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Human health risk assessment of endosulfan: II. Dietary exposure assessment

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ABSTRACT

The California Department of Pesticide Regulation (CDPR) and the United States Environmental Protection Agency (USEPA) performed dietary exposure assessments for endosulfan in 1998 and 2002, respectively. Results of the USEPA assessment showed an increased risk for the population sub group "Children 1 6 years" (>100% of the Population Adjusted Dose [PAD]). USEPA then required registrants to satisfy database uncertainties by performing subchronic neurotoxicity and developmental neurotoxicity studies and, based on the results, USEPA decreased the Food Quality Protection Act (FQPA, 1996) Safety Factor from 10× to 1×. Additionally, several tolerances on commodities consumed in quantity by children were cancelled in 2006. CDPR re evaluated the dietary risk initially performed in 1998 after review of these same studies. Based on a review of the revised USEPA tolerances, decreased usage, decreased consumption, cancellations, and prior health protective margins of exposure (MOEs > 100), CDPR determined that it was not necessary to redo the 1998 exposure assessment. In 2007, USEPA conducted a new human health risk assessment for endosulfan combining food + drinking water residues that characterized dietary risk as %PAD ([Exposure ÷ PAD] × 100). For all relevant USEPA population sub groups, the %PADs were < 100% (health protective benchmark).

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1. 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), patented in 1956 (Ware, 1994), is an organochlorine pesticide consisting of two isomers (α : 64 67%; β : 29 32%; Maier Bode, 1968; NRCC, 1975). Endosulfan binds to and blocks the Cl channel linked to the γ amino butyric acid ($GABA_A$) receptor (Abalis et al., 1986; Ffrench Constant, 1993; Lawrence and Casida, 1984).

In a series of four papers, the CDPR risk assessment for endosulfan is described, including Part I: The Toxicology and Hazard Identification (Silva and Beauvais, 2009); Part II: Dietary Exposure Assessment (this paper); Part III: Occupational Handler Exposure and Risk (Beauvais et al., 2009a); and Part IV: Occupational Reentry and Public Non Dietary Exposure and Risk (Beauvais et al., 2009b). As one of the few organochlorines still registered for use, endosulfan has elicited worldwide concern for many reasons. Besides the known toxicity to fish and aquatic organisms, it is considered a worldwide Persistent Organic Pollutant because it is ubiquitously found in multiple media (air, soil, water and plants; Carrera et al., 2002; Fan, 2008; IPEN, 2008; Naqvi and Vaishnavi, 1993; Suntio et al., 1988; Toledo and Jonsson, 1992; USEPA, 2002a; Usha and Harikrishnan, 2005). The Pesticide Action Network of North America (PANNA, 2008) has campaigned for a total worldwide ban of endosulfan due to concerns that it is a carcinogen, teratogen and a male reproductive toxicant. There is ample evidence that endosulfan is acutely poisonous to humans through accidental and intentional exposure as documented in California by Beauvais et al. (2009a,b), in the United States (USEPA, 2002a), Canada (Health Canada, 2007) and throughout the world (WHO, 1998) with the generally observed effect of neurotoxicity.

CDPR is mandated under the Assembly Bill 2161, also referred to as the Food Safety Act (California Assembly Bill 2161, 1989; Chapter 2), "to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides." The Food Safety Act (1989) also requires CDPR to "monitor processed foods for pesticide residues and other contaminants and establishes a requirement for full reporting of all pesticides used" (Benbrook and Marquart, 1993). If a pesticide poses a dietary risk to human health, CDPR will take regulatory action. Endosulfan is a food use pesticide; i.e., its use is allowed on crops grown for food. In California endosulfan is applied to a wide variety of crops, including numerous kinds of fruits, vegetables, nuts and grains. Therefore, the general population is theoretically exposed via the diet.

The USEPA performs a dietary risk assessment as part of their comprehensive risk assessment process for each food use pesticide. The Office of Pesticide Programs (OPPs) "regulates pesticides to ensure that their use does not pose unreasonable risks to human health or the environment and that pesticide residues in food are safe,"

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(USEPA, 2000c). The Federal Insecticide, Fungicide, and Rodenticide Act FIFRA, 1997a requires that USEPA consider the risks and benefits of food use pesticides in forming regulatory decisions. The FIFRA risk/benefit analysis process was modified by the Food Quality Protection Act of 1996 (FQPA; USEPA, 1997a), which amended both FIFRA and the Federal Food, Drug and Cosmetic Act (FFDCA).

Endosulfan was determined by CDPR to have low no observed effect levels (NOELs) in a rabbit teratology, a rat reproduction and a chronic dog study (Silva and Beauvais, 2009). Since risk assessment incorporates both exposure and toxicity, the low NOELs signaled the potential for unacceptable dietary risks that could require mitigation or cancellation of some food uses.

In 2002, the USEPA Re registration Eligibility Decision (RED, USEPA, 2002a) used a 10×-Safety Factor (SF) required under the FQPA (1996) due to database uncertainties for endosulfan. This resulted in an unacceptable dietary risk for Children 1 6 years. The FQPA and the amended FFDCA and FIFRA required stricter standards for human health and environmental protection for pesticide use (USEPA, 2009). Specifically, additional protection for infants and children was required by the use of additional safety factors in setting an exposure standard. The USEPA updated their dietary risk assessment in 2007 after the database uncertainties for developmental neurotoxicity (DNT; Gilmore et al., 2006) and subchronic neurobehavioral toxicity (Sheets et al., 2004) studies were satisfied. In this paper, the CDPR and USEPA dietary exposure assessments for endosulfan are compared (Carr, 1998; Carr, 2006; Silva, 2008; USEPA, 2002a, 2007). Dietary risk characterizations, as performed by each agency, are also presented.

2. Methods

2.1. CDPR exposure

2.1.1. CDPR residue database and exposure analysis

An acute and chronic dietary exposure assessment were conducted for "total endosulfan" (α and β isomers) and the main metabolite, endosulfan sulfate (USEPA, 1997b), since the relative toxicity of the isomers and the sulfate metabolite are similar. The majority of the raw agricultural commodity (RAC) residue data used for the 1998 CDPR endosulfan dietary exposure analysis were obtained from the following sources: a) registrant commodity field residue studies (Hinstridge, 1968) b) CDPR residue monitoring data (CDPR, 1994, 1995, 1997), and c) USDA 1996 Pesticide Data Program (PDP) monitoring (USDA, 1994c, 1995,1998a).

There were extensive findings of total endosulfan residues detected on USEPA registered RACs in the CDPR market basket surveillance program during 1993, 1994 or 1995 (CDPR, 1994, 1995, 1997). The USDA has a multi residue screen analytical program and the results for total endosulfan are reported in the PDP. The PDP program targets RACs that are likely to be significantly consumed by infants and children.

The acute and chronic analyses were conducted at CDPR with the Exposure 4™ and Exposure 1™ programs, respectively, from the Technical Assessment Systems, Inc. EX™ dietary exposure software (TAS, 1996a,b). The Exposure 4™ program estimates the distribution of user day (consumer day) acute exposure for the US population and specific sub groups (TAS, 1996a). A user day is any day in which at least one food from the label approved commodities is consumed. Potential acute dietary exposures were estimated using the highest measured residue values, the 95th percentile of all values, or the minimum detection limit (MDL) for each commodity (TAS, 1996a; USDA, 1989 92). For commodities with no detected residues a value equal to the MDL is assigned to each commodity. When the residue values were derived from monitoring programs, CDPR assumed that the data represent high end dietary residue levels. When processing data were available, residue levels for the RACs and related food forms were reduced to account for the loss of residues due to washing and other processing methods.

The Exposure 1™ program estimates the chronic (annualized) average exposure for all members of a designated population sub group (TAS, 1996b). Potential chronic dietary exposures were estimated using the average measured residues of all values for each commodity. For commodities with no detected residues a value equal to one half (50%) the MDL is assigned to each commodity. When the residue values are derived from monitoring programs, the assumption is that data represent annual average level in the diet. If percent of the crop treated (%CT) data are available, the average residue was further adjusted by this factor.

Endosulfan is also used seasonally in California. The TAS program does not perform a subchronic dietary analysis; therefore, potential subchronic dietary exposures were estimated using chronic exposure data (average measured residue values of all values for each commodity). Alternatively, both the acute and chronic dietary exposures were used as a bounding range to represent seasonal exposure. There are so many food uses for endosulfan that the "chronic" exposure levels for spring, summer and autumn seasons and all seasons are very similar (0.19, 0.19, 0.21, 0.19 μg/kg/day, respectively, with %CT; Silva, 2008) and do not vary as one might expect if endosulfan had limited uses. The overall exposure for the subchronic scenario would probably be closer to chronic than acute because it is unlikely that a commodity would be consumed at the highest detected residues for the entire season. For a shorter duration (e.g., 1 4 weeks), exposure may likely be closer to the acute rather than the chronic values.

2.1.2. CDPR drinking water data

Endosulfan has been monitored over several years in both surface and ground water in California (detailed in Beauvais et al., 2009b). To detect endosulfan in ground water, between 1986 and 2003 a total of 2758 well water samples collected in 48 California counties (out of 58 counties total) were tested for the presence of endosulfan and endosulfan sulfate (Schuette et al., 2003). Endosulfan was detected in 10 samples, at concentrations ranging from 0.01 to 34.7 μg/L. However, all 10 detections were classified as "unverified," because follow up sampling failed to detect endosulfan or endosulfan sulfate. The lack of confirmed detections, along with reported non detection of endosulfan residues in monitoring of drinking water systems (USDA, 2003, 2004, 2005), indicate that drinking water systems in California drawing from ground water are not likely to be a source of human exposure to endosulfan (Fellers et al., 2004; Fleck et al., 1991; Gonzalez et al., 1987; Ross et al., 1996, 1999, 2000; Troiano et al., 2001). Therefore, CDPR did not incorporate drinking water into the dietary risk assessment.

2.1.3. Tolerances in California

The California Food Safety Act (California Assembly Bill 2161, 1989) requires that each specific commodity tolerance be evaluated individually. Tolerance is the maximum legal residue concentration of a pesticide allowed on RACs and processed foods. They are established by the USEPA at efficacious levels for application rate and frequency but not expected to produce deleterious health effects in humans from dietary exposure (Federal Food, Drug, and Cosmetic Act; FFDCA, Sections 408 409; USEPA, 1997a). For a pesticide that is used on numerous commodities, tolerance assessments are conducted for selected fruits and vegetables. Generally, commodities are selected based on the potential for high levels of exposure. For endosulfan, the tolerances for the following 20 RACs were evaluated: carrot, sweet corn, lettuce, milk fat, potato, strawberry, beans, cauliflower, spinach, peas, peach, summer squash, pear, pineapple, winter squash, broccoli, apple, melon, tomato

and grape (Carr, 2006). These RACs were selected because of high consumption rates or high tolerance values.

2.2. USEPA 2007 exposure

2.2.1. USEPA residue database and exposure analysis

The 2002 USEPA dietary exposure assessment used the Dietary Exposure Evaluation Model (DEEM™) software (USEPA, 2002b). In 2007, the USEPA updated their 2002 dietary assessment with new acute and chronic dietary assessments (USEPA, 2007; Wilbur, 2007). The DEEM software with the Food Commodity Intake Database (DEEM FCID™, Version 2.03) which incorporates consumption data from USDA's Continuing Survey of Food Intake for Individuals (CSFII) from 1994 to 1996 and 1998, was used (USDA, 1994–1998; Exponent, 2004a,b). The same input files (PDP monitoring data, FDA data, %CT data, and drinking water exposure data) from the 2002 dietary assessment were used in this new analysis, while incorporating the FQPA SF change from 10× to 1× (USEPA, 2002c, 2007). A probabilistic refined (Tier 3 acute Monte Carlo) dietary exposure assessment was used to estimate dietary risks as in the 2002 assessment (USEPA, 2000a,b). The 1994–96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days (USDA, 1994–1998). Risks to population sub-groups from pesticide exposures are based on patterns of that sub-group's food consumption and water intake. CSFII data are analyzed and categorized by population sub-groups based on age, season of the year, ethnic group, and region of the country.

For acute dietary exposure assessments with DEEM™, individual one day food consumption data are used and the amounts consumed of each food item can either be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. USEPA uses a "*per capita*" consumption estimate that includes both consumers and non-consumers, whereas CDPR uses "user day" consumption (active food consumption, including only people who consume at least one of the commodities of interest). When the active consumer percentage is high (relative to *per capita* consumption), the variability of consumption is subsequently lower. If variability is low, then the comparative survey commodity consumption rates are therefore more reliable. *Per capita* consumption values can result in lower dietary exposure in individual commodities when compared with active consumers (user days). The differences between *per capita* and active consumer consumption results become less relevant in frequently eaten, ubiquitous commodities (i.e., corn and other grain products, milk, soybean, and refined sugar). Therefore, there is no difference between the intake rate of *per capita* and active consumers (user days) when specific consumption approaches 100% of the total person days.

For chronic exposure assessment with DEEM™, consumption data and residue data are averaged for the entire US population as well as within population sub-groups. An estimate of the residue level is also averaged for each food (whole food, e.g., apple; food form, e.g., apple juice) on the food commodity residue list and then is multiplied by the average daily consumption estimate for a particular food item that will give a residue intake estimate. This residue intake estimate is summed with the residue intake estimates for all other RACs or food forms on the commodity residue list to give the total average estimated exposure (USEPA, 2000a).

2.2.2. USEPA drinking water data

Drinking water residues were not directly incorporated into the 2002 dietary assessment (USEPA, 2002a). At that time, "drinking water levels of comparison" (DWLOC) were compared to the "estimated environmental concentrations" (EEC). In 2007, a screening level assessment of drinking water was performed for endosulfan and residues were determined (Khan, 2002; Wilbur, 2007). The Environmental Fate and Effects Division (EFED) conducted a revised Tier II assessment that calculated EECs in surface water for total endosulfan (α and β isomers and endosulfan sulfate). Water residues, added into DEEM FCID™ program were categorized as "water, direct, all sources" and "water, indirect, all sources."

2.2.3. Tolerances for USEPA

In 1996, the FQPA amended the overall regulation of pesticide residues under FIFRA (USEPA, 1998, 2002c) and FFDCA (USEPA, 2009). Existing tolerances are required to be health based, explicitly with respect to infants and children, using the same standards to establish new tolerances for RACs and their processed forms. Therefore, under FQPA, USEPA was required to reassess all existing endosulfan tolerances using a tiered approach, for all active label approved commodities (USEPA, 2000a).

2.3. Residue adjustments: percent of the crop treated (%CT)

Both CDPR and USEPA use %CT with chronic dietary exposure analysis (CDPR, 2006a; USEPA, 2000a). %CT is an estimate of the acreage under cultivation that is actually treated with a pesticide at least once (e.g., %CT = percentage of total acreage for that crop). The default assumption is that 100% of any crop is treated with a given pesticide. When quality data are available indicating less than 100% is treated, then the default need not be used. The actual %CT varies annually. Using the existing %CT data, it is reasonable to revise the 100% treated assumption downward using more realistic pesticide treatment rates and use patterns. Commodities that used residues data from field trial studies obtained from the registrants (FMC, 1967; Gowan, 1967; Hinstridge, 1968) or state and federal monitoring data in the chronic dietary exposure assessment were considered for %CT adjustments (CDPR, 1994, 1995, 1996a,b, 1997; USDA, 1994a,b, 1996a,c, 1997).

2.4. Highest measured acute residue values: CDPR versus USEPA

With the acute dietary exposure analysis for endosulfan, CDPR used the 95th percentile residue values. This was because CDPR used a deterministic approach by selecting values (point estimates) from the commodities with the highest residues or tolerances. Since the highest residue values were selected on an individual commodity basis, CDPR considered the 95th percentile to be health protective (CDPR, 2009). USEPA sometimes chooses to use a deterministic approach at the 95th percentile for an unrefined (Tier 1 or Tier 2) dietary assessment; however, they used a more refined (Tier 3) method.

USEPA estimates consumption by use of DEEM FCID™ software where pesticide residue values are randomly paired with the CSFII consumption data. The 99.9th percentile of exposure represents the joining of each individual's consumption data set with randomly selected residue values from the residue data set as estimated by probabilistic (e.g., Monte Carlo) analysis (USEPA, 2000b). Due to the randomness of the probabilistic methodology, use of the highest (99.9th) percentile is considered health protective, because unlike in the deterministic estimate you are sampling from the full range of values. CDPR sometimes uses a probabilistic approach (e.g., Monte Carlo) at the 99.9th percentile for a refined dietary assessment. This approach, however, was not selected by CDPR for endosulfan since dietary exposure estimates were acceptable without further refinement.

2.5. Risk characterization methods for CDPR

In the assessment of single route of exposure, the risk for non-oncogenic effect was characterized in terms of a margin of

exposure (MOE), defined as the ratio of the NOEL to the estimated human exposure levels (MOE = NOEL ÷ Exposure). Generally, an MOE of at least 100 is considered protective of human health by CDPR when the NOEL for an adverse systemic effect is derived from an animal study. This MOE allows for the possibility of humans being 10 times more sensitive than animals (10× uncertainty factor [UF] for interspecies variability) and for a 10 fold variation in sensitivity between the lower range of the normal distribution in the overall population and a sensitive sub group (10× UF for intraspecies variability; Dourson et al., 2002).

2.6. Risk characterization methods for USEPA

For acute and chronic USEPA dietary assessments, the risk is characterized as a percentage of a maximum acceptable dose (i.e., a dose resulting in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). Considered to be a safe dose, it reflects the Reference Dose (RfD) that has been adjusted to account for the FQPA SF (USEPA, 2000a,b, 2002c).

$$\text{RfD} \quad \frac{\text{NOAEL}}{\text{UF}\ (10\times\ \text{interspecies}\ \times\ 10\times\ \text{intraspecies}\quad 100)} \quad \text{and}$$

$$\text{PAD} \quad \frac{\text{RfD}}{\text{FQPA SF}}$$

A risk estimate (%PAD) that is less than 100% of the acute (aPAD) or chronic (cPAD) PAD does not exceed the USEPA risk level of concern. The same calculations for dietary %PAD were also used for drinking water.

$$\%\text{PAD} \quad \frac{\text{Dietary/Drinking water exposure}}{\text{PAD}} \times 100$$

3. Results

3.1. CDPR 1998/2007 dietary exposure (Table 1)

3.1.1. Toxicology

The toxicology data used to characterize the risk for the dietary exposure has been described in Silva and Beauvais (2009). An acute NOEL of 0.7 mg/kg/day from a rabbit teratology study (Nye, 1981); a subchronic NOEL of 1.18 mg/kg/day from a rat reproduction study (Edwards et al., 1984) and a chronic NOEL of 0.57 mg/kg/day from a 1 year dog study (Brunk, 1989) were used to calculate dietary risk (Silva and Beauvais, 2009).

3.1.2. Acute (daily) exposure (Table 1)

Potential acute dietary exposures were estimated using the highest measured residue values, the 95th percentile of all values (CDPR, 2009), or the MDL for each commodity (TAS, 1996a; USDA, 1989 92). CDPR evaluated endosulfan residues in the diet for several sub groups; however, three were selected to represent those at highest risk for occupational exposure and/or exposure to the general public (Beauvais et al., 2009a,b) in addition to dietary exposure (Table 1). The sub groups of interest are (1) "Females (13+), nursing," represented the highest dietary exposure level (2.06 μg/kg/day) for adults who could also be occupationally (dermal and air) exposed to endosulfan and also exposed as swimmers in surface water (dermal and non ingested dietary). (2) "Infants (non nursing,<1 year)" was selected as a sub group potentially receiving both a high dietary (3.18 μg/kg/day) and air exposure as application site bystanders. (3) Children (1 6 yr) had the highest dietary exposure of all sub groups (3.30 μg/kg/day) and also had the potential to be exposed (dermal and non ingested dietary) as swimmers (Beauvais et al., 2009a,b). These data are in bold in Table 1.

3.1.3. Subchronic (seasonal) and chronic (annual) exposure (Table 1)

Potential subchronic dietary exposures were estimated using the chronic exposure data (average measured residue values of all values for each commodity), since the TAS, Inc. EX™ (TAS, 1996b) software does not perform subchronic analyses. The same sub groups were selected for the subchronic/chronic dietary exposure analyses as for acute (Table 1).

3.1.4. Lifetime (oncogenic) dietary exposure

There is no calculated oncogenic potency factor for endosulfan since it is not considered oncogenic based on studies performed in animals and has not been reported as carcinogenic in humans (Silva, 2008). Therefore, no cancer risk from lifetime (chronic) die

Table 1
CDPR acute and chronic dietary exposure to anticipated endosulfan residues on raw agriculture commodities (RACs) and the resulting dietary margins of exposure (MOE).

Population sub-groups	Acute exposure 95th percentile[a,c]	Chronic exposure[b,c]	Acute MOE[d]	Subchronic MOE[d]	Chronic MOE[d]
	CDPR 1998 and 2006 (μg/kg/day)		CDPR 1998 and 2006		
US population	1.85	0.19	378	621	3001
All infants < 1 yr	3.08	0.22	227	536	2597
Infant nursing < 1 yr	1.90	0.08	367	1475	7421
Infant non-nursing,<1 yr	**3.18**	**0.28**	**220**	**421**	**2039**
Children 1–6 yr	**3.30**	**0.41**	**212**	**288**	**1407**
Children 7–12 yr	2.09	0.29	336	407	1943
Female 13–19 yr not pregnant, not nursing	1.37	0.18	511	656	3187
Female 20 + yr not pregnant, not nursing	1.51	0.14	462	843	4082
Females 13–50 yr	1.39	0.15	504	787	3840
Female 13 + yr pregnant, not nursing	1.57	0.15	441	787	3846
Females 13 + yr nursing	**2.06**	**0.17**	**340**	**694**	**3448**
Males 13–19 yr	1.37	0.21	513	562	2668
Males 20 + yr	1.38	0.15	508	787	3725
Seniors 55 + yr	1.65	0.14	425	843	4132

Bold indicates groups of concern for CDPR dietary risk assessment.

[a] Exposure based on 1989–1992 Continuing Survey of Food Intakes of Individuals (CSFII; USDA, 1989–92) and residue data from CDPR (CDPR, 1994, 1995, 1996a, 1996b, 1997), Food and Drug Administration (FDA, 1998) and USDA (1994c, 1995, 1996b, 1998). Acute and chronic residue files used anticipated residue values for the commodities.

[b] %CT = Adjustments were made for % crop treated (CDPR, 2006a; USEPA, 2000a).

[c] "Acute" users were consumers (95th percentile based on deterministic, point estimates for residues (Exponent, 2004a). Chronic was "*per capita*" (consumers + non-consumers; Exponent, 2004b).

[d] MOE = NOEL ÷ Exposure Dose. Acute NOEL = 0.7 mg/kg/day (rabbit developmental toxicity; Nye, 1981). Subchronic NOEL = 1.18 mg/kg/day (rat reproductive toxicity; Edwards et al., 1984). Chronic NOEL = 0.57 mg/kg/day (chronic dog study; Brunk, 1989). Chronic dietary exposure data used to calculate subchronic MOE. MOEs based on all USEPA registered RACs.

Table 2
USEPA summary of dietary exposure and risk for endosulfan (2007).

Population sub-group	Acute dietary 99.9th percentile[a]		Chronic dietary	
	Exposure (μg/kg/day)	%aPAD[b]	Exposure (μg/kg/day)	%cPAD[b]
Exposure and risk for drinking water only				
US population	0.47	31	0.003	0.5
All infants < 1 yr	1.21	80	0.010	1.7
Children 1–2 yr	0.47	32	0.005	0.8
Children 3–5 yr	0.46	30	0.004	0.7
Children 6–12 yr	0.28	19	0.003	0.5
Youth 13–19 yr	0.31	20	0.002	0.4
Adults 20–49 yr	0.35	23	0.003	0.5
Adults 50 + yr	0.24	16	0.003	0.5
Females 13–49 yr	0.33	22	0.003	0.5
Exposure and risk for food only				
US population	0.11	7	0.004	0.6
All infants < 1 yr	0.14	9	0.004	0.7
Children 1–2 yr	0.24	16	0.013	2.1
Children 3–5 yr	0.18	12	0.009	1.6
Children 6–12 yr	0.13	9	0.003	1.0
Youth 13–19 yr	0.085	6	0.003	0.6
Adults 20–49 yr	0.090	6	0.003	0.4
Adults 50 + yr	0.10	7	0.003	0.4
Females 13–49 yr	0.090	6	0.003	0.4
Exposure and risk for food and drinking water				
US population	0.48	32	0.007	1.1
All infants < 1 yr	1.21	81	0.015	2.4
Children 1–2 yr	0.53	35	0.017	2.9
Children 3–5 yr	0.55	37	0.014	2.3
Children 6–12 yr	0.30	20	0.009	1.5
Youth 13–19 yr	0.32	21	0.006	0.9
Adults 20–49 yr	0.35	24	0.006	0.9
Adults 50 + yr	0.26	17	0.006	0.9
Females 13–49 yr	0.34	22	0.005	0.9

[a] The USEPA uses the 99.9th percentile of exposure from consumption of food alone (USEPA, 2000b).
[b] The PAD incorporates the Reference Dose (PAD = RfD ÷ FQPA SF); RfD = NOEL ÷ (UF = 10× interspecies variability and 10× intraspecies variability). Risk (%PAD) = ([Exposure ÷ PAD] × 100). A risk estimate < 100% of acute (aPAD) or chronic (cPAD) PAD does not exceed USEPA's level of concern (USEPA, 2000b, 2007). Acute oral NOAEL = 1.5 mg/kg/day (neurobehavioral toxicity, rat; Bury, 1997). Chronic oral NOAEL = 0.6 mg/kg/day (chronic/oncogenicity, rat; Ruckman et al., 1989). A subchronic %PAD was not calculated by USEPA.

tary exposure to endosulfan or any of its degradation products was determined.

3.2. CDPR risk characterization 2007 (Table 1)

The dietary exposure values selected for each population sub group were used to estimate acute, subchronic and chronic MOEs (Table 1). The MOEs for the sub groups of interest for CDPR are de scribed in Table 1.

All MOEs were greater than 100 which signified that they are considered above the health protective benchmark levels for each dietary exposure scenario.

3.3. USEPA 2007 dietary exposure (Table 2)

3.3.1. Toxicology

The USEPA selected an acute NOAEL (USEPA uses the term "no observed adverse effect level") of 1.5 mg/kg/day from an oral (ga vage) neurotoxicity study in rats (Bury, 1997) and a chronic oral NOAEL of 0.6 mg/kg/day from a 2 year dietary feeding study in rats (Ruckman et al., 1989) to calculate dietary risk (USEPA, 2007).

3.3.2. Acute (daily) and chronic (annual) exposure (Table 2)

Analysis of the 1994 96, 1998 CSFII consumption data (USDA, 1994 1998), which took into account dietary patterns and survey respondents, provided the basis for the USEPA selection of the fol lowing population sub groups for acute and chronic exposure in food, drinking water and food plus drinking water: the general US population, all infants (<1 year old), children 1 2, children 3 5, children 6 12, youth 13 19, adults 20 49, females 13 49, and adults 50 + years old (Table 2). When using a refined (Tier 3) acute dietary assessment, USEPA typically bases its regulatory decision at the 99.9th percentile of exposure. More sub groups for children were included than previously (USEPA, 2002a) and "Youth 13 19" was added. Exposures were expressed as μg/kg/day.

3.4. USEPA risk characterization 2007 (Table 2)

In 2002, the USEPA RED showed an unacceptable acute dietary risk for children 1 6 years old (150% PAD) with use of a 10× FQPA SF (USEPA, 2002a). In 2006, a DNT study (Gilmore et al., 2006) and a subchronic neurobehavioral toxicity study (Sheets et al., 2004) were submitted by registrants on request of USEPA due to database uncertainties related to effects of endosulfan as having potential developmental (endocrine disruptor), reproductive and/or neuro behavioral toxicity. Based upon the submitted data, the FQPA SF was reduced to 1× by USEPA while remaining protective of child rens' health (USEPA, 2007). A subchronic risk characterization was not performed by USEPA.

The aPAD and cPAD and the dietary, drinking water and dietary plus drinking water exposure values for each population sub group were used to estimate acute and chronic risk characterization (%PAD; Table 2). The %aPAD and %cPAD were all below the level of concern (LOC) (<100% PAD) for all the sub groups examined for food, drinking water and food plus drinking water (Table 2), sig nifying that they are considered to be at a health protective level.

Table 3
Average annual endosulfan use in California.

Time period	Average annual use[a] (lb)	Highest use crops[b] (lb)
1993–1995	356,970	Cotton (192,000), grapes (47,000), cantaloupe (20,000), head lettuce (20,000)
1996–2000	187,900	Alfalfa (46,420), cotton (36,000), head lettuce (23,800), tomato (15,900)
2001–2004[c]	147,968	Cotton (61,460), tomato (19,850), head lettuce (17,675), alfalfa (14,470)

[a] Average of California CDPR Pesticide Use Report (PUR) data (CDPR, 1994, 1995, 1997, 2002a, 2006b).
[b] The top four crops for each time period based on average annualized pounds used from CDPR PUR. Endosulfan use on California pears averaged 1197 lb/yr 1993–95 (CDPR, 1996a); 259 lb/yr 1996–00 (CDPR, 2002a); 59 lb/yr 2001–2004 (CDPR, 2002b, CDPR, 2006a,b).
[c] 2004 was the most recent year available in 2006 for complete data on individual products on a year by year basis.

4. Re-evaluation of the 1998 CDPR dietary risk assessment

4.1. Lack of necessity for an updated dietary risk assessment by CDPR

The CDPR dietary exposure assessment was re evaluated in 2006 after reviewing the studies (Gilmore et al., 2006; Sheets et al., 2004) required by USEPA and it was determined that a com plete dietary revision and update would not alter the conclusions of the 1998 dietary risk characterization (Carr, 1998; Carr, 2006). The USEPA is the agency responsible for lowering of the FQPA SF from10× to 1× since the FQPA is a federal law (FQPA, 1996; USEPA, 2002c, 2009). CDPR, however, is in agreement with this decision. The following discussion presents the rationale for CDPR's decision not to perform an updated dietary risk assessment.

4.1.1. Updated tolerance assessment

In 1998 there were 72 commodities with human consumption that had USEPA endosulfan tolerances (USEPA, 1999, 2001). The USEPA announced in the Federal Register (USEPA, 2006a,b) the fi nal rule to revoke, remove, modify and establish tolerances that were named in the RED (USEPA, 2002a). Because there are no ac tive registrations, nine of these tolerances have since been revoked (artichoke, canola, mustard seed, raspberry, safflower seed, sugar beet, sugarcane, sunflower seed, and watercress; USEPA, 2006a,b). Tolerances for five commodities, frequently consumed by infants and children, were revoked (beans [succulent], grape [including juice and raisin], peas [succulent], pecan, and spinach), leaving 58 remaining tolerances (USEPA, 2006b). The USEPA con cluded that the revocation of the above tolerances would mitigate acute dietary exposure concerns to acceptable levels for infants and children (USEPA, 2002a).

4.1.2. Revised endosulfan use (Table 3)

Endosulfan use in California (reported in thousands of pounds) over the 15 year interval 1993 2007 peaked in 1994 at 477,187 lb (219,903 kg) and decreased by nearly an order of magnitude, to 52,403 lb (23,820 kg) in 2007 (see the accompanying paper by Beauvais et al., 2009b) (Table 3). The 1996 2000 California annual average use was 187,900 lb. of endosulfan (CDPR, 2002b). The most current four years (2001 2004) available for the CDPR 2006 re evaluation of the dietary risk assessment showed endosulfan annu alized use in California averaged 147,968 lb per year (CDPR, 2006b). A measurable downward trend in California endosulfan use is apparent even when considering annual variability due to weather and pest pressure.

4.1.3. Revised residue data (Table 4)

A complete reassessment of the previous (1998) dietary expo sure would have required an extensive revision of the endosulfan residue database. However, a complete reassessment was unneces sary for three reasons: (1) The existing 1998 dietary exposure assessment resulted in acceptable MOEs for both the acute and chronic scenarios (Silva, 2008). (2) A revised dietary exposure assessment would also result in acceptable MOEs because of post 1998 USEPA endosulfan product label changes, commodity tolerance revocations, decreased use, and residue data changes (Carr, 2006; USEPA, 2006a,b). (3) A new CDPR acute dietary expo sure analysis would be very similar to the recently revised acute dietary analysis by USEPA (USEPA, 2007).

The USDA PDP annual summaries published since the 1998 endosulfan dietary exposure assessment contain residue data rep resenting all 20 commodities that had previously used CDPR data (USDA, 1998a,b, 2000, 2001, 2002, 2003, 2004, 2005, 2006). The 20 commodity residues originating from the CDPR monitoring pro gram would be replaced by PDP values. This could have a meaning ful impact on detected residue values, primarily due to the differences in PDP sample preparation versus the CDPR methods. The following commodities currently use CDPR monitoring data and could be replaced by USDA PDP monitoring data in an updated dietary exposure analysis: broccoli, cantaloupe, cherry, cucumbers, pear, peppers, pineapple, squash, and strawberry. In addition, broc coli would be used as a surrogate to represent five other Brassica varieties with tolerances, cantaloupe would be a surrogate for all melons, squash would represent pumpkins, and cherry could serve as a surrogate for apricot, plum, and prune. Several of these com modities recorded frequent consumption by infants and children in the CSFII databases. The current CDPR dietary exposure guide lines allow for use of representative surrogate residue data. The 1998 dietary exposure assessment did not use this currently ac cepted CDPR and USEPA methodology. Table 4 presents the maxi mum measured value (non distributional) for each monitoring program.

Table 4
Comparative CDPR and PDP maximum measured endosulfan residues.

Commodity	Monitoring program residue (ppm)[a]		
	CDPR[b]	USDA PDP[b]	Comparison
Broccoli[c]	0.1	0.19 (2002)	PDP residue is higher
Cantaloupe[c]	0.57	0.091	CDPR residue is higher
Cherry	0.18	0.041	CDPR residue is higher
Cucumber[c]	0.57	0.44 (2003)	CDPR residue is higher
Pear[c]	0.25	0.16	CDPR residue is higher
Pepper[c]	0.71	1.1	PDP residue is higher[e]
Pineapple[c]	0.09	0.005	Non-detect for each program
Squash[c]	0.31	Fresh: 0.048	CDPR residue is higher
	NA[d]	Processed: 0.02	
Strawberry[c]	0.18	Fresh: 0.68	PDP fresh value higher[e]
	NA	Processed: 0.008	

[a] Maximum detected deterministic values represent both monitoring programs' residues.
[b] CDPR = California Department of Pesticide Regulation. PDP = USDA Pesticide Data Program. CDPR residues used in the 1998 analysis from 1993 to 1995 market basket program (CDPR, 1994, 1995, 1997). PDP data from 1994 (broccoli only) and 1997–2004 annual summaries (USDA, 1994–1998; USDA, 1998a,b, 2000, 2001, 2002, 2003, 2004).
[c] Frequently consumed commodity and a primary candidate for a distributional analysis.
[d] NA = not applicable.
[e] The CDPR program analyzed only raw agricultural commodities.

Table 5
Comparison of percent user-day rates between the 1989–92 and 1994–98 CSFII[a].

Raw agricultural commodity	Apple		Pear		Potato		Tomato	
Population sub-groups	1989[b]	1994[b]	1989[b]	1994[b]	1989[b]	1994[b]	1989[b]	1994[b]
Western US (%)	33	34	7	11	43	71	60	67
Children age 1–6	46	61	8	22	48	78	54	64
Nursing infant	15	25	5	8	11	17	5	8
Non-nursing infant	47	44	15	15	30	35	24	17

[a] A percent user-day rate is the ratio of actual consumers divided by the combination of consumers and non-consumers (*per capita*) for each population sub-group (definition in Carr, 2006).
[b] The 1989–92 CSFII survey used DEEM™ (USDA, 1989–92) and the 1994–98 CSFII (USDA, 1994–1998) used the DEEM-FCID™ program. Comparisons were performed at the 95th percentile of consumption.

4.1.4. User days versus per capita consumption

The increased number of surveyed infants and children in cluded in the 1994 98 CSFII database by USEPA appears to have had an impact on percent user day rates. The percent user day rate is the ratio of actual consumers divided by *per capita* consumption for each commodity. Overall, the percent user day rates for the four surveyed groups in the 1994 98 CSFII database were generally equal to or higher than the consumption rates seen in the 1989 92 populations; however, the two consumption databases were not substantially different (Table 5). The exception was the "non nurs ing infants (<1 year)" sub group (apple and tomato only).

A review of the tolerance, usage, residue, consumption, prior MOEs, and CSFII survey information indicate that an update of the 1998 CDPR endosulfan dietary exposure assessment is there fore not necessary.

5. Discussion

There were several differences in the way CDPR and USEPA per formed their respective dietary risk assessments for endosulfan and they are directly compared below.

5.1. Software

CDPR and USEPA both performed dietary risk assessments for endosulfan in 1998 (Carr, 1998) and in 2002 (USEPA, 2002a). In 2006, after review of the DNT study (Gilmore et al., 2006) and the neurobehavioral toxicity study (Sheets et al., 2004) CDPR re evalu ated their 1998 dietary risk assessment for endosulfan that had been performed with TAS, Inc. EX™ (TAS, 1996a,b). At that time (2006) CDPR was no longer using the TAS, Inc. EX™ software but was using the DEEM FCID™ program (software also used by USEPA). However, it was determined by CDPR that complete reassessment of the previ ous (1998) dietary exposure, requiring an extensive revision of the endosulfan residue database, was unnecessary since the existing 1998 dietary assessment resulted in acceptable MOEs for both the acute and chronic exposure scenarios. Because of post 1998 USEPA endosulfan product label changes, tolerance revocations, decreased use, and residue data changes (discussed in Section 5.4), a revised assessment would also result in acceptable MOEs. A comment by the USEPA on CDPR's 2008 Risk Characterization Document was in agreement with this conclusion (Silva, 2008).

The 2007, USEPA dietary exposure assessment was conducted using the same inputs as the 2002 assessment but using DEEM FCID™ for the update. The only changes were with respect to reduc ing the FQPA SF from10× to 1× after review of the dietary DNT study (see Section 5.3; Gilmore et al., 2006) and incorporating drinking water exposure directly into the analysis.

5.2. Drinking water

CDPR did not calculate risk for drinking water in California be cause there were no endosulfan residues detected. As noted previ ously (Section 2.2.2), endosulfan in drinking water is not considered to be a source of human exposure to endosulfan in California.

The USEPA did not incorporate drinking water into their 2002 dietary risk assessment. It was added to the 2007 update using the DEEM FCID™ as drinking water alone or a combined dietary exposure (food and drinking water). Drinking water was a higher source of exposure when compared to food. Acute exposure for drinking water plus food in the population sub group "All In fants < 1 year" had the highest risk (81% of aPAD). This value, how ever, was still below the LOC for USEPA (<100% of aPAD).

5.3. Food Quality Protection Act (FQPA, 1996; USEPA, 2002c, 2009)

The FQPA SF is generated by USEPA under federal law resulting from passage of the FQPA (1996). The 2002 dietary exposure assessment performed by USEPA concluded that the acute dietary risk from endosulfan was too high (exceeded the USEPA LOC) for the "Children 1 6 years" sub group (150% of aPAD). These conclu sions were based on calculations that incorporated all 72 regis tered uses and an FQPA SF of 10× due to toxicological database uncertainty. After review of the studies required by USEPA (sub chronic neurotoxicity study, Sheets et al., 2004; DNT study, Gil more et al., 2006) the data uncertainty was removed and the USEPA reduced the FQPA SF from 10× to 1×. CDPR agreed with the decision and rationale for decreasing the SF to 1×.

5.4. Tolerance revisions

The USEPA in 2002 proposed that endosulfan tolerances on five commodities should be revoked and their uses cancelled due to dietary concerns, primarily for infants and children. Infants and children comprised the highest exposed groups and, therefore, the groups at greatest health risk. The revocations were for foods frequently consumed by those population sub groups (succulent beans, grapes [including juice and raisin], succulent peas, pecan, and spinach). Pecan is the only RAC on the revocation list not fre quently consumed by infants and children. The USEPA concluded that the revocation of these tolerances would mitigate the acute dietary concerns for infants and children (USEPA, 2006b; final rule). The endosulfan registrants of technical endosulfan also pro posed cancellation of nine uses: artichoke, canola, mustard seed, raspberry, safflower seed, sugar beet, sugarcane, sunflower seed, and watercress (USEPA, 2005). Further, the 2002 RED also de creased the maximum label application rates for a number of com modities. When all 14 uses cancelled, there would be 58 registered uses for endosulfan remaining. When these label changes are made, the dietary exposure risk estimates will further decrease.

5.5. Risk characterization

CDPR characterized dietary risk for endosulfan by use of MOE, while USEPA expressed it as a %PAD. The NOEL/NOAELs from the

acute, subchronic and chronic studies (Silva and Beauvais, 2009; USEPA, 2007) selected by each agency were used to calculate the risk characterization values. An MOE (MOE = NOEL ÷ Exposure) of 100 or greater, based on UFs (10× interspecies × 10× intraspecies = 100) is generally accepted by CDPR to be health protective. USEPA characterizes risk by use of the %PAD (%PAD = [Exposure ÷ PAD] × 100); PAD = RfD [NOEL ÷ UF 10× interspecies, 10× intraspecies] ÷ FQPA SF). The %PAD must be less than 100% of the PAD in order to be health protective, according to USEPA. For CDPR, the acute calculations were done with a NOEL of 0.7 mg/kg/day and for USEPA the NOAEL was 1.5 mg/kg/day (Silva and Beauvais, 2009). Although the acute NOELs were different, the USEPA added drinking water in addition to food exposures, and USEPA used the 99.9th percentile for residue values (USEPA, 2000b; compared with 95th percentile for CDPR; CDPR, 2009), the acute MOEs and the %aPADs were within health protective benchmarks for all population subgroups examined by each agency (Tables 1 and 2). For the calculation of MOEs, CDPR has selected the 95th percentile of the user day exposure levels for each population subgroup as the default upper bound of exposures. USEPA assessment is generally based on *per capita*, rather than user days as practiced by CDPR.

Despite there not being a significant variation in seasonal exposure to endosulfan, subchronic MOEs were calculated due to its use on a seasonal basis in California. All of the subchronic MOEs, calculated with a NOEL of 1.18 mg/kg/day and the chronic dietary residue data (Silva and Beauvais, 2009), were greater than 100 and, therefore, in a health protective range (Table 1).

CDPR and USEPA had chronic NOELs that were similar (CDPR NOEL = 0.57 mg/kg/day; USEPA NOAEL = 0.6 mg/kg/day; Silva and Beauvais, 2009). MOEs (>100) and %cPAD (<100% cPAD) were within health protective levels (Table 2).

USEPA calculated %PAD for drinking water and, while drinking water exposure residues were higher than dietary, the risk associated with the combination of dietary plus drinking water residues did not exceed the level of concern. As a result of the combined exposure, the risk did not exceed the USEPA level of concern (<100% of the PAD) for all acute and chronic subpopulations.

6. Conclusions

CDPR and USEPA initially performed dietary exposure assessments for endosulfan in 1998 and 2002, respectively. Results of the USEPA dietary assessment showed a dietary exposure to be 150% of the aPAD (FQPA SF = 10× due to database uncertainty) for the population subgroup "Children 1 6 years" and was above the LOC (USEPA, 2002a). USEPA thus required the registrants to satisfy the database uncertainties by performing a subchronic neurotoxicity study (Sheets et al., 2004) and a DNT study (Gilmore et al., 2006). After receipt of the required studies, CDPR re evaluated their dietary risk assessment performed in 1998 and the USEPA performed a new dietary risk assessment for endosulfan (using different software: DEEM FCID™ and adding drinking water and food + drinking water residues). The MOEs generated by CDPR were all greater than 100 and the USEPA %PAD values for all population subgroups were less than 100% LOC. Therefore, at the dietary exposure levels analyzed for each agency, endosulfan dietary risk was characterized as within the health protective benchmark goals.

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