Office of Environmental Health Hazard Assessment

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MEMORANDUM

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DATE: September 12, 2007

SUBJECT: FINDINGS ON THE HEALTH EFFECTS OF THE ACTIVE INGREDIENT: **ENDOSULFAN**

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) findings for the active ingredient endosulfan. These findings were prepared in response to the risk characterization document revision 1 SRP Draft (RCD, dated May 25, 2007) and the final draft exposure assessment document (EAD, dated June, 2007) for endosulfan prepared by the Department of Pesticide Regulation (DPR). The information contained in these documents served to identify endosulfan as a candidate toxic air contaminant (TAC).

Office of Environmental Health Hazard Assessment's Findings On the Health Effects of Endosulfan

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (Cal/EPA) provides consultation and technical assistance to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings. OEHHA previously reviewed and commented on the draft documents prepared by DPR on the evaluation of human health risks associated with potential exposure to endosulfan. These documents are used by DPR in considering whether to list endosulfan as a TAC. As part of its statutory responsibility, OEHHA has also prepared these findings on the health effects of endosulfan which are to be included as part of DPR's Risk Characterization / Toxic Air Contaminant (RCD/TAC) documents.

Chemical Identification

1. Endosulfan is an insecticide used to kill a wide variety of insects infesting a range of crops. It is classified as a chlorinated hydrocarbon of the cyclodiene group, or organochlorine. Endosulfan exists in α and β isomeric forms. The α isomer is a more potent inhibitor of chloride flux in nerve cells (see Mechanisms of Toxicity below) and has been found at higher concentrations in air monitoring studies (see below).

Usage and Reported Illnesses

2. Today the crops most commonly treated with endosulfan are grapes, melons, lettuce, tomatoes and cotton. Currently there are six formulated products containing endosulfan that are registered for use in California. The yearly use of endosulfan in California has been declining, from 180,000 pounds in 1998 to 153,000 pounds in 2004.

3. Between 1992 and 2004, the Pesticide Illness Surveillance Program of DPR recorded 63 illnesses that likely involved exposure to endosulfan. Of these, nine resulted from drift in the air following endosulfan application. Most of the illnesses were skin and/or eye irritation. It was not indicated in the report how many of these illnesses were non-occupational.

Environmental Fate

4. Endosulfan in the environment is subject to both hydrolysis and photolysis. Fungi and bacteria degrade endosulfan under both aerobic and anaerobic conditions. Endosulfan adsorbs strongly to soil. California drinking water systems drawing their water from surface water bodies or from wells were monitored for endosulfan from 1986 to 2003. The absence of endosulfan from surface-derived

samples, and the low percentage of positive samples from well water, suggest that drinking water is not a significant source of human exposure to endosulfan.

5. Air monitoring in California shows that endosulfan can drift many miles after aerial application to field crops. It also volatilizes from soil, water and plants. Thus, populations close to or far from agricultural fields can be exposed via the air.

6. Endosulfan bioaccumulates in aquatic plants and animals. It is rapidly cleared from aquatic animals post-exposure.

Endosulfan in Ambient Air

7. The ambient air is defined as the air away from agricultural sites of endosulfan application. Endosulfan has been detected in ambient air sampled from urban and unpopulated areas in three studies relating to agricultural applications in California in 1985, 1996 and 1999. In 1985 DPR monitored the air at three residential sites near agricultural fields in Monterey County. In 1996 the California Air Resources Board (ARB) sampled air in Fresno County over a five-week interval during the summer; these included four monitoring sites located in populated areas in the vicinities of agricultural land and one urban site. In 1999 the ambient air was also monitored in Tulare County in a study designed to determine if endosulfan moved up-slope into the Sierras as a result of its application in the Central Valley. The 1996 ARB study was chosen for estimating ambient air exposures for two reasons: it contained the greatest number of endosulfan detections and the levels were higher than those of the other two studies. The monitoring period (July 29 to August 29) approximately corresponded to the period of greatest endosulfan use (June-August). Air samplers were placed approximately 1.5 meters above single-story school buildings in vicinities of agricultural fields. The sampler at the urban site was placed above a two-story building. For α-endosulfan, 66 of 75 samples taken from the sites near agricultural land contained concentrations above the limit of quantification (LOQ, determined by the analytical limit of detection and quantity of air sampled), ranging from 0.0093 to 0.32 $\mu g/m^3$. For β-endosulfan, only two of 75 samples (0.016 and 0.031 $\mu g/m^3$) were above the LOQ. None of the samples from the urban site had endosulfan levels above the LOQ. These monitoring data were used to calculate the seasonal and annual human exposures to endosulfan via the ambient air.

Endosulfan In Air Near Application Sites (For Bystander Exposures)

8. Persons near pesticide application sites are subject to relatively high exposures via inhalation should the chemical drift in the air into the area immediately surrounding the field (termed bystander exposure). The ARB monitored endosulfan concentrations near an apple orchard treated by airblast application of endosulfan in San Joaquin County in 1997. Four monitoring sites surrounded the

orchard within approximately ten meters of an edge. Application occurred on April 8 between 5:45 and 7:45 am. Monitoring was for three days, starting on the day of application. For 28 samples, 27 α-endosulfan concentrations were above the LOQ, ranging from 0.0078 to 1.4 $\mu g/m^3$. For β-endosulfan, 16 samples had concentrations above the LOQ, ranging from 0.012 to 0.33 $\mu g/m^3$. A 24-hour time-weighted average (TWA) concentration for the day of application, and a 3-day TWA concentration that included the two days post-application are estimated in the RCD/TAC document. The TWA concentrations of endosulfan were used to calculate short-term (24-hour TWA), seasonal (3-day TWA) and annual (3-day TWA) bystander exposures. The short-term bystander exposures were anticipated to equal or exceed short-term exposures via the ambient air.

Calculating Human Exposure via Ambient Air

9. Seasonal (one week to one year) and annual (one year) exposures via the ambient air are estimated in the RCD/TAC document using the following values. The ambient air concentration was the mean endosulfan concentration measured at the monitoring site (ARB Fresno study) that detected the highest levels (mean = 0.062 $\mu g/m^3$). Breathing rates were 0.59 m^3/kg-day for infants and 0.28 m^3/kg-day for adults. Inhalation absorption was assumed to be 100 percent. The Seasonal Absorbed Daily Dosage (SADD, Table 1) is calculated by multiplying the breathing rate by the air endosulfan concentration. The Annual Absorbed Daily Dosage (AADD, Table 1) is calculated by multiplying the SADD by 7/12 based on the reported seven month high use period per year for endosulfan in Fresno County from 2000 to 2004. Short-Term Absorbed Daily Dosage (STADD) was not calculated for exposure to ambient air. The short-term exposures via the ambient air were anticipated to equal or less than the short-term bystander exposures. OEHHA agrees with this approach.

Table 1. Seasonal and Annual Exposures to Endosulfan via the Ambient Air

	Infants	Adults
STADD mg/kg-day	See bystander in Table 2	See bystander in Table 2
SADD mg/kg-day	0.000037	0.000017
AADD mg/kg-day	0.000021	0.000010

Calculating Bystander Exposures

10. Short-term (up to one week), seasonal (one week to one year) and annual (approximately one year) bystander exposures (Table 2) are estimated in the RCD/TAC document. For monitoring performed near an apple orchard treated by airblast application of endosulfan (see above), the monitoring station with the highest measured values gave a 24-hr TWA of 1.63 $\mu g/m^3$ and a 3-day TWA of 0.952 $\mu g/m^3$. The 24-hr TWA was adjusted upward because an application rate of 1.5 lbs of active ingredient per acre (AI/acre) was used instead of the maximum application rate allowed of 2.5 lbs AI/acre. Therefore, the 24-hr TWA was multiplied by 2.5/1.5 to yield 2.72 $\mu g/m^3$. Seasonal and annual exposure

estimates were not adjusted in this manner. Breathing rates and percent inhalation absorption were as described above for ambient air exposures. Short-Term Absorbed Daily Dosage (STADD) was calculated by multiplying the adjusted 24-hr TWA (2.72 $\mu g/m^3$) by the breathing rate. Seasonal Absorbed Daily Dosage (SADD) was calculated by multiplying the 3-day TWA (0.952 $\mu g/m^3$) by the breathing rate. Annual Absorbed Daily Dosage (AADD) was calculated by dividing the SADD by 12, since it was considered unlikely that repeated applications of endosulfan would occur near the same individual for longer than one month. OEHHA agrees with this approach.

Table 2. Short Term, Seasonal and Annual Bystander Exposures to Endosulfan

	Infants	Adults
STADD mg/kg-day	0.00160	0.00076
SADD mg/kg-day	0.00056	0.00027
AADD mg/kg-day	0.000047	0.000022

Mechanisms of Toxicity

11. Endosulfan binds to the γ-amino-butyric acid (GABA)-gated chloride channel receptor, thereby inhibiting chloride flux. This is thought to be the primary mechanism by which endosulfan causes generalized brain stimulation and neurotoxicity in mammals. Effects of endosulfan on developing male reproductive organs suggest it is also an endocrine disruptor. This may also occur through inhibition of GABA-gated channels, or possibly through direct binding of endosulfan to endocrine receptors. This latter mechanism is supported by the estrogenic, antiandrogenic and proliferative effects of endosulfan tested in cultured MCF-7 human breast carcinoma cells (Andersen et al., 2002; VanParys et al., 2006). Thus, endosulfan is a potential accelerant of estrogen-dependent tumor growth (e.g., breast cancer).

Pharmacokinetics

12. Almost 90 percent of orally administered endosulfan (rats) was eliminated via the urine and feces (bile) within 120 hours. Therefore, it is reasonable to assume that oral absorption is close to 100 percent. Despite the chemical's lipophilicity, it is rapidly eliminated via feces and urine. Shortly after oral administration, endosulfan concentrated in the kidney and liver, where it was metabolized into endosulfan sulfate, lactones and ethers. In toxicity studies, the kidneys and liver were also sites of increased organ mass and induction of metabolizing enzymes. Dermal absorption was 47 percent over five days in rats. No pharmacokinetic data were located for inhalation exposures. Therefore, it is appropriate to assume 100 percent absorption via inhalation.

Acute Toxicity Studies in Animals

13. The lowest oral LD_{50}s for endosulfan were 7.38 mg/kg in male mice and 9.58 mg/kg in female rats (both by gavage). For the oral route, the lowest acute no-observed-adverse-effect level (NOAEL) was 0.7 mg/kg-day in a rabbit developmental toxicity study (see below) based on clinical signs in does during the first day of treatment. Inhalation LC_{50} values in rats (four-hour exposure) were 34,500 $\mu g/m^3$ (5.52 mg/kg) for males and 12,600 $\mu g/m^3$ (2.02 mg/kg) for females (Hollander and Weigand, 1983). At 3,600 $\mu g/m^3$, where no animals died, the following were observed: dyspnea, trembling, passivity and disturbed equilibrium. At higher concentrations causing some lethality the following were observed: tremors, tonic-clonic convulsions, decreased corneal reflex, decreased papillary light reflex, decreased righting reflex, decreased startle reflex, decreased paw reflex and decreased cutaneous reflex. There was no NOAEL for this acute inhalation study; the lowest observed adverse effect level (LOAEL) was 3,600 $\mu g/m^3$ air (0.567 mg/kg) based on the clinical signs described above. The subchronic inhalation study in the rat (see below) however, did identify a NOAEL (0.194 mg/kg-day). This subchronic inhalation NOAEL was lower than the lowest acute oral NOAEL (0.7 mg/kg-day from the rabbit developmental study). Accordingly, the most appropriate NOAEL for evaluating acute inhalation exposures in people is the rat subchronic inhalation NOAEL.

Subchronic Toxicity Studies in Animals

14. Over 16 subchronic studies were available, with all but one performed in the rat. Clinical signs of neurotoxicity included tonic/clonic convulsions and behavioral (memory) effects. Pathological effects were most often noted in the liver and kidney and in hematology. For the oral route, the lowest NOAEL was 1.18 mg/kg-day from a rat reproduction study based on increased kidney and liver weights in parental animals treated for 24 weeks. For the inhalation route (Hollander *et al.*, 1984), rats were exposed nose-only for 21 days at six hours per day (five days per week). A NOAEL of 0.194 mg/kg-day (1,000 $\mu g/m^3$) was identified based on clinical signs of neurotoxicity, decreased bodyweight gain, food and water consumption, and clinical chemistry parameters. The subchronic NOAEL for the inhalation route is six fold lower than the subchronic NOAEL for the oral route. Therefore, the subchronic inhalation NOAEL of 0.194 mg/kg-day is the critical NOAEL for evaluating seasonal inhalation exposures in people.

Chronic Toxicity and Carcinogenicity Studies in Animals

15. A total of seven chronic studies were available. A two-year dietary study in the rat (Ruckman *et al.*, 1989) and a one-year dietary study in the dog (Brunk, 1989) both identified a NOAEL of 0.6 mg/kg-day. In rats the NOAEL was based on aneurysms, glomerulonephrosis/nephritis, enlarged kidneys, proteinuria and decreased bodyweight gain at 2.9 mg/kg-day. Reduced testis weight was observed at all dose levels (statistically significant at the two highest dose levels),

with no histopathological correlates. In dogs the NOAEL was based on clinical signs of neurotoxicity, premature termination due to animal morbidity and decreased bodyweight gain/food consumption at 2.09 mg/kg-day. No chronic inhalation study was available. Therefore, the subchronic inhalation NOAEL of 0.194 mg/kg-day in the rat was divided by an uncertainty factor of 10 for extrapolation to chronic exposures, yielding an estimated no-effect level (ENEL) of 0.0194 mg/kg-day. Since the critical NOAELs for acute, subchronic and chronic dosing of rats via the oral route were 2.0, 1.18 and 0.6 mg/kg-day, respectively, OEHHA finds that this relatively narrow range (3.3-fold) suggests that the 10-fold uncertainty factor for subchronic to chronic exposure extrapolation used to derive the ENEL is sufficiently health-protective. This chronic inhalation ENEL is more than 30-fold lower than the chronic dietary NOAELs discussed above that were used in both the risk characterization document (RCD) and by U.S. EPA to evaluate chronic oral exposures. Therefore, the ENEL is the appropriate value for evaluating chronic inhalation exposures in people.

Two carcinogenicity studies were available that were compliant with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), one performed in the rat (Ruckman *et al.*, 1989) and one performed in the mouse (Donaubauer, 1988). Both were negative for carcinogenicity. Three older rodent studies (Hazelton for NCI, 1978; Powers *et al.*, 1978 for NCI; WHO, 1984) were also negative for carcinogenicity, although each had unacceptably high animal mortality and/or other serious methodological problems. A reanalysis of pathology slides from the two National Cancer Institute (NCI) studies of 1978 suggested that both were positive for carcinogenicity (Reuber, 1981, Sci Total Environ **20**: 23-47). Based on this information, we find that there is insufficient evidence to suggest endosulfan is carcinogenic.

Reproductive Toxicity Studies in Animals

16. There was a single two-generational reproductive toxicity study available in the rat (Edwards *et al.*, 1984). The parental NOAEL was 1.1 mg/kg-day in males and 1.3 mg/kg-day in females based on increased kidney and liver weights and decreased bodyweight gain. These were also the reproductive NOAELs, based on a slight decrease in mean litter weight. Since this was a relatively old study, a number of developmental markers were not assayed including crown-rump length, skeletal stains, vaginal opening and preputial separation. Effects consistent with endocrine disruption of the male reproductive system have been observed in the testis (Ahmad *et al.*, 1993; Chitra *et al.*, 1999; Dalsenter *et al.*, 1999; Sinha *et al.*, 2001a), which in some cases occurred at lower doses in neonatal and prepubescent animals compared to adults (Sinha *et al.*, 1995; Sinha *et al.*, 1997). These effects included decreased sperm counts, altered spermatogenesis and decreased metabolism in the testis. When male reproductive performance was measured in rats (Edwards *et al.*, 1984), however, it was not affected by exposure to endosulfan. Thus, there is evidence that endosulfan

induces male reproductive toxicity in rats, albeit at somewhat higher exposure levels than those causing subchronic neurotoxicity (see Finding 14).

Developmental Toxicity Studies in Animals

17. Two developmental toxicity studies were available in the rat and one in the rabbit. A developmental neurotoxicity study was also available in the rat. Only one of the two rat developmental studies identified NOAELs: a maternal NOAEL of 2.0 mg/kg-day based on clinical signs and decreased bodyweights and a developmental NOAEL of 2.0 mg/kg-day based on reduced fetal weight and length and small or unossified sternbrae (Fung, 1980a). In the rabbit study (Nye, 1981) the maternal NOAEL was 0.7 mg/kg-day based on mortality and clinical signs. No developmental toxicity was observed (developmental NOAEL = 12 mg/kg-day). In the developmental neurotoxicity study in rats (Gilmore *et al.*, 2006), neonates and pups had decreased bodyweights at the lowest dose level tested (3.74 mg/kg-day). This was also the LOAEL for maternal effects, based on lower bodyweights and food consumption. This study detected small delays in preputial separation in males at 10.8 mg/kg-day and vaginal opening in females at 3.74 mg/kg-day. There were no effects on sperm motility, sperm count (normalized to gram of testis or epididymis) or sperm morphology at the highest dose level tested (30 mg/kg-day); however, data on total sperm counts, testis weights, and epididymis weights were not presented. Thus, developmental toxicity has not been detected at the low exposure levels that caused subchronic neurotoxicity (see Finding 14).

Neurotoxicity Studies in Animals

18. A number of neurotoxicity studies were available, primarily in the rat. An acute neurotoxicity study in rats (gavage) showed a greater sensitivity of females compared to males (Bury, 1997). The female NOAEL was 1.5 mg/kg and the male NOAEL was 12.5 mg/kg, both based on mortality and clinical signs. The developmental neurotoxicity study in the rat (dietary) covered the dosing of females from gestation day six through lactation day 21. The maternal LOAEL and pup developmental LOAEL were both 3.74 mg/kg-day (lowest dose level tested), based on decreased bodyweights. No neurological effects were observed in either the dams or pups (highest dose level tested = 30 mg/kg-day). In some other studies from the literature, younger rats appeared to be more sensitive to the neurotoxic effects of endosulfan than adults (Zaidi *et al.*, 1985; Seth *et al.*, 1986). A study in hens failed to detect any delayed neurotoxicity (Roberts and Phillips, 1983).

Genotoxicity

19. Gene mutation studies were performed with endosulfan in bacteria, yeast, mouse lymphoma cells and *Drosophila* (sex-linked recessive lethals). Both positive and negative results were reported. Chromosome damage was tested *in vivo* and in

cultured cells by measuring chromosome aberrations (positive, *in vivo*, germ cell *in vivo* {e.g., Pandey *et al.* 1990, Mutat Res **242**: 1-7}, negative, *in vitro, in vivo*), micronuclei (negative, *in vivo*, positive *in vivo* {e.g., Lajmanovich *et al.*, 2005, Mutat Res **587**: 67-72, Neuparth *et al.*, 2006, Bull Environ Contam Toxicol **76**: 242-8}, positive *in vitro* {e.g., Pistl *et al.*, 2001, Vet Hum Toxicol **43**: 78-82}), sister chromatid exchange (SCE) (positive *in vivo, in vitro* {e.g., Lu *et al.*, 2000, Environ Health Perspect **108**: 559-61}), and dominant lethal induction (positive, negative). Additional studies included unscheduled DNA synthesis in cultured rat hepatocytes (negative), DNA adduct formation in cultured human and rat cells (positive), gene conversion in yeast (positive and negative) and DNA strand breaks (positive, *in vitro* {e.g., Bajpayee *et al.*, 2006, Environ Mol Mutagen **47**: 682-92}, *in vivo* {e.g., Pandey *et al.*, 2006, Ecotoxicol Environ Saf **65**: 56-61}). Thus, while several standard assays were negative, there is some evidence that endosulfan is genotoxic.

Calculating Margins of Exposure (MOEs) for Characterizing Human Health Risks

20. OEHHA agrees with the critical NOAELs selected in the RCD for calculating short-term, seasonal, and annual margins of exposure. The critical study for all three timeframes is the inhalation study of Hollander *et al.* (1984). This was performed with male and female rats, exposed nose-only for 6 hr/day, 5 days/week for 21 days. The LOAEL was 0.387 mg/kg-day based on clinical signs, decreased bodyweight gain and food consumption, increased water consumption and clinical chemistry parameters. The NOAEL was 0.194 mg/kg-day. This NOAEL was used directly for short-term and seasonal MOE calculations. For calculating annual MOEs, an estimated no-effect level, or ENEL, was derived by dividing the NOAEL from the 21-day inhalation study by an uncertainty factor of 10 for extrapolation from subchronic (seasonal) to chronic (annual) exposures. As discussed in more detail in Finding 15, OEHHA would use the same approach for extrapolating to chronic (annual) exposures.

21. In the RCD, MOEs were calculated by dividing the appropriate NOAEL (or ENEL) by the exposure. Short-term inhalation MOEs were calculated for infants and adults exposed as bystanders. Seasonal and annual inhalation MOEs were calculated for infants and adults exposed through the ambient air or as bystanders. The inhalation MOEs are shown below in Table 3. When using NOAELs from animal studies, DPR regulations specify MOEs of greater than 100 to be health protective, regardless of the route of exposure. Specifically for inhalation exposures to the general public, MOEs of less than 1000 indicate that a chemical is a candidate for listing as a TAC.

    Aggregate MOEs, based on inhalation and dietary exposures, are shown in Table 4. The dietary components are based on the 95th percentile of daily dietary intake of endosulfan by nursing females 13+years old (for short-term aggregate MOEs) or the mean daily dietary intake of endosulfan by nursing females 13+ years old (for seasonal and annual aggregate MOEs).

Table 3. Margins of Exposure (MOEs) in the RCD for Short-Term, Seasonal and Annual Inhalation Exposures via the Ambient Air or as Bystanders

	Infants Ambient Air	Adults Ambient Air	Infants Bystanders	Adults Bystanders
Short-term MOEs	Not calculated	Not calculated	121	255
Seasonal MOEs	5243	11415	346	719
Annual MOEs	970	1940	413	882

Table 4. Aggregate Margins of Exposure (MOEs) in the RCD for Short-Term, Seasonal and Annual Exposures via the Diet and Inhalation either of Ambient Air or as Bystanders

	Infants Ambient Air	Adults Ambient Air	Infants Bystanders	Adults Bystanders
Short-term Aggregate MOEs	Not calculated	Not calculated	78	146
Seasonal Aggregate MOEs	1468	2648	296	595
Annual Aggregate MOEs	657	1241	343	702

22. In the RCD, for endosulfan exposures via the ambient air, inhalation MOEs (Table 3) ranged from 970 to 11415. Adding dietary exposure (Table 4) gave lower MOEs, ranging from 657 to 2648. For bystander exposures, inhalation MOEs (Table 3) ranged from 121 to 882. Adding in dietary exposure (Table 4) gave lower MOEs, ranging from 78 to 702. Bystander infants had a short-term aggregate MOE of 78. This was the only MOE below 100. For this group, 67 percent of the exposure to endosulfan was through the diet and 33 percent was through the air. We note that a number of MOEs, both inhalation-only and aggregate, were below 1000, making endosulfan a potential TAC.

23. Reference concentrations (RfCs) from the RCD for acute, subchronic and chronic exposures to endosulfan based on the NOAEL of 0.194 mg/kg-day from the subchronic rat inhalation study by Hollander *et al.* (1984) are shown in Table 5. For acute and subchronic RfCs, an uncertainty factor of ten was applied for animal to human extrapolation and ten for human variability. For chronic RfC calculation, an uncertainty factor of ten was applied to extrapolate from subchronic to chronic exposure. As discussed in Finding 25 below, OEHHA would add an uncertainty factor to protect infants and children due to their increased sensitivity to the endocrine and neurotoxic effects of endosulfan.

Table 5. Reference Concentrations (RfCs) in the RCD for Acute, Subchronic and Chronic Exposures to Endosulfan

	Infants	Adults
Acute	3.3 $\mu g/m^3$	6.9 $\mu g/m^3$
Subchronic	3.3 $\mu g/m^3$	6.9 $\mu g/m^3$
Chronic	0.33 $\mu g/m^3$	0.69 $\mu g/m^3$

These RfC values can be compared to the concentrations calculated for infants and adults exposed to endosulfan via the ambient air or as bystanders (Table 6). Seven of ten fractional RfC values are greater than ten percent, indicating that for these exposure scenarios, endosulfan should be evaluated further as a possible TAC. Note that if the RfCs were further reduced to protect infants and children from increased susceptibility to the endocrine disrupting and neurotoxic effects of endosulfan, the percent RfC values would be even larger.

Table 6. Percent Reference Concentrations for Ambient Air or Bystander Inhalation Exposures Estimated in the RCD

	Endosulfan Air Concentration as a Percentage of RfC*	
	Infants	Adults
Ambient Air		
Acute (short-term)	Not calculated	Not calculated
Subchronic (seasonal)	2%	1%
Chronic (annual)	11%	5%
Bystanders		
Acute (short-term)	82%	39%
Subchronic (seasonal)	29%	14%
Chronic (annual)	24%	11%

*Endosulfan air concentration as a percentage of RfC was calculated by dividing the exposure rate for each exposure scenario (Tables 1 and 2 of these findings) by the breathing rate, and expressing each of those values as a percentage of the corresponding RfC

Additional Findings

24. No biomonitoring data were available for endosulfan. Therefore, exposure calculations were based solely on air monitoring. Since the five-week period of air monitoring in Fresno County in 1996 did not completely cover the period of highest endosulfan usage that year, ambient concentrations may have been underestimated. On the other hand, since endosulfan usage in California has declined approximately 60 percent from 1996 to 2005, using the 1996 data may overestimate present day exposures.

25. A fairly extensive literature indicates that endosulfan has endocrine-disrupting properties, particularly with regard to the development of male reproductive organs. Effects include reductions in testis weight and/or function (Ruckman *et al.*, 1989; Singh and Pandey, 1990; Ahmad *et al.*, 1993; Chitra *et al.*, 1999; Dalsenter *et al.*, 1999; Sinha *et al.*, 2001a). In addition, there are reports of enhanced neurotoxicity or endocrine disruption by endosulfan in young rats compared to adults (Zaidi *et al.*, 1985; Seth *et al.*, 1986; Sinha *et al.*, 1995; Sinha *et al.*, 1997). Although these effects occurred at higher dose levels than the subchronic inhalation NOAEL of 0.194 mg/kg-day (Finding 14), many of these

studies only had LOAELs and did not have NOAELs. Also, since the subchronic inhalation study used six-week old rats, it is unknown if younger rats would have defined a lower LOAEL and NOAEL under the same conditions. Thus, uncertainty exists as to whether the subchronic inhalation NOAEL is low enough to prevent neurotoxicity and endocrine disruption in young rats or in young humans. Therefore, in calculating an RfC, OEHHA would add an uncertainty factor to protect infants and children due to their greater sensitivity to the endocrine disrupting and neurotoxic effects of endosulfan.

26. In animal tests, technical grade endosulfan caused dermal irritation but was not irritating to the eye. Endosulfan formulated products caused both dermal and ocular irritation. In the guinea pig dermal sensitization test, two endosulfan formulations were negative and one was a moderate dermal sensitizer. Thus, there is a potential risk of dermal sensitization in humans exposed to endosulfan.

27. One study from the published literature found no evidence for cumulative toxicity involving endosulfan and other organochlorine compounds.

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Linda S. Adams
Secretary for Environmental Protection

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September 12, 2007

Dear SRP Members:

The Office of Environmental Health Hazard Assessment (OEHHA) is mandated to review the reports on pesticide candidate Toxic Air Contaminants developed by DPR, and to generate "Findings" as a third party reviewer. DPR has already sent the endosulfan report to you. We are forwarding the OEHHA Findings on endosulfan to you separately. This document and our Findings will be discussed at the September 26th meeting in South San Francisco.

If you have any questions, please call Dr. David Ting at (510) 622-3200.

Sincerely,

David Ting for Anna Fan

Anna Fan, Ph.D., Chief
Pesticides and Environmental Toxicology Branch