

Appendix M. Health Effects Division Effects Table for Endosulfan



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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 13 November 2007

SUBJECT: **Endosulfan.** The Health Effects Division's Addendum and Update to the 2002 Risk Assessment.

<i>DP Number:</i>	D345935	<i>MRID:</i> None	
<i>PC Code:</i>	079401		
<i>40 CFR:</i>	180.182	<i>Chemical Class:</i>	Organochlorine insecticide

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This document updates the 2002 Health Effects Division (HED) Risk Assessment (D. Locke, D250471, 05/30/2002) that was used to prepare the 2002 Reregistration Eligibility Decision (RED) document for endosulfan. This addendum focuses on the changes in HED's risk assessment based on the review of a recently submitted developmental neurotoxicity (DNT) study.

I. Executive Summary

The Agency completed the Reregistration Eligibility Decision (RED) document for endosulfan in November 2002 based upon the HED risk assessment completed in May 2002 (D. Locke, D250471, 05/30/2002). Since the completion of the RED in 2002, the Agency has received and reviewed a developmental neurotoxicity study (DNT) (Gilmore et al, 2006; MRID 46968301) (D. Anderson and J. Facey, D327215, 03/15/2007). Based on the toxicological effects observed in the DNT, endpoints for risk assessment were re-evaluated for endosulfan (E. Reaves, D338576, 04/02/2007). After reviewing the DNT and all other available data, HED has concluded that:

- The 10X FQPA safety factor could be reduced from 10X to 1X while still being protective of children's health.
- In order to effectively protect the most sensitive population (female workers) from endosulfan, the DNT was deemed to be the most appropriate study for short and intermediate term dermal exposure (LOAEL = 3.7 mg/kg/day).
- All other endpoints established for endosulfan remain unchanged from the 2002 HED assessment.

An abbreviated summary of the changes that these conclusions have on the HED risk assessment will be discussed in the following sections. For the full details of each exposure assessment, please refer to the individual exposure assessment chapters listed in the reference section.

Based on the reduced FQPA safety factor of 10X to 1X and use of the same input files as in the 2002 dietary assessment, the combined dietary exposure to endosulfan residues (food and drinking water) **does not exceed** the Agency's level of concern (>100% of the PAD) for chronic or acute exposures.

Potential areas of environmental justice concerns, to the extent possible, were considered in this document, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>). Since endosulfan has routinely been detected in arctic regions and the Indigenous Peoples of the arctic region of the U.S. (Alaska) rely heavily on subsistence diets (i.e. - fish) as their food source, it is appropriate for the Agency to consider dietary risk and exposure to this specific population subgroup from the worldwide use of endosulfan. Since no specific data are available for residues of endosulfan in/on commodities consumed in subsistence diets, the Agency has concerns for dietary exposure of indigenous populations to endosulfan based upon its persistence and potential for bioaccumulation.

With the revised dermal endpoint and level of concern, many of the occupational handler scenarios **exceed HED's level of concern** even with maximum personal protective equipment or engineering controls. In addition, for many of the occupational postapplication scenarios, the restricted-entry interval (REI) would be **several days longer** than the REIs established in the 2002 RED.

II. 2007 Hazard Assessment

Table 1 below highlights the studies and endpoints used in the Agency's 2002 endosulfan risk assessment and the current 2007 addendum. The Agency has re-evaluated the toxicological endpoints for endosulfan (E. Reaves, D338576, 04/02/2007) based upon recently submitted data. This memo outlines the rationale and characterization for endpoint selection for the endosulfan risk assessment following the review of a developmental neurotoxicity study (D. Anderson and J. Facey, D327215, 03/15/2007).

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

The Agency recently received and reviewed a developmental neurotoxicity study with endosulfan in wistar rats in December 2006 (D. Anderson and J. Facey, D327215, 03/15/2007). The study findings were presented to the Developmental Neurotoxicity Committee (DNT) on January 10, 2007. Based on the review of the study by the DNT Committee, the Committee concluded that there was no NOAEL (No Observed Adverse Effect Level) for pups. The LOAEL (Lowest Observed Adverse Effect Level) 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 maximum dose tested (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.

FQPA Safety Factor

The FQPA factor for endosulfan has changed over the past few years mainly due to database uncertainties. In November 1998, the FQPA Committee recommended a 3X factor due to the lack of a developmental neurotoxicity study. The 5/30/2002 risk assessment, however, retained the 10x FQPA factor due to database uncertainties. These database uncertainties included: 1) lack of subchronic and developmental neurotoxicity studies; 2) concerns for effects on sperm parameters reported in the literature; 3) the lack of evaluation of sperm parameters in guideline studies; 4) testicular lesions observed in the chronic rat study; and 5) increased pituitary and uterine weight in the two-generation reproduction study. Since the 5/30/2002 evaluation, a subchronic neurotoxicity study and a developmental neurotoxicity study have been submitted and reviewed by the Agency. Therefore, the FQPA factor was again re-evaluated and is discussed in the endosulfan endpoint memo (E. Reaves, D338576, 04/02/2007). This endpoint memo describes the residual uncertainties from the 5/30/2002 risk assessment and outlines how recent neurotoxicity data and published literature demonstrate that the uncertainties associated with the previous FQPA evaluation have been addressed. Therefore, it was recommended that the FQPA factor be reduced (i.e., 1X) since there were no residual uncertainties for pre and/or post-natal toxicity.

Dermal Exposure (Short-& Intermediate Term)

Previously, two available 21-day dermal toxicity rat studies were the basis of quantifying dermal risk. The dermal NOAEL was 12 mg/kg/day with a LOAEL of 48 mg/kg/day based on mortality. However, the results of the recently submitted DNT shows concern for offspring toxicity (decreased pre-weaning body weight) which is not evaluated in the

21-day dermal study (conducted in adult animals only). Additionally, the DNT was examined to address the concern for changes in the uterine and pituitary weights that were seen in adults at the highest dose only (6.2 mg/kg/day) in the two-generation reproduction study. The use of an offspring endpoint from the DNT study (LOAEL = 3.7 mg/kg/day) is the most appropriate endpoint in order to be protective of the most sensitive population (female workers). This decision is supported by the pup weight decrements being observed only during lactation (i.e., the pup body weights were not affected at birth AND the pups recovered after post-weaning (PND 22)) and therefore are likely due to nursing. Furthermore, the 2-generation reproduction study (MRID 00148264) noted a similar effect (decrease litter weight) during the lactation to weaning period in both matings in the F0 generation, which was significant at the high dose (6.18 mg/kg) level in the first mating and at the mid (1.23 mg/kg) and high dose (6.18 mg/kg) levels in the second mating. Since a NOAEL was not established in the DNT, a LOAEL to NOAEL factor is necessary for the dermal assessment. Based on the degree of pup weight loss in the DNT and pup weight loss in the 2-generation reproduction study, a 3X is most appropriate. The dermal absorption factor of 45% remains consistent with the 2002 assessment.

Inhalation Exposure (Short-& Intermediate Term)

No changes have been made to the inhalation endpoint and assessment since the 2002 risk assessment.

Published Literature

A 2007 literature study concerning autism spectrum disorder and pesticide applications in southern California (Roberts et al., 2007) also was reviewed by HED (C. Christensen, D342660, 10/18/07). Although this study attempts to correlate pesticide application with the development of autism spectrum disorder, the study failed to provide data that is useful in the quantification of risk to endosulfan.

Table 1. Comparison of Toxicological Data for Endosulfan

Exposure Scenario		EPA 2002	EPA 2007
Acute Dietary (general population including infants and children)	<i>PoD, UF</i>	NOAEL = 1.5 mg/kg/day UF = 100 FQPA = 10x	NOAEL = 1.5 mg/kg/day UF = 100 FQPA = 1x
	<i>Level of Concern for Risk Assessment with UFs</i>	aRfD = 0.015 mg/kg/day aPAD = 0.0015 mg/kg/day	aRfD = 0.015 mg/kg/day aPAD = 0.015 mg/kg/day
	<i>Critical Study and Endpoints</i>	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.
	<i>Reference</i>	MRID 44403101	MRID 44403101
	<i>PoD, UF</i>	NOAEL = 0.6 mg/kg/day UF = 100 FQPA = 10x	NOAEL = 0.6 mg/kg/day UF = 100 FQPA = 1x

Exposure Scenario		EPA 2002	EPA 2007
Chronic Dietary <i>(all populations)</i>	<i>Level of Concern for Risk Assessment with UFs</i>	cRfD = 0.006 mg/kg/day cPAD = 0.0006 mg/kg/day	cRfD = 0.006 mg/kg/day cPAD = 0.006 mg/kg/day
	<i>Critical Study and Endpoints</i>	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.
	<i>Reference</i>	MRID 41099502	MRID 41099502
Dermal <i>Short (1-30 days) and Intermediate-term (1-6 mos)</i>	<i>PoD, UF</i>	NOAEL = 12 mg/kg/day 45% absorption	NOAEL not established. 45% dermal absorption
	<i>Level of Concern (LOC) and Margins of Exposure (MOE)</i>	Occupational LOC MOE = 100	Occupational LOC MOE = 300
	<i>Critical Study and Endpoints</i>	<i>21-Day Dermal-Rat</i> LOAEL= 27 mg/kg/day, based on mortality in females	<i>DNT- rat:</i> LOAEL = 3.74 mg/kg/day, based on decreased pup weight. UF = 100 NOAEL to LOAEL UF = 3x

Exposure Scenario		EPA 2002	EPA 2007
	<i>Reference</i>	MRID 00146841/00147744 MRID 00146841	MRID 46968301
Dermal <i>Long-term (> 6 months)</i>	<i>PoD, UF</i>	NOAEL = 12 mg/kg/day 45% absorption	Long-term dermal exposure is not expected for endosulfan.
	<i>Level of Concern (LOC) and absorption rate</i>	Occupational LOC MOE = 100	
	<i>Critical Study and Endpoints</i>	21-Day Dermal-Rat LOAEL= 27 mg/kg/day, based on mortality in females	
	<i>Reference</i>	MRID 00146841/00147744 MRID 00146841	
Inhalation <i>Short (1-30 days) and Intermediate term (1 – 6 months)</i>	<i>PoD, UF</i>	NOAEL = 0.2 (0.001 mg/L)	NOAEL = 0.2 (0.001 mg/L)
	<i>Level of Concern (LOC) and absorption rate</i>	MOE = 100 100% absorption	MOE = 100 100% absorption

Exposure Scenario		EPA 2002	EPA 2007
	<i>Critical Study and Endpoints</i>	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
	<i>Reference</i>	MRID 00147183 MRID 41667501	MRID 00147183 MRID 41667501
Inhalation <i>Long-term (> 6 months)</i>	<i>PoD, UF</i>	None Established	Long-term inhalation exposure is not expected for endosulfan.
	<i>Level of Concern (LOC) and absorption rate</i>		
	<i>Critical Study and Endpoints</i>		
	<i>Reference</i>		
Cancer	<i>Classification</i>	Group E- Evidence of non-carcinogenicity for humans	Group E- Evidence of non-carcinogenicity for humans
	<i>Statistical Analysis</i>	Q1* not calculated	Q1* not calculated

III. 2007 Dietary Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) Program which used food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1989-1992) in 2002 (S. Kinard, D281201, 02/28/2002) in support of the Reregistration Eligibility Decision (RED). At that time, drinking water exposure was not directly incorporated into the dietary evaluation; rather, estimated environmental concentrations (EECs) were compared with drinking water levels of concerns (DWLOCs). The acute and chronic population adjusted doses (PAD) at that time were calculated using an FQPA Safety Factor of 10x due to toxicological database uncertainties, including the absence of a developmental neurotoxicity study (DNT). In 2006, a DNT study (Gilmore et al, 2006) was submitted and reviewed by the Agency (D. Anderson and J. Facey, D327215, 03/15/2007). Based on a 01/10/2007 DNT Committee meeting and subsequent follow-up (E. Reaves, D338576, 04/02/2007) HED concluded that based upon these submitted data, the FQPA Safety Factor could be reduced from 10x to 1x while still being protective of children's health.

To update the RED, new acute and chronic dietary exposure assessments (food only, drinking water only, and food plus drinking water) were conducted (D. Wilbur, D336646, 03/14/2007) using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The same input files (PDP monitoring data, FDA data, % crop treated data, and drinking water exposure data) from the 2002 dietary assessment were used in this new analysis, while incorporating the FQPA Safety Factor change from 10x to 1x. The combined dietary exposure (food and drinking water) **does not exceed** the Agency's level of concern (>100% of the PAD) for chronic or acute exposures.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this document, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant, and when data are

available. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure based on traditional dietary patterns among specific subgroups.

Endosulfan is a volatile and persistent organochlorine pesticide that can migrate over long distances through various environmental media such as air, water, and sediment. Recent studies suggest that endosulfan continues to recycle in the global system while slowly migrating and redepositing via wet deposition in the northern Hemisphere. The occurrence of endosulfan in remote regions such as the arctic is well documented. Therefore, since the Indigenous Peoples of the arctic region of the U.S. (Alaska) rely heavily on subsistence diets (i.e. fish) as their food source, it is appropriate for the Agency to consider dietary risk and exposure to this specific population subgroup from the worldwide use of endosulfan. Based upon its octanol-water coefficient ($\log K_{ow} = 3.5$ to 4.5), endosulfan shows appreciable lipophilicity and, therefore, a potential to bioaccumulate in fatty tissues. Since subsistence diets often consist of fish and other traditional subsistence food harvests (e.g., polar bear, walrus, caribou, moose), exposure to tissues into which endosulfan has bioaccumulated is possible.

As specific residue data in/on commodities consumed in subsistence diets are not available for endosulfan, risk estimates for these population subgroups have not been evaluated by HED. However, based upon the chemical and toxicity profile of endosulfan, the Agency has concerns for dietary exposure of indigenous populations to endosulfan.

IV. 2007 Occupational Assessment

Endosulfan currently is formulated into liquid concentrate and wettable powder end-use products. It is registered for occupational-use on terrestrial food and feed crops, indoor food crops, and terrestrial non-food crops. There currently are no end-use products registered for use at residential sites. Application equipment for occupational use includes fixed-wing aircraft, chemigation (potatoes only), groundboom sprayer, airblast sprayer, handgun sprayer, low-pressure handwand sprayer, high-pressure handwand sprayer, and dip treatment.

The updated occupational assessment for endosulfan indicates short- and intermediate-term risk for mixers, loaders, and applicators for the majority of crop scenarios, even with maximum personal protective equipment or engineering controls. In addition, postapplication risks are such that the majority of reentry intervals (REIs) would need to be extended by several days. [See Tables 9-18 for mixer/loader/applicator risks and Tables 24-27 for postapplication risks in the revised occupational assessment, S. Recore, D339509, 05/03/2007.]

Please note that while the revised occupational assessment presents risk estimates for grapes, pecans, spinach, succulent beans, and succulent peas, these crops are no longer allowed on endosulfan labels with the implementation of the 2002 RED mitigation. HED

clarifies that where two rates are presented for a crop (i.e., “label” rate and “proposed” rate), the “proposed” rate reflects the rates required in the 2002 RED.

V. 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
2. DP Barcode: D250471
Subject: Endosulfan: Reevaluation of the HED Risk Assessment for the Endosulfan Reregistration Eligibility Decision (RED) Document.
From: D. Locke
To: R. McNally
Dated: 05/30/2002
3. DP Barcode: D327215
Subject: A Developmental Neurotoxicity Study with Technical Grade Endosulfan in Wistar Rats. Project Number: 201563
From: D. Anderson and J. Facey
Dated: 03/15/2007
MRID(s): 46968301
4. DP Barcode: D338576
Subject: Endosulfan. Hazard Characterization and Endpoint Selection Reflecting Receipt of a Developmental Neurotoxicity Study and Subchronic Neurotoxicity Study.
From: E. Reaves
To: T. Perry
Dated: 04/02/2007
5. 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

6. DP Barcode: D336646
Subject: Acute and Chronic (Food and Drinking Water) Dietary Exposure Assessment to update the 2002 Reregistration Eligibility Decision
From: D. Wilbur
To: T. Perry
Dated: 03/14/2007
7. DP Barcode: D339509
Subject: Endosulfan: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document.
From: S. Recore
To: T. Perry
Dated: 05/03/2007
8. DP Barcode: D342660
Subject: A Review of “Maternal Residence near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley” Roberts et al., 2007 [EHP, 115; 10: 1482-1489] (Endosulfan (PC code 079401) and Dicofol (PC code 010501)
From: C. Christensen
To: T. Perry
Dated: 10/18/2007