseline attire and addition of PPE, including gloves, double layer, and respirator. As per the WPS, applicators using enclosed cabs are assessed with baseline attire.
Mixer/Loader/Applicators (backpack, low-pressure handwand, high-pressure handwand and handgun applications)	Assume baseline attire plus gloves plus respirator	Assesses baseline attire and addition of PPE, including gloves, double layer, and respirator.
Mixer/Loader/Applicators (dip applications)	Assumes closed system for mixing/loading and assumes all handlers wearing baseline attire plus gloves plus respirator. Amount handled per day is not specified	Assesses open-system mixing/loading with baseline attire and addition of PPE, including gloves, double layer, and respirator. As per the WPS, assesses closed-system mixing/loading with baseline attire plus gloves and apron. No data for applying dips. Assumes 100 gallon/day.
Worse-Case Scenario Selection: Aerial	• Max application rate of 2.5 lb ai/A (for tree nuts) and 350 acres treated per day	• High acreage: max application rate of 1.5 lb ai/A (for cotton and sorghum) and 1200 acres treated per day; • Typical acreage: max current application rate of 3 lb ai/A (tree fruit and nuts) and max proposed application rate of 2.5 lb ai/A (tree fruit) and 350 acres

OCCUPATIONAL HANDLER EXPOSURE DATA	CDPR ASSESSMENT – 2006	HED ASSESSMENT
		treated per day
Worse-Case Scenario Selection: Groundboom	• Max application rate of 2.0 lb ai/A (strawberry, pineapple, and crucifer) and 80 acres treated per day	• High acreage: max application rate of 1.5 lb ai/A (for cotton and sorghum) and 1200 acres treated per day; • Typical acreage: max current application rate of 2.0 lb ai/A (same as CA plus vegetables grown for seed) and 80 acres treated per day
Worse-Case Scenario Selection: Airblast	Max application rate of 2.5 lb ai/A (tree nuts) and 40 acres treated per day	Max current application rate of 3 lb ai/A (tree fruit and nuts) and max proposed application rate of 2.5 lb ai/A (tree fruit) and 40 acres treated per day
Worse-Case Scenario Selection: Backpack and Low-Pressure Handwand	Max application rate of 0.01 lb ai/gal (macadamia nuts) and 40 gallons per day	Max application rate of 0.025 lb ai/gal (postharvest bark treatment to apricots, nectarines, peaches, SE States only) and 40 gallons per day
Worse-Case Scenario Selection: Handgun and High-Pressure Handwand	Max application rate of 0.01 lb ai/gal (macadamia nuts) and 1000 gallons per day (does not assess handgun)	Max application rate of 0.025 lb ai/gal (postharvest bark treatment to apricots, nectarines, peaches, SE States only) and 1000 gallons per day
Worse-Case Scenario Selection: Dip	Max application rate of 0.05 lb ai/gal (nursery stock dip) and no gallons per day given	Max application rate of 0.05 lb ai/gal (nursery stock dip) and 100 gallons per day

Table 3. Comparison of Postapplication Exposure Data for Endosulfan

OCCUPATIONAL POSTAPPLICATION EXPOSURE DATA	CDPR ASSESSMENT – 2006	HED ASSESSMENT
Dermal absorption	47.3%	45%
Body Weight	70 kg	60 kg for dermal; 70 kg for inhalation
Duration Assessed	Short-term, Seasonal, Annual	Short- and Intermediate-Term
Short-Term Assumptions	Assumes entry after 2-day REI expires for all activities, except harvesting; Assumes entry after PHI for harvesting	Assesses all days following application (starting 12 hours after application) until MOE is 100 or greater; Does not consider PHI in calculations, since these are based on dietary considerations and can change without affecting the REI
Personal Protective Equipment	No PPE after REI expires	No PPE after REI expires
Exposure Route Assessed	Dermal only	Dermal only
DFR Data Used	Used endosulfan-specific DFR data from grape, lettuce, melons, and peaches, but doesn't state which DFR data were used to represent which crops	Used endosulfan-specific DFR data from grape, lettuce, melons, and peaches
Crop Scenarios Assessed	Assesses worse-case (highest transfer coefficient) for major crop groupings	Assesses all crops and all transfer coefficients applicable to each crop
Scenario: Almond, Thinning	TC of 1500 cm^2/hour	Worse-case TC of 2500 cm^2/hour (represents hand harvesting, hand pruning)
Scenario: Broccoli, Hand Harvesting	TC of 5000 cm^2/hour	Worse-case TC of 5000 cm^2/hour (represents hand harvesting, irrigating, hand pruning)
Scenario: Broccoli, Scouting	TC of 4,000 cm^2/hour	Worse-case TC of 4,000 cm^2/hour (represents scouting)
Scenario: Citrus, Thinning	TC of 3,000 cm^2/hour	Worse-case TC of 400 cm^2/hour (represents all tasks – nonbearing citrus only)
Scenario: Sweet Corn, Hand Harvesting	TC of 17,000 cm^2/hour	Worse-case TC of 17,000 cm^2/hour (represents detasselling, hand harvesting)
Scenario: Cotton, Scouting	TC of 2,000 cm^2/hour	Worse-case TC of 2,500 cm^2/hour (represents hand harvesting; TC of 1,500 cm^2/hour (represents irrigating, scouting, hand weeding)
Scenario: Cucumber, Hand Harvesting	TC of 2,500 cm^2/hour	Worse-case TC of 2,500 cm^2/hour (represents hand harvesting, hand pruning, thinning)

OCCUPATIONAL POSTAPPLICATION EXPOSURE DATA	CDPR ASSESSMENT – 2006	HED ASSESSMENT
Scenario: Grape, Cane Turning	TC of 10,000 cm^2/hour	Worse-case TC of 10,000 cm^2/hour (represents girdling, cane turning, tying)
Scenario: Lettuce, Scouting	TC 1,500 of cm^2/hour	Worse-case TC 2,500 of cm^2/hour (represents Hand harvesting); TC 1,500 of cm^2/hour (represents scouting and irrigating)
Scenario: Ornamental Plants, Hand Harvesting	TC of 400 cm^2/hour	Worse-case TC of 400 cm^2/hour (represents all tasks, except harvesting flowers or foliage grown for cutting)
Scenario: Ornamental Cut Flowers, Hand Harvesting	TC of 7,000 cm^2/hour	Worse-case TC of 5,100 cm^2/hour (represents harvesting flowers or foliage grown for cutting – short-term endpoint)
Scenario: Peach, Thinning	TC of 3,000 cm^2/hour	Worse-case TC of 3,000 cm^2/hour (represents peach thinning)
Scenario: Potato, Scouting	TC of 1,500 cm^2/hour	Worse-case TC of 1,500 cm^2/hour (represents irrigating, scouting)
Scenario: Strawberry, Hand Harvesting	TC of 1,500 cm^2/hour	Worse-case TC of 1,500 cm^2/hour (represents hand harvesting, hand pruning, pinching, training)
Scenario: Tomato, Hand Harvesting	TC of 1,000 cm^2/hour	Worse-case TC of 1,000 cm^2/hour (represents (hand harvesting, hand pruning, staking thinning, training, tying)
Scenario: Public Exposure to Ambient Air and to Bystanders	Estimated concentration of endosulfan in air and uptake of endosulfan from air	Not assessed
Scenario: Swimmer Exposure	Estimated swimmer exposure using the Swimmodel	Not assessed

References

1. DP Barcode: D272431
   Subject: Endosulfan: HED Risk Assessment for the Endosulfan Reregistration Eligibility Decision (RED) Document.
   From: D. Locke
   To: R. Dumas
   Dated: 01/31/2001
   MRID(s): None

2. DP Barcode: D327215 *[DRAFT]*
   Subject: A Developmental Neurotoxicity Study with Technical Grade Endosulfan in Wistar Rats. Project Number: 201563
   From: J. Facey
   To: N/A
   Dated: January 2007 *[DRAFT]*
   MRID(s): 46968301

3. DP Barcode: D281201
   Subject: Endosulfan. Anticipated Residues, and Revised Acute and Chronic Dietary Exposure Analysis.
   From: S. Kinard
   To: D. Locke
   Dated: 02/28/2002
   MRID(s): None

4. DP Barcode: D327222 *[DRAFT]*
   Subject: Endosulfan: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document.
   From: S. Recore
   To: T. Perry
   Dated: February 2007 *[DRAFT]*
   MRID(s): None