dpr Department of Pesticide Regulation

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December 22, 2006

Tina Levine, Director
U.S. Environmental Protection Agency
Office of Pesticide Programs 7509C
Health Effects Division
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Dear Ms. Levine:

Enclosed for your review is a draft of the Department of Pesticide Regulation's Risk Characterization document (RCD) and Exposure Assessment document (EAD) for the pesticide active ingredient, endosulfan.

If you have questions regarding the draft RCD, please contact Dr. Joyce Gee at (916) 324-3465. If you have questions concerning the draft EAD, please contact Dr. Joseph Frank at (916) 324-3517.

Please provide comments by **January 31, 2006.**

In the event that you cannot provide a review or meet the deadline, please notify Dr. Gary Patterson at (916) 445-4233.

Sincerely,

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Enclosure

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I. SUMMARY

Introduction:

Endosulfan (6, 7, 8, 9, 10, 10-hexachloro-1, 5, 5a, 6, 9, 9a-hexahydro-6, 9-methano-2, 4, 3-benzodioxathiepin-3-oxide) is a broad-spectrum organochlorine insecticide used to control more than 100 different insect pests (aphids, leafhoppers, borers, worms etc.) that infest a large number of crops in California. It serves as a contact and stomach insecticide for more than 60 food and non-food crops but has proven to be extremely toxic to fish and other aquatic organisms. In California, the food crops are primarily grapes, melons, lettuce and tomatoes, as well as cotton, both a food (cotton seed oil) and a non-food crop. Patented in 1956, it is usually included among pesticides of the "chlorinated hydrocarbons of the cyclodiene group." CAS classifies it as a "dioxathiepin."

Environmental Fate:

Endosulfan hydrolysis increases with increased pH, binds tightly to some soils and is not mobile in soil. Surface and well water have not been sampled since 1996, as endosulfan is not considered to be a potential drinking water contaminant. Air monitoring shows that endosulfan can volatilize from water, soil and plant surfaces for 1 to 11 days post application. Endosulfan is translocated to roots after application to leaves and is metabolized within the plant. Bioaccumulation occurs in both aquatic (mussels, fish, shrimp, algae) and terrestrial (mosquito, snail) wildlife.

Pharmacology:

The majority of endosulfan, regardless of exposure route, is excreted rapidly in feces, with virtually no retention in tissues, despite the lipophilicity of endosulfan and its primary metabolite, endosulfan sulfate. Enterohepatic circulation, conjugation and elimination in the urine is not a major route for endosulfan metabolism. At 120 hours, 88% of α-[^{14}C]endosulfan and 87% of β-[^{14}C]endosulfan had been eliminated. The default policy for DPR is that if oral absorption is $\geq$ 80%, the absorption is assumed to be 100%. After endosulfan was dermally administered to rats, within 5 days 47.3% of the dose was absorbed and 95% of the absorbed material was eliminated. Fatty tissues had the highest endosulfan concentrations after dermal treatment. After oral treatment in rats, liver and kidney were the sites of greatest endosulfan concentration. These organs are likely the primary sites of biotransformation, since their weights increase after treatment as do the concentrations and activities of xenobiotic metabolizing enzymes such as P450s and glutathione-transferases.

Toxicology:

NEUROTOXICITY: Neurotoxicity is the primary effect observed both acutely and chronically in both humans and animals (where clinical signs were recorded). Documented human data have shown the central nervous system to be the major target of endosulfan action.

ENDOCRINE DISRUPTION: Effects to testes and reproductive tract occurred at lower doses in prepubertal and neonatal rats than in adults following repeat exposures. The observations were from studies in the open literature (not FIFRA Guideline studies) and they occurred at doses

greater than those that induced neurotoxicity. Due to these results, the USEPA considers endosulfan to be a potential endocrine disruptor. It is notable, however, that the developmental neurotoxicity study, recently received and reviewed by DPR showed no indication of neurotoxicity or endocrine disruption in rats treated with endosulfan in diet during both pre- and post-natal development. Dams, fetuses and pups showed a decrease in body weight during treatment and male pups had a slight delay (4-5%) in preputial separation at 10.8 mg/kg/day and greater.

TARGET ORGANS: Liver and kidney are the primary target organs. Endosulfan induced xenobiotic metabolizing enzymes.

In FIFRA Guideline acceptable animal studies, endosulfan did not result in developmental or reproductive effects, was not oncogenic nor was it genotoxic.

Hazard Identification:

ACUTE TOXICITY: The adverse effects observed in the LD_{50}/LC_{50} studies in laboratory animals with acute exposure to technical endosulfan include clinical signs of neurotoxicity, deaths, neurobehavioral effects, reductions in body weight, and increased gross and histopathological effects. The dose levels, however, were too high to establish a NOEL. A developmental toxicity study performed in the rabbit (by gavage), however, 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. 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). Therefore, the critical NOEL for acute exposure was 0.7 mg/kg.

SUBCHRONIC TOXICITY:

Dietary, Rat

Most commonly observed after subchronic treatment with endosulfan were death, clinical signs, increased liver and kidney weights and liver and kidney histopathological effects, decreases in body weights and food consumption and effects in hematology and in clinical chemistry parameters, including decreases in acetylcholinesterase activities. A rat reproduction study, where parental effects were observed after an exposure of 24 weeks throughout premating, mating, gestation, lactation and weaning for 2 generations, was selected as the definitive study (Edwards et al., 1984). The oral, systemic NOEL was 1.18 mg/kg/day based on increased relative liver and kidney weights, decreased food consumption, and decreased body weights. Although there was an acceptable subchronic rat dietary study, the reproduction study is preferable because it provides the lower NOEL. The common endpoint for the reproduction and subchronic oral dietary study was an increase in both kidney and liver weights. Therefore, the critical NOEL for subchronic exposure is 1.18 mg/kg/day. Subchronic dermal (1.0 mg/kg/day) NOEL was within range of the dietary NOEL and these routes are the most likely for occupational and swimmers in surface water scenarios.

Inhalation, Rat

The definitive study for subchronic inhalation exposure was performed in rat, where endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29 day recovery (Hollander et al., 1984). The NOEL for inhalation was 0.0010 mg/L based on emaciation, pale skin, squatting position and high-legged position, decreased bodyweight gain and food consumption, increased water consumption, and clinical chemistry parameters (reversed during recovery). This study was acceptable according to FIFRA Guidelines and was the only study available for evaluation of endosulfan exposure by inhalation. This study was therefore selected as the definitive study for the critical NOEL of 0.0010 mg/L (0.194 mg/kg/day) and a LOEL of 0.0020 mg/L (0.3873 mg/kg/day). This NOEL will be used to estimate the margins of exposure for seasonal endosulfan public (non-occupational) ambient air and bystander exposure in adults and children.

CHRONIC TOXICITY: The definitive study for the critical chronic NOEL was performed in the dogs where neurotoxicity was the most sensitive endpoint for chronic endosulfan toxicity (exposure by gelatin capsule). The critical chronic dietary NOEL was 0.57 mg/kg/day based on clinical signs of violent contractions of the upper abdomen, convulsive movements, extreme sensitivity to noise, frightened reactions to optical stimuli and jerky or tonic contractions in facial muscles, chaps and extremities and impairment of the reflex excitability and postural reactions (Brunk, 1989). It was necessary to sacrifice some of the dogs prematurely due to the clinical signs of neurotoxicity. In addition, body weights and food consumption were decreased.

ONCOGENICITY: When considering the results of all available *in vivo* studies performed in rats and mice, there is no evidence indicating endosulfan is oncogenic. There were no indications of genotoxicity induced by endosulfan (technical), as measured by the gene mutation, chromosomal aberration and other genotoxic effects in tests submitted to DPR. Although there were some studies reported to be positive in the open literature, none were acceptable by FIFRA Guidelines. Results from the genotoxicity studies were considered to be equivocal by USEPA.

Exposure Assessment:

Assumptions for all exposure scenarios, unless otherwise indicated, were 47.3% dermal absorption, based on a rat study (Craine, 1988), a 70 kg body weight (Thongsinthusak et al., 1993), and inhalation absorption of 100% (USEPA, 2001b).

OCCUPATIONAL EXPOSURE ASSESSMENT:

- **Acute, short term exposures:** For short-term exposures, DPR estimates the highest exposure an individual may realistically experience during or following legal endosulfan uses. For this "upper bound" of daily exposure the estimated population 95th percentile of daily exposure is used. A higher percentile is not used because the higher the percentile the less reliably it can be estimated and the more it tends to overestimate the population value (Chaisson et al., 1999).

- **Seasonal (1 week to 1 year) and annual (1 year):** To estimate seasonal and annual exposures, the average daily exposure is of interest because over these periods of time, a worker is

expected to encounter a range of daily exposures (i.e., DPR assumes that with increased exposure duration, repeated daily exposure at the upper-bound level is unlikely). To estimate the average, DPR uses the arithmetic mean of daily exposure (Powell, 2003). In most instances, the mean daily exposure of individuals over time is not known. However, the mean daily exposure of a group of persons observed in a short-term study is believed to be the best available estimate of the mean for an individual over a longer period.

- **Surrogate Data (short-term, seasonal and annual)**: Although no acceptable studies were available in which handler exposure to endosulfan was monitored, one acceptable study was submitted in which dermal and inhalation exposure of airblast applicators to the surrogate compound, carbaryl, was monitored (Smith, 2005). This study provided acceptable data for estimating exposure of airblast applicators driving open-cab tractors. Carbaryl was applied in three orchard crops (peaches, apples, and citrus) in three states (Georgia, Idaho, and Florida). With the exception of airblast applicators and handlers dipping nursery stock, exposure estimates were derived using the Pesticide Handler Exposure Database (PHED, 1995).

When using surrogate data to estimate short-term exposure, DPR uses the 90% upper confidence limit (UCL) on the 95th percentile. The UCL is used to account for some of the uncertainty inherent in using surrogate data and to increase the confidence in the estimate

When using surrogate data to estimate seasonal or annual exposure, DPR uses the 90% UCL on the arithmetic mean. The 90% UCL is used for the reasons listed in the previous paragraph. As with short-term exposure estimates based on PHED subsets, a multiplier corresponding to the median sample size over body regions is used. If the median sample size is greater than 15, the multiplier is 1 (Powell, 2002).

Surrogate data from the PUR also were used to estimate intervals for seasonal and annual exposures. However, PUR data show that in many parts of the state and in many crops endosulfan use does not occur throughout the year, and that at other times relatively few applications are made. It is reasonable to assume that an individual handler is less likely to be exposed to endosulfan during these relatively low-use intervals. Thus, rather than assume that handlers are exposed throughout the year, annual use patterns are plotted based on monthly PUR data from one or more counties with the highest use. Annual exposure to endosulfan is assumed to be limited to the months when use is relatively high (defined as 5% or more of annual use each month). Seasonal, annual, and lifetime exposure estimates for workers handling endosulfan in support of aerial and ground applications are given in Table 17.

USEPA (2002b) assumed that handler exposure durations would only be one day to one month. The basis for this assumption was not explained.

AERIAL AND GROUND APPLICATIONS: STADD for aerial applications ranged from 0.021 mg/kg (airblast M/L-WSP) to 2.63 mg/kg (aerial M/L-WP). SADD exposure values ranged from 0.005 (groundboom applicators) to 0.385 mg/kg/day (aerial M/L-WP). AADD values ranged from 0.001 mg/kg (airblast M/L-WSP and EC) to 0.128 mg/kg (aerial M/L-WP). Mitigation measures proposed by USEPA (2002) would require all WP to be packaged in WSP.

BACKPACK, HIGH AND LOW PRESSURE HANDWAND APPLICATIONS AND NURSERY STOCK DIP: PHED data were used in exposure estimates for handlers applying endosulfan with a backpack sprayer, and both high and low pressure handwands. High and low-pressure handwands can be used to apply endosulfan to the same crops as backpack sprayers. Due to infrequent use, seasonal and annual exposures to endosulfan are not anticipated to occur by nursery stock dip, and only short-term exposures were estimated. STADD exposure estimates range from 0.00003 mg/kg/day (Dip, M/L-EC) to 41.4 mg/kg/day (Dip applicator). SADD exposures range from 0.003 mg/kg/day (LPHW M/L-EC) to 0.153 mg/kg/day (HPHW M/L/A) and AADD ranges were from 0.0005 mg/kg/day (LPHW M/L-EC) to 0.026 mg/kg/day (HPHW M/L/A).

REENTRY EXPOSURE: Representative exposure scenarios for reentry workers were selected as described in the document provided by the DPR Worker Health and Safety Branch (Beauvais, 2006). No exposure data were available for workers reentering crops treated with endosulfan. Because of this, exposures of workers reentering crops treated with endosulfan were estimated from dislodgeable foliar residue (DFR) values and from transfer coefficients (TCs) from studies with surrogate chemicals (residue transfer assumed not chemical-specific) (Beauvais, 2006).

Most reentry activities are not expected to result in pesticide exposure throughout the year. Annual exposure to endosulfan is assumed to be limited to the months when use is relatively high (defined as 5% or more of annual use each month). It was assumed that scouting occurred after all applications were completed.

STADD for reentry exposures ranged from 0.009 mg/kg/day (almond, thinning and ornamental plants, hand harvesting) to 0.533 (sweet corn, hand harvesting); SADD reentry exposures ranged from 0.004 mg/kg/day (potato, scouting; lettuce, scouting) to 0.141 mg/kg/day (grape, cane turning) and for AADD, ranges went from 0.001 mg/kg/day (cucumber, hand harvesting) to 0.047 mg/kg/day (grape, cane turning).

AMBIENT AIR and BYSTANDER EXPOSURES:

Ambient air and application site air monitoring detected endosulfan, suggesting that the public may be exposed to endosulfan in air. Individuals might be exposed to endosulfan if they are working adjacent to fields that are being treated or have recently been treated (bystander exposure). In addition, air monitoring conducted in Fresno County suggests that airborne endosulfan exposures are possible in areas that are far from application sites (ambient air). Public exposure to airborne endosulfan was estimated based on monitoring studies of endosulfan at application sites and in ambient air.

- **Ambient Air**: Short-term exposures to ambient air are anticipated to be equal to or less than the acute bystander exposure, which addresses exposure of an individual who is adjacent to an application. Ambient air STADD was not estimated as the highest short-term ambient air exposure is anticipated to be adjacent to an application, which is estimated by bystander STADD. SADD is 0.000019 mg/kg/day for infants and 0.000009 mg/kg/day for adults. AADD is 0.000011 mg/kg/day for infants and 0.000005 mg/kg/day for adults.

- **Bystanders at application sites:** STADD for bystanders was 0.00124 mg/kg/day for infants and 0.00059 mg/kg/day for adults. Seasonal ADD estimates for bystander exposures to endosulfan were 0.00046 mg/kg/day for infants and 0.00022 mg/kg/day for adults. Annual

ADD estimates for bystanders were 0.000038 mg/kg/day for infants and 0.000018 mg/kg/day for adults.

Water

SURFACE WATER: Historically, endosulfan has been detected numerous times in California surface waters. Endosulfan sulfate has been detected more frequently in surface water samples than α- or β-endosulfan, and generally at higher concentrations. Endosulfan residues have been detected in California surface waters in the Central Valley (Ross et al., 1996 and 2000) and in the Sierra Nevada Mountains (Fellers et al., 2004). Movement of endosulfan into surface water via rainfall runoff and irrigation drainage has been documented (Gonzalez et al., 1987; Fleck et al., 1991).

In surface water systems, endosulfan residues have also been detected in sediment (Gonzalez et al., 1987; Fleck et al., 1991; Ganapathy et al., 1997; Weston et al., 2004); mussels (Singhasemanon, 1996; Ganapathy et al., 1997); amphibians (Sparling et al., 2001); and fish (Singhasemanon, 1995; Brodberg and Pollock, 1999). Because endosulfan has been detected in surface water, sediment and aquatic organisms, and in response to concerns about endosulfan's toxicity, in 1991 DPR began requiring permit conditions to prevent use of endosulfan where it might be allowed to reach surface water (Okumura, 1992).

SWIMMER EXPOSURES: Exposures of adults and children swimming in surface waters were estimated based on equations listed in U.S. EPA (2003). Both STADD and SADD were calculated from absorbed dose rate and potential dose rate by dividing by default body weights of 70 kg for an adult (Thongsinthusak *et al.*, 1993) and 24 kg for a 6 year-old child (USEPA, 1997c). Inhalation exposure was assumed to be negligible, and was not included in swimmer exposure estimates. The total exposure was calculated by summing dermal and non-dietary ingestion exposure estimates. Total STADD was 0.00027 mg/kg/day for adults and 0.00156 mg/kg/day for children. Total SADD was 0.00000468 mg/kg/day for adults and 0.000048 mg/kg/day for children. Total AADD was 0.00000128 mg/kg/day for adults and 0.0000131 mg/kg/day for children.

Dietary Exposure:

DPR evaluates the risk of human exposure to an active ingredient in the diet using two processes: (1) use of residue levels detected in foods to evaluate the risk from total exposure, and (2) use of tolerance levels to evaluate the risk from exposure to individual commodities. For evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established USEPA tolerances. The potential exposure from residues in the water and certain commodities without tolerances are also assessed in some cases. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

The dietary exposure to endosulfan and its metabolites was assessed initially in 1998 by Medical Toxicology Branch staff. The 1998 assessment used the TAS, Inc EX™ acute and chronic dietary exposure software (TAS, 1996a, b). All of the acute and chronic dietary margins-of-exposure (MOEs) exceeded 100 at the 95th percentile. A revised DPR dietary exposure assessment was assessed and it was concluded that the previous 1998 assessment was the more health protective (Carr, 2006).

ACUTE (and short term): The potential acute dietary exposure of endosulfan from all labeled uses ranged from 1.37 ug/kg/day, males 13-19 years (females 13-19 years = 1.37) to 3.30 ug/kg/day, children 1-6 years for the 95th percentile of user-days exposures. Male and female values (13-19 years), when rounded to two significant figures, were both 1.37 ug/kg/day. The complete acute dietary exposure analysis includes all current USEPA label approved endosulfan uses.

The exposure to endosulfan through the diet was also considered for pesticide workers in combination with occupational exposure. For acute dietary exposure, the value for Females (13+), nursing, was used for adult acute occupational, adults in the general public for ambient air and bystanders and for adult swimmers in surface water. This population subgroup was selected, since it was a relatively high exposure in a population that would be found amongst all exposure scenarios for adults. The potential acute dietary exposure was estimated to be 2.06 ug/kg/day, based on the 95th percentile of user-day exposure for females age 13+ years, nursing. The acute dietary exposure levels for infants (non-nursing, < 1 year) was selected to represent infants exposed to endosulfan in ambient air and to bystanders (95th percentile, 3.18 ug/kg/day). Children exposed to endosulfan while swimming in surface water had the acute dietary component of 3.30 ug/kg/day from the population subgroup of Children (1 – 6 years).

SUBCHRONIC (seasonal) AND CHRONIC (annual) EXPOSURE: The TAS program does not perform a subchronic dietary analysis; therefore, potential subchronic dietary exposures were estimated using the chronic exposure data (average measured residue values of all values for each commodity). The subchronic NOEL, however, was different from the chronic. Therefore, subchronic dietary exposure is likely different even when using chronic RAC residues. For commodities with residues at "below detection limit," a value equal to one-half (50%) of the MDL was assigned to each commodity. When the residue values are derived from monitoring programs, the assumption is that the data represent annual average level in the diet (%CT). Therefore, for subchronic dietary exposure, the chronic value for Females (13+), nursing, was used for adult subchronic occupational, adults in the general public for ambient air and bystanders and for adult swimmers in surface water. The potential subchronic dietary exposure was estimated to be 0.17 ug/kg/day, based on the %CT annualized average for females age 13+ years, nursing. The dietary subchronic exposure levels for infants (non-nursing, < 1 year) was selected to represent infants exposed to endosulfan in ambient air and to bystanders (0.28 ug/kg/day). Children exposed to endosulfan while swimming in surface water had the subchronic dietary component of 0.41 ug/kg/day from the subgroup of Children (1 – 6 years). Chronic dietary exposure data were the same as those used for subchronic esposure estimations.

Combined (Occupational or Public + Dietary) Exposure

COMBINED EXPOSURE: The exposure to endosulfan through the diet was considered in combination with the potential exposure for pesticide workers and to the public through ambient air and for bystanders and for the public (children and adults; dermal and non-dietary ingested) swimming in surface water.

- **Occupational Combined Exposure:** The predominant factor for mitigating human exposure to endosulfan is the occupational exposure. About half of the occupational exposure scenarios (acute, subchronic, chronic), had dietary components of less than 3% (40/89 = 55%) of the

combined exposure. The majority of the exposures where diet comprised a higher percentage (3% or greater) were observed in the STADD (51%) and AADD (41%), where SADD (22%) was less than half the other scenarios. The highest percentages for dietary contribution were re-entry scenarios where STADD was 60%, SADD was 30% and AADD was 80%.

- **Combined Dietary and Exposure in Ambient Air and to Bystanders:** For adults and children with combined exposure to endosulfan in ambient air or as bystanders plus diet showed that the dietary component for STADD, SADD and AADD is the major exposure. However all of the non-dietary exposure components for all air scenarios are very low and that is why the dietary contribution (while also quite low) appears to be so much greater. The dietary percentage of exposure was lowest in SADD infant bystanders (38%; non-dietary exposure was 0.00074 mg/kg/day). The dietary exposure was highest in ambient air for adults (AADD, 97%), where the non-dietary exposure was 0.000005 mg/kg/day.

- **Combined Dietary and Exposure to Swimmers in Surface Water:** STADD for child non-diet ingestion (and total) had the lowest dietary component for combined exposure (68%). The non-dietary exposure for this was 0.00156 mg/kg/day and was the highest exposure of all scenarios. STADD for adult non-dietary ingestion (and total) was 0.00027 mg/kg/day and the dietary comprised 88% of the combined exposure. The SADD for child non-dietary and total was the same with an 88% dietary contribution. For all other groups, the non-dietary exposure was so comparatively low that the dietary comprised 97% to 100% of the combined exposure.

Risk Characterization: Margins of Exposure

The risks for potential adverse human health effects with occupational, public (swimmers in surface water, dermal and non-dietary ingested), ambient air and dietary exposure to endosulfan were evaluated using margins of exposure (MOE) estimates. The MOEs for acute, subchronic and chronic exposure were calculated using no-observed-effect levels (NOELs) from the available guideline and literature toxicity studies for endosulfan. Generally, an MOE greater than 100 is considered sufficiently protective of human health when the NOEL for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower distribution of the overall human population and the sensitive subgroup.

Short Term Margins of Exposure (MOE):

OCCUPATIONAL SCENARIOS: The majority of occupational exposure scenarios (33 of 35, 94%) for STADD had MOEs that were less than 100. Of those, 17% of the MOEs (6/35) were less than or equal to 1. STADD MOEs were greater than 100 for root dip M/L (both EC and WP), ranging from 233 (M/L WP) to 23,333 (M/L EC).

NON-DIETARY BYSTANDER SCENARIOS: All short term MOEs for non-dietary infant and adult bystander scenarios were greater than 100, ranging from 565 to 1186 for infant and adult bystanders, respectively. It must be noted that since the bystander, infant scenario has an MOE of less than 1000, endosulfan may be listed as a potential toxic air contaminent (TAC, 2001).

NON-DIETARY INTAKE FOR SWIMMERS IN SURFACE WATER: All short term non-dietary MOEs for swimmers in surface water were greater than 100 and ranged from 449 (child non-diet ingested and total) to 321,101 (adult dermal).

Seasonal Margins of Exposure

OCCUPATIONAL SCENARIOS: Approximately half of occupational exposure scenarios (14/27, 52%) had SADD MOEs that were less than 100. None was less than or equal to 1. Aerial M/L – WP (3), Aerial Applicator (7), HPHW M/L/A - EC (8) and grape, cane turning (8), all less than 10, were the lowest MOE values. The remaining MOEs below 100 ranged from 13 to 98. All aerial scenarios (M/L, applicator and flagger) had MOEs of less than 100. MOEs that were more than 100 ranged from 107 (backpack sprayer M/L/A EC) to 393 LPHW, M/L/A—EC.

NON-DIETARY AMBIENT AIR and BYSTANDER SCENARIOS: All seasonal exposure MOEs for the infant and adult ambient air and bystander scenarios were greater than 100, ranging from 422 (bystander, infant) to 21,556 (ambient air, adult). Note that since the bystander, infant scenario has an MOE of less than 1000, endosulfan may be listed as a potential toxic air contaminent (TAC, 2001).

NON-DIETARY INTAKE FOR SWIMMERS IN SURFACE WATER: All seasonal MOEs for swimmers in surface water were greater than 100 and ranged from 24,583 (child: non-diet ingested + dermal) to 31,216,931 (adult dermal).

Annual Margins of Exposure

OCCUPATIONAL SCENARIOS: More than half of occupational exposure scenarios (16 of 27, 59%) had AADD MOEs of greater than 100, however there were 11 (41%) that were less than 100. All aerial scenarios (M/L, applicator and flagger) had MOEs of less than 100 but no scenario had an MOE of less than or equal to 1. Aerial M/L – WP (4) had MOE of less than 10. MOEs that were more than 100 ranged from 114 (2 scenarios: reentry workers scouting broccoli and peach, thinning) to 1140 for LPHW M/L/A-EC.

NON-DIETARY AMBIENT AIR and BYSTANDER SCENARIOS: All annual exposure MOEs for the infant and adult ambient air and bystander scenarios were greater than 1000, ranging from 15,000 (bystander, infant) to 114,000 (ambient air, adult).

NON-DIETARY INTAKE FOR SWIMMERS IN SURFACE WATER: All annual MOEs for swimmers in surface water were greater than 100 and ranged from 43,511 (child: non-diet ingested and total) to 55,339,806 (adult dermal).

Dietary Exposure Estimates and Margins of Exposure (MOEs)

ACUTE and SHORT TERM DIETARY EXPOSURE: Acute dietary MOEs were calculated for the various population subgroups using the NOEL for acute toxicity (0.7 mg/kg). Estimates of exposure ranged from 1.37 ug/kg in Females (13- 19 years), not pregnant, not nursing to 3.30 in Children (1-6 years). Females (13+ years, nursing) was selected for the acute dietary

exposure group for adults (based on the 95th percentile of user-day exposure). Acute dietary exposure for infants (non-nursing, < 1 year) was 3.18 (based on the 95th percentile of user-day).

All population subgroups have MOEs (acute 95th percentile) greater than 100 and these dietary MOEs are based on anticipated endosulfan residues on RAC. None of the MOEs for categories involving acute dietary exposure infants and children is greater than 1000 (all are greater than 100), as recommended under the FQPA (1996), however all are greater than 1000 for chronic dietary exposure.

The MOEs for acute dietary exposure ranged from 212 in children (1 -6 years) to 513 in males (13-19). Acute MOE for Females (13+, nursing) was 340. For infants (non-nursing, < 1 year old) it was 220 and for children (1-6 years) it was 212. All MOEs in these population subgroups were greater than 100.

SUBCHRONIC and CHRONIC DIETARY EXPOSURE: The chronic dietary exposures ranged from 0.08 ug/kg/day in infants (nursing, < 1 year old) to 0.041 in children (1 - 6 years). Since there are no subchronic dietary data for endosulfan, chronic data were used for subchronic calculations. Chronic dietary exposure for infants (non-nursing, < 1 year) was 0.28 ug/kg/day; 0.41 ug/kg/day was used for children (1 – 6 years) exposed to endosulfan (dermal and non-dietary ingestion) by swimming in surface water and 0.17 ug/kg/day (Females (13+, nursing)) was used to represent adults, both occupational and in the general public. There were no percent crop treated (%CT) adjustments used in these calculations.

MOEs for chronic dietary exposure were calculated from data for the various population subgroups and the definitive NOEL from the chronic dog study (0.57 mg/kg/day). The MOEs ranged from 1407 in children (1 - 6 years) to 7,421 in infants (nursing < 1 year of age). Percent crop treated (%CT) adjustments were used in these calculations. The chronic dietary exposures were the same as the subchronic subpopulations used for adults (Females (13+ years, nursing = 340), infants (infants non-nursing, < 1 year = 220) and children (children 1 – 6 = 212).

Drinking water is not a likely source of uncertainty with regard to endosulfan dietary exposure. Surface and well water samplings have been negative for endosulfan residues since 1996. In addition, the PDP samples from 2001 to 2003 (PDP, 2003, 2004, 2005) have been negative for endosulfan in drinking water.

Dietary Margins of Exposure

ACUTE DIETARY MOEs: For acute dietary exposure, the MOEs were calculated for the various population subgroups using the NOEL for acute toxicity (0.7 mg/kg). MOEs ranged from 212 (Children, 1-6 years) to 513 (Males 13-19 years). Females (13+ years, nursing), selected for the acute dietary exposure group for adults in all exposure scenarios had a dietary MOE of 340, based on the 95th percentile of user-day exposure. Acute dietary MOE for infants (non-nursing, < 1 year) was 220 (95th percentile of user-day). The acute MOE for children (1–6 years) was 212. All acute dietary MOEs were greater than 100.

SUBCHRONIC and CHRONIC DIETARY MOEs: Subchronic dietary MOEs were calculated using the definitive NOELs from the subchronic rat reproduction study (1.18 mg/kg/day) for

all of the seasonal occupational studies and for the adult and child exposure to endosulfan in surface water. For the subchronic inhalation MOE calculations for adults and infants exposed to ambient air and for bystanders, the subchronic rat inhalation NOEL was used (0.194 mg/kg/day). There were, however no subchronic (seasonal) dietary exposure data for endosulfan, therefore chronic dietary exposure data were used as a default.

Chronic dietary MOEs were calculated using the definitive, dog study for the critical NOEL (0.57 mg/kg/day). The chronic MOEs were the same as the for the subchronic subpopulations used for adults (Females (13+ years, nursing = 340), infants (infants, non-nursing, < 1 year = 220) and children (children 1–6 = 212). The chronic MOEs ranged from 1407 in children (1-6 years) to 7,421 in infants (nursing < 1 year of age). There were no percent crop treated (%CT) adjustments used in these calculations. All MOEs in these population subgroups were greater than 100.

Combined (non-dietary plus dietary) Margins of Exposure for Occupational, or Public (ambient air; bystander; swimmers in surface water) Scenarios

COMBINED MOEs OCCUPATIONAL EXPOSURE:

- **Combined MOEs for Aerial and Ground Application**: Aerial application MOEs for all combined scenarios (STADD, SADD and AADD) were less than 100, ranging from less than 1 (aerial M/L WP and applicator) to 30 (airblast M/L WSP). SADD combined MOEs for airblast and groundboom were all greater than 100, except for airblast M/L WP (16) and applicator (25) and for groundboom M/L WP (13). AADD combined MOEs for airblast and groundboom were all greater than 100, except for airblast M/L WP (47) and applicator (70) and for groundboom M/L WP (15). The greatest MOEs (487) were for combined AADD for airblast M/L-WSP and M/L-EC.

- **Combined MOEs for Handlers Using Handheld Equipment:** All combined STADD MOEs were below 100 for handlers using handheld equipment, with dip applicator (<1) and HPHW M/L/A EC (1) being the lowest. STADD combined MOEs for dip M/L-EC and dip M/L-WP were 345 and 140, respectively. SADD and AADD combined MOEs for HPHW M/L/A-EC were less than 100 (8 and 22, respectively) as was SADD LPHW M/L/A-WP (78). The other combined scenarios were all greater than 100 and ranged from an SADD of 106 for BP M/L/A-EC to an AADD of 851 for LPHW M/L/A-EC.

- **Combined MOEs for Reentry Workers:** All scenarios for STADD for reentry workers had combined MOEs that were less than 100, with a range of 1 for sweet corn, hand harvesting to 64 for hand harvesting ornamentals and for almond thinning. For SADD, 4/10 combined MOEs were less than 100, however one of the MOEs was 97 (range = 8 for grape, cane turning to 97 for broccoli, scouting). The highest SADD MOE was 283 for both lettuce, scouting and for potato, scouting. The only AADD MOEs less that 100 were sweet corn, hand harvesting (92) and grape, cane turning (12). All other AADD MOEs (8/10) were greater than 100 (110 = peach, thinning to 487 for cucumber, hand harvesting).

COMBINED MOEs in NON-OCCUPATIONAL SCENARIOS:

- **Combined MOEs for Ambient Air and for Bystanders:** All combined scenarios for ambient air and for bystanders had STADD, SADD and AADD MOEs that were greater than 100. For STADD Combined MOEs the lowest was for bystander infants (158) and the highest was for bystander adults (270). There were no STADD ambient air scenarios. For SADD the lowest combined MOEs were for bystander infants (262) and the highest was for ambient air adults (671), however the combined MOE for ambient air in adults (649) was similar to that of infants. The combined AADD MOEs were very close to 2000 for all scenarios and ranged from 1792 (bystander infants) to 2000 (adults in ambient air). Since all the combined STADD and SADD MOEs for infants and adults were less than 1000, endosulfan would potentially be evaluated as a toxic air contaminant (TAC, 2001). In addition, the acute combined STADD MOEs for infants (bystanders) was less than 1000 and therefore must be flagged for further evaluation under the Food Quality Protection Act (1996).

- **Combined MOEs for Swimmers in Surface Water:** All combined scenarios for swimmers in surface water had STADD, SADD and AADD MOEs of greater than 100. Combined MOEs for STADD ranged from 144 for child non-dietary ingestion and for child total (144; non-dietary ingestion and dermal) to 350 for adult dermal. Within scenarios for STADD, SADD and AADD the combined MOEs for adults or for children there was not much variation. For example MOEs for STADD combined scenarios had adult MOEs of 308 to 350 and child MOEs of 144 to 212. SADD combined MOEs for adults ranged from 6755 to 6940 and child MOEs of 2634 to 2949. AADD combined MOEs for adults ranged from 3328 to 3353 and for children, ranged from 1380 to 1425.

Tolerance Assessment

ACUTE: There are currently more than 72 human consumption RACs that have endosulfan tolerances (CFR, 2004). A total of 20 commodities, including milk, were analyzed for tolerance level acute dietary exposure. There were 15 commodities that had MOEs of less than 100 for 1 or more population subgroups when assessed using tolerance level values. The MOEs were based on tolerance levels of endosulfan. RACs (apple, melon and tomato) acute 95th pecentile MOEs ranged from 5 for apples (nursing infants < 1 year) to greater than 100 for tomatoes (seniors 55+). All commodities for all population subgroups listed had acute 95th percentile MOEs less than 100 for apples, melons and tomatoes, except seniors (55+). Apples and melons are the only two commodities with endosulfan tolerances that have all 20 of their analyzed populations with MOEs less than 100. Tomatoes had 19 of its analyzed populations with MOE values of less than 100.

CHRONIC TOLERANCE ASSESSMENT: A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. This conclusion is supported by data from both federal and DPR pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (DPR,1994,1995,1997).

TOLERANCE ASSESSMENT – 2006: In 1998 there were 72 commodities with human consumption that had USEPA endosulfan tolerances (USEPA, 1999) and in 2001 (most recent year available) USEPA stated that the endosulfan tolerances remained the same for those 72 commodities (USEPA, 2001a). However, 9 commodity tolerances have either been canceled or proposed for cancellation by the registrants of technical endosulfan.

The USEPA July 2002 draft endosulfan re-registration eligibility decision (RED) document proposed that the tolerances for 5 commodities should be revoked (USEPA, 2002). Several of these commodities are sources of frequent consumption by infants and children.

The USEPA draft endosulfan RED also decreased the maximum label application rates by approximately 17-33%, depending on commodity, for a number of commodities that will still have tolerances. These reductions in maximum annual application rates are expected to be reflected in a corresponding decrease in the magnitude of the residues detected on endosulfan treated commodities. In 2006, the USEPA announced in the Federal Register (September 15, 2006 (Volume 71, Number 179)] the final ruling on endosulfan tolerance actions that carried out the proposed tolerance changes that were described in the RED for endosulfan (USEPA, 2002).

Conclusions

OCCUPATIONAL RISK MARGINS OF EXPOSURE (MOEs): In each occupational risk scenario there were MOEs that were less than 100. The scenarios with MOEs less than 100 were primarily short term, and these in several cases were also less than 1. There were, however, cases where MOEs were less than 100 for both seasonal and annual exposures.

DIETARY MOEs: The MOEs from anticipated endosulfan residues for acute toxicity (95^{th} percentile, UB) were all well above 100; however, the acute 95^{th} percentile MOEs from tolerance levels of endosulfan for apple, menon and tomato in the selected population groups were all, except for seniors 55+ years, less than 100.

For dietary exposure all population subgroups have MOEs (acute 95^{th} percentile and chronic) greather than 100 for acute and 1000 for chronic.

COMBINED (Occupational plus Dietary) MOEs: There is a preponderance of scenarios in the dietary plus occupational categories that are well below a MOE of 100.