

ENDOSULFAN
RISK CHARACTERIZATION DOCUMENT

Executive Summary

**Department of Pesticide Regulation
California Environmental Protection Agency**

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Introduction

The Department of Pesticide Regulation (DPR) conducts risk assessments for pesticides used in California to determine whether the use poses a present or potential human health hazard in California. Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations. This type of assessment includes a quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. After the completion of the risk assessment, the risk management phase takes place at DPR. Risk management refers to the process by which regulatory actions are chosen to deal with hazards identified in the risk assessment process. Risk managers consider scientific evidence and risk estimates, along with statutory, engineering, economic, social, and political factors, in evaluating alternative regulatory options and choosing among those options.

Risk assessments are mandated by the California Food and Agriculture Code (CFAC) Section 12824; the Birth Defect Prevention Act of 1984 (CFAC 13121-13135); and the Toxic Air Contaminant Act (CFAC 14021-14027). The Birth Defect Prevention Act of 1984 is often identified as Senate Bill 950 (SB 950), and the Toxic Air Contaminant Act is often identified as Assembly Bills 1807 and 3219 (AB 1807 and 3219). Under SB 950, the risk assessment is comprehensive and considers the potential exposures of various population groups, which may include workers, residents, and bystanders, depending on how the pesticide is used. A bystander is defined as any person not directly involved with the pesticide application process who is in the vicinity of the application site. For each group, multiple routes of exposure, when appropriate, are assessed. These include inhalation of airborne pesticide, absorption through the skin, and consumption of treated food. AB 1807 and 3219 establish a procedure for identification and control of toxic air contaminants (TACs) in California. The statutes define TACs as air pollutants that may cause or contribute to an increase in mortality or in serious illness, or that may pose a present or potential hazard to human health. DPR's TAC program focuses on the evaluation and control of pesticides in ambient community air.

This report describes the risk assessment for the inhalation exposure to endosulfan in the products Drexel Endosulfan 3E, Thionex® 3E Insecticide, Gowan Endosulfan 50W, Thionex® 50W Insecticide, and Thionex® 50WSB Insecticide, under both SB 950 and AB 1807 mandates. In preparing this report, DPR staff reviewed pertinent scientific literature and reports through the Spring of 2007. Based on the results of this comprehensive evaluation, the Director of DPR will determine whether endosulfan is a TAC, and whether mitigation measures are needed to reduce the exposure of workers and the general population in California. If endosulfan is designated a TAC, the risk management provisions of the law mandate the DPR to determine the need for and develop appropriate control measures for endosulfan uses in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), the Air Resources Board, the air pollution districts, air quality management districts, and county agricultural commissioners of the affected counties.

What is contained in the report?

This report evaluates the potential for endosulfan exposure and includes:

A review of the available scientific evidence on α -endosulfan, β -endosulfan, and endosulfan sulfate regarding their physical properties, sources in the environment, and fates in the environment; a summary of toxicology studies conducted with endosulfan; estimates of human exposure to airborne endosulfan; and an assessment of the risk to humans resulting from current or anticipated exposure to airborne endosulfan.

What is endosulfan, what are the primary sources of endosulfan in the environment, and how it is used?

Endosulfan is an insecticide and acaricide belonging to the chemical family of organochlorine, sub-class chlorinated cyclodiene and containing only one double bond. Its chemical formula is $C_9H_6Cl_6O_3S$ with a molecular weight of 406.96 g/mole. The molecular structures have two stereochemical isomers, α - and β -endosulfan. The end-use product of endosulfan is a mixture of two isomers, typically in a 2:1 ratio. Pure endosulfan is a colorless crystal; but technical grade is brown in color, and similar to hexachlorocyclopentadiene, sometimes mixed with sulfur dioxide in odor. Endosulfan is relatively poorly soluble in water with solubility of 0.33 mg/L at 25 °C, but readily soluble in common organic solvents. It is moderately volatile and adsorptive onto soil particles. The vapor pressure is 3.0×10^{-6} and 7.2×10^{-7} mm Hg (25 °C) for α - and β -endosulfan; and the corresponding Henry's Law Constant is 4.9×10^{-6} and 1.2×10^{-6} atm-m³-mol⁻¹, respectively. The adsorption coefficients (Koc) were estimated to be 10600 and 13600 cm³/g for α - and β -endosulfan, respectively.

The primary source of endosulfan in the environment is almost exclusively from pesticide application. There are no known natural sources of endosulfan. It is a broad-spectrum non-systemic insecticide and acaricide with contact and stomach action. It is used to control sucking, chewing, and boring insects on a wide variety of vegetables, fruits, grains, cotton, and tea, as well as ornamental shrubs, vines, and trees. Currently, there are six registered products containing active ingredient of endosulfan in California. Its formulations include emulsifiable concentrate, wettable powder, and technical grade endosulfan. The labels all bear signal word "DANGER-POISON".

Endosulfan is applied via chemigation, groundboom sprayer, airblast sprayer, rights-of-way sprayer, low pressure handwand sprayer, high pressure handwand sprayer, backpack sprayer, fixed-wing aircraft, and dip treatment. Endosulfan is compatible with many other pesticides and may be found in formulations with dimethoate, malathion, methomyl, monocrotophos, pirimicarb, triazophos, fenoprop, parathion, petroleum oils, and oxine-copper. It is not compatible with alkaline materials because it is vulnerable to hydrolysis.

Endosulfan use in California decreased from 238,635 pounds in 1997 to 83,242 pounds of active ingredient in 2005. Both total pounds used and acreages applied in 2005 were almost 1/3 of those in 1997. However, the use patterns, frequency distribution for pounds used, acres applied, and application rates of individual endosulfan application, were similar compared 1997 to 2005. The six top use counties were Fresno, Kings, Imperial, Kern, Tulare, and Riverside. The peak use months were from June to September. For the six top use counties, the peak use months were June to August in Fresno; June and July in imperial; August and September in Kern; June to September in Kings; May to August in Riverside; and July to September in Tulare counties. Endosulfan was mainly used on cotton, alfalfa, lettuce, tomato, melons, grapes, and various vegetables in California.

What is the fate of endosulfan in the environment?

Endosulfan can be found in almost all media in the environment and all over the world. The α -isomer is more volatile and dissipative, while the β -isomer is generally more adsorptive and persistent. Its overall moderately volatile property enables it to be transported as vapor and spray drift to multiple media, while its moderate adsorptive and persistency properties enable it to stay in the environment for an extended period and can be transported via runoff to surface water bodies or via dust dispersion to atmosphere and redeposit to different areas. Therefore, endosulfan has been detected in areas where it was not used, *e.g.*, the Lake Tahoe Basin and the Sequoia National Park in California, and even in the Arctic. Photolysis and subsurface leaching are negligible.

Endosulfan degradation can be via abiotic or biotic processes in aerobic and anaerobic conditions. Oxidation and hydrolysis are the main routes for endosulfan degradation. Both α - and β -endosulfan can be oxidized to endosulfan sulfate via biotic metabolism. Endosulfan sulfate is of comparable toxicity as its parents and more persistent with half-life of 100-2148 days, two or more times longer than its parents. Estimated half-lives for α - and β -endosulfan in different soils and other environmental conditions ranged 19-124 and 42-265 days respectively, and those for the combined toxic residues (α - and β -endosulfan plus endosulfan sulfate) ranged from 9 months to 6 years. They all can, when in water, hydrolyze abiotically or biotically to endosulfan diol. Endosulfan diol is more hydrophilic and less toxic. Hydrolysis is favored in neutral to alkaline media. Estimated half-lives at 25 °C were 11 and 19 days at pH 7, 4 and 6 days at pH 9 for α - and β -endosulfan, respectively. However, at pH 5, they were more than 200 days for both α - and β -endosulfan.

Who will be exposed to endosulfan, and what are the exposure levels?

Individuals might be exposed to endosulfan if they live, work, or perform other activities adjacent to fields that are being treated or have recently been treated (bystander exposure). Also, air monitoring studies in Fresno, Monterey, and Tulare counties suggest that airborne endosulfan exposures to the public are possible in areas that are far from application sites (ambient air exposure). In this report, exposures are expressed as absorbed doses, which account for differences in the age-related inhalation rate and in the exposure duration under the various scenarios. For ambient air exposures, durations are seasonal (intermediate-term intervals, lasting from one week to one year) and annual. For bystanders, the exposures are primarily short-term (i.e., intervals of 7 days or less), although seasonal and annual exposures are possible for individuals living and working adjacent to multiple tomato and potato fields.

Bystander exposures to airborne endosulfan were estimated using data from air monitoring conducted 6 – 86 m from the edges of a San Joaquin County apple orchard during an application of endosulfan. The estimated short-term exposures of bystanders to endosulfan were 0.00124 mg/kg/day (1.24 μ g/kg/day) for infants and 0.00059 mg/kg/day (0.59 μ g/kg/day) for adults. Seasonal exposure and annual exposure durations were estimated to be 1 month, as repeated applications adjacent to any one individual are considered unlikely for longer intervals. Seasonal ADD estimates for bystander exposures to endosulfan were 0.00046 mg/kg/day (0.46 μ g/kg/day) for infants and 0.00022 mg/kg/day (0.22 μ g/kg/day) for adults. Annual ADD estimates for bystanders were 0.000038 mg/kg/day (0.038 μ g/kg/day) for infants and 0.000018 mg/kg/day (0.018 μ g/kg/day) for adults.

Ambient air exposures were estimated based on monitoring of endosulfan in ambient air in Fresno County and assuming high-use period of 7 months, based on use reported in Fresno County. Seasonal ADD estimates for ambient air exposures to endosulfan were 0.000019 mg/kg/day (0.019 μ g/kg/day) for infants and 0.000009 mg/kg/day (0.009 μ g/kg/day) for adults. Annual ADD ambient air estimates were 0.000011 mg/kg/day (0.011 μ g/kg/day) for infants and 0.000005 mg/kg/day (0.005 μ g/kg/day) for adults.

What are the potential health effects from acute and repeated exposures to endosulfan?

ACUTE TOXICITY:

a) Acute Oral No Observed Effect Level (NOEL)

The adverse effects observed in laboratory animals following acute oral exposure to endosulfan include clinical signs of neurotoxicity, deaths, neurobehavioral effects, reductions in body weight, and increased gross and histopathological effects. The possible acute oral effects from endosulfan included effects observed in the LD₅₀/LC₅₀ studies and in a rabbit developmental study. The effects observed in the LD₅₀/LC₅₀ studies included death, clinical signs, and liver, kidney, intestine, lung and adrenal

toxicity. Liver changes were a granular-appearance, degeneration of hepatocytes with foamy cytoplasm and bile duct proliferation. Kidneys appeared congested and proximal convoluted tubules were necrotic and desquamated. Adrenal cortex showed swollen foamy cytoplasm, with eccentric nuclei. Congested lungs containing hemorrhagic areas were observed, along with irritation of the small and large intestine. Clinical signs were increased preening, salivation, excessive masticatory movements, lacrimation, exophthalmia, hyperresponsiveness to sudden sound and tactile stimuli, hyperexcitability, dyspnea, decreased respiration, ataxia, depression of activity, discharge from eyes, nasal discharge, sprawling of the limbs, decreased reflexes (placement, pain, corneal, pupillary light, righting, startle, paw, cutaneous) and tremors, tonic and clonic convulsions and death.

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. 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. In these studies the lowest observed effect levels 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 this study and it provided the lowest acute oral NOEL for evaluating exposure and to calculate the margin of exposure (MOE) for potential acute single-day (non-inhalation) human exposures to endosulfan.

b) Acute Dermal NOEL

There were no FIFRA Guideline acceptable studies for acute dermal exposure to endosulfan technical. Therefore, the oral acute NOEL (0.7 mg/kg) was used for determinations of MOEs for acute dermal occupational exposure and for swimmer exposure in surface water.

c) Acute Inhalation NOEL

An acceptable acute inhalation exposure study was not available to obtain an acute inhalation NOEL. However an acceptable subchronic rat inhalation (the only one acceptable by FIFRA Guidelines) study with a NOEL of 0.0010 mg/L (0.194 mg/kg/day) was used to calculate the potential for acute single-day inhalation exposure to workers, and for exposure to endosulfan in ambient air or to bystanders. In this study, endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29-day recovery. The NOEL for inhalation was 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). The NOEL of 0.194 mg/kg/day is lower than the oral NOEL of 0.7 mg/kg/day from the rabbit developmental study and more importantly, it is route-specific. The study was therefore selected as the definitive study for the critical inhalation 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 was used to estimate the margin of exposure (MOE) for acute inhalation (occupational and (non-occupational) ambient air and bystander exposure).

SUBCHRONIC TOXICITY:

a) Subchronic Oral NOEL

For the definitive subchronic oral NOEL a rat dietary reproduction study was selected. In this study parental effects were observed after an exposure of 24 weeks throughout pre mating, mating, gestation, lactation and weaning for 2 generations. 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. The NOEL was used to estimate the subchronic dietary exposure to endosulfan.

b) Subchronic Dermal NOEL

There were no FIFRA Guideline acceptable studies for subchronic dermal exposure to endosulfan technical. Therefore, the reproduction oral NOEL in rat (1.18 mg/kg/day) was used for determinations of MOEs for seasonal dermal occupational exposures and for exposures to swimmers in surface water.

c) Subchronic Inhalation NOEL

The definitive study for subchronic inhalation exposure was a study performed in the rat, where endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29 day recovery. 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. It was therefore selected as the definitive study for the critical inhalation NOEL of 0.0010 mg/L (0.194 mg/kg/day) to estimate the MOE for seasonal (non-occupational) ambient air and bystander exposure.

CHRONIC TOXICITY:

a) Chronic Oral NOEL

Chronic dietary endosulfan exposure to dogs showed that neurotoxicity was the most sensitive endpoint for chronic oral endosulfan toxicity. The NOEL was 0.57 mg/kg/day for males and 0.65 mg/kg/day for females, based on clinical signs of violent contractions of the upper abdomen and 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. 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. This study was acceptable according to FIFRA Guidelines and the NOEL of 0.57 was used to determine MOE for both dietary and worker exposure.

b) Chronic Dermal NOEL

There were no FIFRA Guideline acceptable studies for chronic dermal exposure to endosulfan technical. Accepted default procedure is to use the chronic oral NOEL in dog (0.57 mg/kg/day) for determinations of MOEs for chronic dermal occupational exposures and for exposures to swimmers in surface water.

c) Chronic Inhalation NOEL

An acceptable chronic inhalation exposure study was not available to obtain a chronic inhalation NOEL. Therefore, an acceptable subchronic rat inhalation study with a NOEL of 0.0010 mg/L (0.194 mg/kg/day) was used to calculate the potential for chronic inhalation exposure to workers, and for exposure to endosulfan in ambient air or to bystanders. In this study, endosulfan was administered by aerosol (nose-only) for 21 days at 6 hours per day, followed by a 29-day recovery. The NOEL for inhalation was 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). A 10x uncertainty factor for extrapolation from subchronic to chronic was applied to the NOEL of 0.194 mg/kg/day to give a final critical ENEL of 0.0194 mg/kg/day. This dose is lower than the chronic oral NOEL of 0.57 mg/kg/day from the chronic dog dietary study and more importantly, it is route-specific. The study was therefore selected as the definitive study for the critical NOEL of 0.0194 mg/kg/day and a LOEL of 0.03873 mg/kg/day. This NOEL will be used to estimate the MOE for chronic occupational and (non-occupational) ambient air and bystander exposure.

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. These observations, however, were from studies in the open literature (not FIFRA Guideline studies) and they occurred at doses greater than those that induced neurotoxicity. The developmental neurotoxicity study recently received and reviewed by DPR (acceptable, according to FIFRA Guidelines) 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. Due to these results, the USEPA is re-evaluating their current position on endosulfan as a potential endocrine disruptor and they are re-evaluating their use of the FQPA safety factors for acute and chronic exposures.

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.

Is there any potential cancer risk from exposure to endosulfan?

No evidence observed from *in vivo* studies or *in vitro* genotoxicity studies.

Does the concentration of endosulfan in the air pose a potential health hazard for humans?

The risk for non-carcinogenic health effects can be expressed as a margin of exposure (MOE), which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human populations and the sensitive subgroup.

Compounds, such as endosulfan that may exceed health protective levels in the air necessitate listing as a TAC. Consideration as a possible TAC applies an additional 10x factor,

meaning that, in this case, an MOE of less than 1000 would meet the criterion for identification as a TAC.

OCCUPATIONAL & PUBLIC RISK MARGINS OF EXPOSURE (MOEs): In each occupational (dermal, oral, inhalation) there were MOEs less than 100 (primarily for short term) and in several cases the MOEs were less than 1.

DIETARY MOEs: The MOEs from anticipated endosulfan residues for acute toxicity (95th percentile, UB) were all well above 100; however, the acute 95th percentile MOEs from tolerance levels of endosulfan for apple, melon and tomato in selected population groups were all, except for seniors 55+ years, less than 100. Therefore for these commodities, current tolerances exceed levels that would be considered health protective for all groups except seniors 55+ years of age. For dietary exposure, all population subgroups have MOEs (acute 95th percentile and chronic) greater than 100 for acute and 1000 for chronic.

AGGREGATE (Combined Occupational plus Dietary) MOEs: There is a preponderance of short-term seasonal and annual scenarios (both aggregate and route-specific) where the MOEs fall well below 100. However, there are also some MOEs that are close to or greater than 100.

PUBLIC RISK MARGINS OF EXPOSURE (MOEs): MOEs for all route-specific and aggregate scenarios (inhalation exposure to bystanders and in ambient air and to swimmers in surface water) were greater than 100 (except for bystander infants, short term). However in cases where the inhalation MOEs were less than 1000, the criterion have been met for identifying endosulfan as a TAC. In cases where MOEs for endosulfan exposure to swimmers in surface water are less than 100, then mitigation procedures may be needed to ensure health protective exposure to the public.

Aggregate short-term inhalation exposure to bystanders [infants (non-nursing, < 1 year of age)] has an MOE of less than 100 (91), however, short-term inhalation exposure alone has an MOE of 156 (diet comprises 72% of the total short-term inhalation exposure). Therefore, it is only the aggregate exposure for this population sub-group on a short-term basis that exceeds health protective levels. All other exposures for infants, and adults in ambient air or as bystanders for all periods are greater than 100.

On that basis, the aggregate inhalation MOE for ambient air [infants (non-nursing, < 1 year of age)] does not exceed 1000 (945), however the inhalation exposure MOE for this group is greater than 1000 (1764). All other exposures for infants, and adults in ambient air for all periods are greater than 1000.

All MOEs (exposure and aggregate) for infant and adult bystander groups (STADD, SADD, AADD) have MOEs less than 1000, except the exposure for adult bystanders (AADD).