TOLERANCE EVALUATION OF MYCLOBUTANIL:

STRAWBERRIES AND ASPARAGUS

Nu-may R. Reed, Ph.D., DABT
Medical Toxicology Branch
Department of Pesticide Regulation
California Environmental Protection Agency

August 4, 2000

EXECUTIVE SUMMARY

This document contains an assessment of myclobutanil tolerances as a part of the label change amendment evaluation for the use of RALLY®40W on strawberries and asparagus. RALLY®40W has previously been used in California under emergency exemption (Section 18) on these two crops. The latest exemption expired for both crops on August 3, 2000. Subsequent to the USEPA's approval of a Section 3 registration for strawberries and asparagus on May 10, 2000, Rohm and Haas Co. requested the Department of Pesticide Regulation for an expedited review of the label change proposal.

The risk associated with the use of RALLY®40W on grapes was evaluated in 1988. Since the completion of the 1988 risk characterization document (RCD), more than one hundred tolerances were added to the list of tolerances for myclobutanil and its metabolite, and new toxicological studies were submitted. In April, 1999, myclobutanil was added to the list of chemicals know to the state of California to cause reproductive toxicity, specifically for developmental toxicity and male reproductive toxicity. In light of these significant developments since 1988, a re-assessment of myclobutanil tolerances is warranted.

The expeditious nature of this request permitted only a screening level dietary exposure assessment for myclobutanil tolerances, including the tolerances for strawberries and asparagus. The potential risk was characterized as margin of exposure (MOE) based on non-oncogenic endpoints of toxicity. MOE is the ratio of the NOEL to the exposure. Therefore, with an established NOEL, a lower exposure will result in a higher MOE.

The assumption used in the exposure assessment was that all commodities that have existing tolerances, not just strawberries and asparagus, contained residue either at the tolerance (for acute exposures) or at one-half of the tolerance (chronic exposures). Of all population subgroups, infants and children 1 – 6 years old have the highest potential exposure. Based on the acute NOEL of 20 mg/kg/day determined in rabbits for body weight reduction, the acute MOEs were 270 – 520 for infants (≤1 year old) and 410 for children 1 – 6 years old. Based on the chronic NOEL of 2.5 mg/kg/day determined in rats for liver toxicity and testicular atrophy, the chronic MOEs were 240 – 660 for infants (≤ 1 year old) and 300 for children 1 – 6 years old. These MOEs were higher than the minimum level of 100 generally required for the protection of human health. The uncertainties associated with these MOEs were presented in this document. It was concluded that that the existing tolerances would likely not pose a risk level of concern.

As a part of the evaluation of tolerances for strawberries and asparagus, all commodities with valid tolerances were included in the analysis. However, for other crops with either high exposures or those that are favored by fewer individuals in a population (i.e., high exposure for fewer "eaters"), it is prudent to also evaluate the tolerances for these crops individually since their patterns of acute exposure distribution are expected to be different from the pattern presented in this document.

The expeditious nature of this assessment does not allow for an assessment of exposure through pathways other than dietary. The reader is referred to USEPA's evaluation of tolerances published in May, 2000 (USEPA, 2000) for issues required to be addressed under FQPA.

TABLE OF CONTENTS

1. INTRODUCTION 1

2. CURRENT TOLERANCES 1

3. 1988 RISK CHARACTERIZATION DOCUMENT 2

4. SIGNIFICANT CHANGES SINCE 1988 RCD 3

4.1. Increased use of myclobutanil 3
4.2. Additional toxicological data submission 3
4.3. Listing under Proposition 65 3

5. TOXICOLOGICAL PROFILE 3

5.1. USEPA Toxicology Database 4
5.2. Acute Toxicity 4
5.3. Subchronic Toxicity 4
5.4. Chronic Toxicity and Oncogenicity 6
5.5. Developmental Toxicity 7
5.6. Illness Report 11

6. DOSE RESPONSE ASSESSMENT 11

6.1. Acute NOEL 11
6.2. Chronic NOEL 13

7. DIETARY EXPOSURE ASSESSMENT 13

8. RISK CHARACTERIZATION 15

8.1. Acute Risk 15
8.2. Chronic Risk 17

9. RISK APPRAISAL 17

9.1. Toxicity Assessment 17
9.2. Dietary Exposure Estimates 18
9.3. Risk Characterization 18
9.4. FQPA Issues 19

10. CONCLUSIONS 20

11. REFERENCES 22

LIST OF TABLES

Table 1. Summary of USEPA toxicity endpoints and database for myclobutanil 5

Table 2. Toxicities of myclobutanil in a 1-year study in dogs by Goldman *et al*., 1986 8

Table 3. Toxicities of myclobutanil in a rat teratology study by Costlow and Kane, 1984a 9

Table 4. Toxicities of myclobutanil in a rabbit teratology study by Costlow and Kane, 1984b 10

Table 5. List of NOELs and LOELs of myclobutanil pertinent for the selection of toxicity thresholds for risk assessment 12

Table 6. The highest residue level (in ppm) detected in 1995-98 USDA and 1997 DPR commodity monitoring programs 14

Table 7. Dietary exposure to myclobutanil and its metabolite from all crops at tolerances and the corresponding MOEs 16

1. INTRODUCTION

This document contains an expedited evaluation of Section 3 tolerances for the use of Rally®40W on strawberries and asparagus. This label amendment review was requested by Rohm and Haas (Letter to Kathy Wynn June 2, 2000), and routed through Kathy Wynn (Kathy Wynn to Van Cheney; June 8, 2000). The active ingredient in RALLY® 40W is myclobutanil, alpha-butyl-alpha-(4-clorophenyl)-1H-1,2,4-triazole-1-propanenitrile. Myclobutanil has been used as a fungicide on a large number of additional crops since its initial registration in 1988 for use on grapes.

2. CURRENT TOLERANCES

On May 10, 2000, USEPA (USEPA, 2000) amended and established tolerances for combined residues of myclobutanil and its alcohol metabolite (free or bound) in or on a variety of food commodities, including strawberries and asparagus. The alcohol metabolite is alpha-(3 hydroxybutyl)-alpha-(4-chloropheyl)-1H-1,2,4-triazole-1-propanenitrile. These tolerances are listed below in parts per million (ppm):

Apple wet pomace	1.3	ppm
Asparagus	0.02	ppm
Caneberry subgroup	2.0	ppm
Cucurbit vegetable group	0.2	ppm
Currant	3.0	ppm
Gooseberry	2.0	ppm
Mayhaw	0.7	ppm
Peppermint & spearmint tops	3.0	ppm
Pome fruit group	0.5	ppm
Strawberry	0.5	ppm
Succulent snap bean	1.0	ppm
Tomato paste	1.0	ppm
Tomato puree	0.5	ppm
Tomato	0.3	ppm

In addition, a tolerance of 0.03 ppm is established for indirect or inadvertent residues for rotational crop groups. These include:

Brassica leafy vegetables group
Cereal grains group
Foliage of legume vegetables group
Forage, fodder and straw of cereal grains group
Fruiting vegetables group
Leafy vegetables (except Brassica vegetables) group
Leaves of root and tuber vegetables group
Legume vegetables group
Non grass animal feeds group
Root and tuber vegetables group

The existing tolerances (CFR, 1999) that are not a part of the action on May 10, 2000 are:

Almond hulls	2.0	ppm
Almond nutmeat	0.1	ppm
Apples	0.5	ppm
Banana (post harvest treatment)	4.0	ppm
Cattle, Goats, Hogs, Horse, Sheep		
Fat	0.05	ppm
Liver	1.0	ppm
Meat	0.1	ppm
Meat by products	0.2	ppm
Cherries	5.0	ppm
Cotton seed	0.02	ppm
Chicken, turkey, poultry, and eggs	0.02	ppm
Grape pomace	10.0	ppm
Grapes	1.0	ppm
Milk	0.2	ppm
Dry plums	8.0	ppm
Raisin waste	25.0	ppm
Raisins	10.0	ppm
Stone fruits except cherries	2.0	ppm

Artichoke was the only crop with an active Section 18 registration (CFR, 2000) that was not a part of the action on May 10, 2000. The expiration date for its tolerance of 1.0 ppm was July 31, 2000.

3. 1988 RISK CHARACTERIZATION DOCUMENT

A risk characterization document (RCD) for myclobutanil conducted under the mandate of SB950 was completed in 1988 for the use of RALLY®40 W on grapes to control powdery mildew and black rot (CDFA, 1988). Adverse effects identified were: liver and kidney toxicities, developmental, and male reproductive toxicities. The No-Observed-Effect Level (NOEL) for characterizing the risk of acute exposures was 31 mg/kg/day (or, 31.3 mg/kg/day as appeared in the study report) in pregnant rats. This was based on the reduction of fetal viability occurred at the Lowest-observed-effect level (LOEL) of 94 mg/kg/day (or, 93.8 mg/kg/day as appeared in the study report). The NOEL for chronic exposures was 2.5 mg/kg/day (50 ppm in the diet) in rats. This was based on testicular atrophy occurring at the LOEL of 10 mg/kg/day (200 ppm in the diet).

Short- and long-term risks were evaluated for workers engaging in various tasks (applicator, mixer/loader, mixer/loader/applicator, re-entry) and the long-term risk through eating foods containing myclobutanil residues. Based on the NOEL of 31 mg/kg/day, the margins of exposure (MOEs) for acute occupational exposures were 3,650 – 155,000. The lowest MOE was for an “unprotected” mixer/loader/applicator who wore short sleeves with no hat nor gloves. Acute dietary risk was not evaluated in 1988. Based on the NOEL of 2.5 mg/kg/day, the MOEs

for chronic occupational exposures were 625 – 125,000. The lowest MOE was for a worker making entry to the field 2 hours after application. The MOE for chronic dietary exposure was 1,300 for non-nursing infants (CDFA, 1988).

4. SIGNIFICANT CHANGES SINCE 1988 RCD

Three areas of significant changes occurred since the completion of RCD in 1988 that address the use of RALLY®40W on grapes alone.

4.1. Increased use of myclobutanil

The 1988 RCD stated that the risk should be re-evaluated for any additional use beyond the 1988 use pattern on grapes alone. A reassessment of dietary exposure is clearly warranted after more than a hundred commodities have been added to the list of tolerances for myclobutanil and its alcohol metabolite.

4.2. Additional toxicological data submission

Subsequent to the 1988 RCD, reviews on genotoxicity data were added to the DPR's Summary of Toxicological Data (STD) on March 16, 1989. In anticipation of this tolerance assessment, reviews of two high-dose oncogenicity studies (Wolfe, 1993; Anderson *et al*., 1993) were added to the DPR STD on June 30, 2000 (signed off on July 28, 2000). These two studies were required by USEPA for fulfilling data requirements as it was determined that the maximum tolerated dose (MTD) had not been reached in the initial oncogenicity studies of 1986. These two 1993 studies are presented in Section 5.4.

4.3. Listing under Proposition 65

Under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1996, the state of California publishes the list of chemicals known to the State to cause cancer or reproductive toxicity. On April 16, 1999, myclobutanil was added to the list of chemicals know to the State to cause reproductive toxicity, specifically for developmental toxicity and for male reproductive toxicity.

5. TOXICOLOGICAL PROFILE

The most predominate toxicological effects reported in laboratory animals included: liver toxicity (degeneration, necrosis, and hypertrophy), testicular atrophy after long-term exposures, and developmental effects (fetal death and skeletal variation). The two 1993 high-dose studies did not reveal any new information regarding the primary endpoints of toxicity. An electronic search on MedLine database revealed no publications on toxicological studies. In addition to the

two high-dose studies, this section also provides detail information for the critical studies that support and/or provide a more thorough context of the NOELs used in this assessment.

5.1. USEPA Toxicology Database

Toxicological data that formed the basis of the recent evaluation by USEPA for many tolerances of myclobutanil (USEPA, 2000) are summarized in Table 1. Corresponding information from the most current DPR's Summary of Toxicological Data and more in depth reviews of the existing database are also given in Table 1 for comparison and subsequent discussions in the following sections.

5.2. Acute Toxicity

Information for the acute toxicity of technical grade myclobutanil (84.5% purity) was presented in the 1988 RCD (CDFA, 1988). The respective acute LD_{50} for oral and dermal exposures was 1.75 - 1.80 g/kg (Toxicity Category III) and > 5.0 g/kg (Toxicity Category IV) in rats. The 4-hour acute inhalation LC_{50} in rats was > 5.0 mg/l (Toxicity Category IV). Technical grade myclobutanil (91.9% purity) was a Category I eye irritant and a Category IV skin irritant. The technical grade myclobutanil was determined to be a weak contact sensitizer (CDFA, 1988). Rally®40WP (39.5%), however, was tested negative for dermal sensitization (CDFA, 1988).

No studies specifically designed for identifying an acute NOEL are available. Overt clinical signs of toxicity reported in the LD_{50} study in rats (Rohm and Haas, 1985) at and above 500 mg/kg/day included: diarrhea, salivation, lacrimation, red-stained muzzle, chromodacryorrhea, chromorrhinorrhea, anogenital stains, lethargy, piloerection. No effects were observed at the next lower dose of 50 mg/kg/day. However, the incidence of diarrhea was 1/6 in the controls, 2/6 at 50 mg/kg, and 4/6 at 500 mg/kg. Based in the apparent increase in the incidence of diarrhea, the 50 mg/kg would be a LOEL, rather than a NOEL.

5.3. Subchronic Toxicity

Three 3-month oral toxicity studies are on file at DPR: a rat study by O'Hara and DiDonato (1984), a mouse study by Goldman and Harris (1986), and a dog study by McLaughlin and DiDonato (1984),. Short summaries of these studies were presented in the 1988 RCD. Detail information is given in this section to provide a more complete reference to the toxicity database listed in Table 1.

In the 3-month rat study by O'Hara and DiDonato (1984), groups of 10 COBS-CD (SD) BR rats per sex were fed diets containing myclobutanil (81.1% purity). The concentrations in the diet were changed twice (once on week 3, and again on week 5), with the final concentrations (from week 5 to the end of the 3-month study period) at 0, 10, 20, 100, 300, 1,000, 3,000, 10,000, and 30,000 ppm. Statistically significant elevated hepatic mixed function oxidase (MFO) activity

Table 1. Summary of USEPA toxicity endpoints and database for myclobutanil.

Species	USEPA, 2000			Remarks - DPR review
	Endpoints	NOEL (mg/kg/day)	LOEL (mg/kg/day)	
Subchronic Feeding Studies				
Rats	liver (wt↑, hypertrophy, necrosis); kidney (tubule pigmentation)	50	150	NOEL at 5.2 mg/kg/day for 73-86% elevation of MFO
Mice	liver (wt↑, hypertrophy, vacuolization); adrenal (hypertrophy)	45	150	calculated NOEL at 42.7 mg/kg/day
Dogs	liver (wt↑, hypertrophy, ↑alkaline phosphatase)	5	20	NOEL at 0.34 mg/kg/day for liver hyper-trophy (incidence: 3/4) at 7.9 mg/kg/day
Subchronic Dermal Study				
Rats	no effects observed (dosing with formulation)	100 (a.i.)	none	
Chronic Feeding Studies				
Rats	testis (wt↓, atrophy); insufficient oncogenicity testing	2.5	9.9	
Rats	testis (wt↓, aspermatogenesis, atrophy); liver effects	none	125	
Mice	liver (wt & MFO↑, hypertrophy, vacuolization, enzymes, necrosis); insufficient oncogenicity testing	13.7	70	NOEL at 2.7 mg/kg/day for MFO activity ↑ NOEL at 13.7 mg/kg/day for liver effects
Dogs	liver (wt↑, hypertrophy, enzyme); slight hematological effects	3.1	14.3	overt NOEL at 100 ppm; other liver effects at as low as 10 ppm (0.31-0.41 mg/kg/day)
Developmental Toxicity Studies (oral)				
Rats	maternal: rough hair coat, salivation, alopecia, desquamation and red exudate around mouth	93.8	312.6	alopecia and increased total number of rats with clinical signs at ≥31.3 mg/kg/day
	fetal: ↑incidence of 14th rudimentary & 7th cervical ribs	93.8	312.6	↓fetal viability index at ≥31.3 mg/kg/day
rabbits	maternal: body wt loss; clinical signs, abortions	60	200	NOEL at 20 mg/kg for wt loss; however, one rabbit at 20 mg/kg/day had abortion
	fetal: ↑resorption, ↓litter size, viability index	60	200	no developmental effects noted
2-Generation Reproductive Toxicity Study (feeding)				
rats	general: liver (wt increase, hypertrophy)	2.5	10	
	reproductive: ↑stillborns, testis and prostate atrophy	10	50	also ↓pregnancy rate at the LOEL
	developmental: ↓pup wt during lactation	10	50	

was reported at and above 300 ppm (a 73-86% increase at 300 ppm). Additional effects noted at 3,000 ppm were: decreased body weight, increased liver and kidney weight, changes in serum chemistry (increased cholesterol, decreased SGOT and albumin/globulin ratio) and gross observations in the liver (dark, swollen, enlarged). None of the rats at 30,000 ppm survived past day 63 of dosing. The NOEL was 100 ppm (5.2 mg/kg/day) based on the elevated MFO at the LOEL of 300 ppm (19.7 mg/kg/day). The NOEL was 1,000 ppm based on overt liver and kidney effects at 3,000 ppm. USEPA established a NOEL of 50 mg/kg/day at 1,000 ppm in the diet.

In the 3-month mouse study by Goldman and Harris (1986), groups of 10 Crl:CD-1 (ICR) BR mice per sex were fed diets containing myclobutanil (81.1% purity) at 0, 3, 10, 30, 100, 300, 1,000, 3,000, or 10,000 ppm. No effects were reported at or below 300 ppm. Effects noted at 1,000 ppm included: elevated MFO and SGPT activities, decreased cholesterol, increased liver weight, and centrilobular necrotic hepatitis. The NOEL was 300 ppm (42.7 mg/kg/day) based on liver effects at the LOEL of 1,000 ppm.

In the 3-month dog study by McLaughlin and DiDonato (1984), groups of 2 beagle dogs per sex were fed diets containing myclobutanil (81.1% purity) at 0, 10, 200, 800, 1,600 ppm. Centrilobular and midzonal hepatocytic hypertrophy was noted at 200, 800, and 1,600 ppm; with the respective incidences of 3/4, 4/4, and 4/4. No incidence of hypertrophy was observed in the controls and 10 ppm groups. Although the report considered hepatic hypertrophy mild and not adverse, it has been one of the most prominent endpoint consistently observed in many toxicity studies of myclobutanil. Dogs at 800 and 1,600 ppm also showed chronic nephritis and increases in liver weights and serum alkaline phosphatase. The NOEL was 10 ppm (0.34 mg/kg/day) based on liver hypertrophy at the LOEL of 200 ppm (7.9 mg/kg/day). Substantial uncertainty existed for the NOEL due to its 20-fold difference from the LOEL. Alternatively, USEPA (2000; Table 1) established a subchronic NOEL of 5 mg/kg/day (estimated from 200 ppm in the diet) based on increases in liver weight and serum alkaline phosphatase occurred at 800 ppm.

5.4. Chronic Toxicity and Oncogenicity

A 2-year study in rats, 2-year study in mice, and a 1-year study in dogs, all completed in 1986, were presented in the 1988 RCD. Only a brief presentation of the two 1993 high-dose studies in rats and female mice is given in this section. Detail information is given for the 1986 dog study to provide the needed perspectives for the relatively low NOEL for liver effects identified in the 3-month subchronic dog study (see: section 5.3).

In the rat oncogenicity study by Wolfe (1993), groups of 60 Crl:CD®BR VAF/Plus® rats per sex (including 10 rats/sex for interim sacrifice at 12 months) were fed diets containing 2,500 ppm myclobutanil (92.9% purity) for 104 weeks. The control groups consisted of 15 rats per sex. As expected, the treatment resulted in decreased body weight (~7%), changes in clinical chemistry parameters, and marked histopathological findings in the liver and testes. No treatment-related oncogenicity was observed.

In the mice oncogenicity study by Anderson *et al* (1993), groups of 60 female Crl:CD®-1(ICR) BR mice (including 10 mice for interim sacrifice at 12 months) were fed diets containing 0 or 2,000 ppm myclobutanil (92.9% purity) for 18 months. The effects observed included lower body weight (2-12%), increased mean white blood cell count, increased liver weight, liver pathology (hypertrophy, necrosis, vacuolization, pigmentation), and adrenal cortical hypertrophy. No treatment related oncogenicity was observed.

In the chronic dog study by Goldman *et al* (1986), groups of 6 beagle dogs per sex were fed diets containing 0, 10, 100, 400, or 1,600 ppm myclobutanil (91.4% purity) for 1 year. No clinical signs were reported. Outstanding toxicological findings are summarized in Table 2. The NOEL was 100 ppm (3.91 mg/kg/day) based on hepatocellular hypertrophy and increased serum alkaline phosphatase in the females. It is interesting to note that this chronic NOEL for hepatocellular hypertrophy was 10-fold higher than the NOEL determined from the 3-month study. However, this difference in the NOEL could partly be due to the study design in selecting treatment levels such that, the difference between the LOELs in these two studies was only 2-fold (i.e., 200 ppm versus 400 ppm). Based on the two studies, a collective NOEL for liver hypertrophy could be established at 100 ppm. On the other hand, it should be noted that liver effects other than hypertrophy occurred at and below this NOEL. These effects included an increase in cholesterol, albeit with unclear dose-related trend, and increases in both absolute and relative liver weight (Table 2). Since these endpoints were consistent with the toxicity reported in many studies, their occurrence at 10 and 100 ppm may suggest that the NOEL of 100 ppm (3.03-3.91 mg/kg/day) based on liver hypertrophy may not be sufficiently low for the protection of health. A long-term NOEL for liver effects may be near 10 ppm (0.41 mg/kg/day).

5.5. Developmental Toxicity

Two teratology studies and their accompanying range-finding studies are on file at DPR. These studies were presented in the 1988 RCD. More detailed information is given in this section to provide a more comprehensive reference to the toxicity database.

In the study by Costlow and Kane (1984a), groups of 25 pregnant Sprague-Dawley (Crl:CD(SD) BR) rats were given myclobutanil (84.5% purity) at 0, 31.3, 93.8, 312.6, and 468.9 mg/kg/day (in corn oil vehicle) through gavage during gestation day 6 through day 15. The results are summarized in Table 3. Many clinical signs were reported in the dams. They generally appeared within 5 days of dosing. The NOEL for maternal toxicity was 93.8 mg/kg/day based on the LOEL of 312.6 mg/kg/day for all five clinical signs listed in Table 3 (i.e., urogenital stain, alopecia, rough haircoat, desquamation, and salivation). It should be noted that there was an apparent increase in the incidence of alopecia at 31.3 and 93.8 mg/kg/day. One dam at 93.8 mg/kg/day also had rough hair coat. Taken all clinical signs together, the total number of animals with no reported clinical signs declined steadily with dose, starting at 31.3 mg/kg/day (Table 3). Therefore, the maternal NOEL for overall toxicity could be lower than 93.8 mg/kg/day. The developmental NOEL was 31.3 mg/kg/day based on the decreased fetal

Table 2. Toxicities of myclobutanil in a 1-year study in dogs by Goldman *et al*., 1986.

	Concentration of myclobutanil in the diet (ppm)				
	0	10	100	400	1,600
MALES					
dose in mg/kg/day (day 182-188)	0	0.34	3.03	14.19	54.41
liver wt in gm[a]	299(295)	265(300)	291(294)	291(337)	389(424)*
FEMALES					
dose in mg/kg/day (day 182-188)	0	0.41	3.91	15.74	56.77
alk. phosphatase (U/L); week 13	72.2	89.0	102.2	102.2	213.7*
alk. phosphatase (U/L); week 25	68.5	73.2	81.2	101.3	211.0*
alk. phosphatase (U/L); week 53	57.5	60.7	59.0	91.7*	187.0*
cholesterol (mg/dl); wk 25	128.8	178.8	152.8	174.0	148.3
cholesterol (mg/dl); wk 53	155.2	186.7*	166.0	201.7*	171.7
liver wt in gm[a]	226(290)	260(346)*	281*(330)	295(370)*	349(441)*
MALES AND FEMALES					
liver enlarged	0/12	2/12	1/12	0/12	3/12
liver accentuated architecture	0/12	0/12	0/12	0/12	3/12
liver hypertrophy(centrilobular)	0/12	0/12	0/12	3/12	11/12

a/ The first value is the absolute weight, the value in the parenthesis is the relative weight.

*: statistically significant from the controls at $p<0.05$. Signs given at the end of each set of liver weight value pertain to both the absolute and relative weight. Signs after the absolute weight pertain only to the absolute weight.

Table 3. Toxicities of myclobutanil in a rat teratology study by Costlow and Kane, 1984a[a].

	Myclobutanil (mg/kg/day)				
	0	31.3	93.8	312.6	468.9
Animals with no clinical signs[b]	22	18	17	13	3
Urogenital stain[b]	1(2)	0(0)	0(0)	1(1)	6(17)
Alopecia[b]	2(20)	7(42)	7(63)	7(67)	15(147)
Rough haircoat[b]	0(0)	0(0)	1(1)	4(8)	8(27)
Desquamation[b]	0(0)	0(0)	0(0)	1(12)	4(31)
Salivation[b]	0(0)	0(0)	0(0)	3(3)	4(4)
Viable fetus/litter	15.3	13.5*	13.3*	13.2*	13.1*
Viability index (live fetus/implantation sites)	0.95	0.94	0.88*	0.88*	0.83*
Rib variations[c]; fetus incidence	8/223	7/213	11/185	34/200*	72/201*
Rib variations[c]; litter incidence	5/22	6/24	7/21	16/23*	20/22*

a/ A total of 25 rats per group.
b/ The first value was the number of rats that showed the clinical sign; the value in parenthesis was the total number of times the effects were scored within the dose group during the entire study period.
c/ Any variation includes 7th cervical, 14th rudimentary, 14th full, or 13th rudimentary rib.
* Statistical significance at $p<0.05$.

viability index and increased skeletal variants at 93.8 mg/kg/day. It should be noted that fetal toxicity became apparent at 31.3 mg/kg/day (i.e., statistically significant decrease in viability index based on number of fetus per liter). Therefore, the developmental NOEL could also be lower than 31.3 mg/kg/day.

In the study by Costlow and Kane (1984b), groups of 18 pregnant New Zealand white rabbits were given myclobutanil (90.4% purity) at 0, 20.0, 60.0, and 200.0 mg/kg/day through gavage during gestation day 7 through day 19. Myclobutanil was adsorbed on amorphous silica Hi-Sil→233 in an aqueous suspension of 1% (w/v) methylcellulose. A "water" control group without Hi-Sil was also included in the study. The results are summarized in Table 4. The maternal toxicity NOEL was 20.0 mg/kg/day based on loss of body weight during dosing period at and above 60.0 mg/kg/day. The depression on body weight gain was apparent on day 11, after 4 days of exposure. The weight gain resumed one day after the termination of treatment. Clinical signs were noted as early as within the first 2 days of dosing. It should also be noted that the gradual rise in the incidence of abortion began at 20.0 mg/kg/day. Abortion at 20.0 mg/kg/day occurred on day 19 and was reported as early resorption. Therefore, the maternal NOEL could be lower than 20.0 mg/kg/day. The developmental NOEL was 60 mg/kg/day based on marked reduction in fetal viability index (live fetus per number of implantation) at 200.0 mg/kg/day.

USEPA established an acute NOEL of 60 mg/kg/day from this developmental toxicity study in rabbits. The NOEL was based on both maternal and fetal effects observed at the LOEL of 200 mg/kg/day. USEPA used this NOEL to evaluate the risk of acute dietary exposures, but restricted its application to assessing only the risk for females of child-bearing age (i.e., 13 – 50 years old).

Table 4. Toxicities of myclobutanil in a rabbit teratology study by Costlow and Kane, 1984b[a].

Observations	Controls		Myclobutanil (mg/kg/day)		
	water	HiSil	20.0	60.0	200.0
Bloody urine[b]	0(0)	0(0)	1(1)	1(3)	8(35)
Bloody anal/urogenital[b]	0(0)	0(0)	0(0)	0(0)	2(4)
Blood in pan[b]	0(0)	0(0)	1(1)	1(4)	7(22)
Aborted material in pan[b]	0(0)	0(0)	0(0)	1(1)	3(3)
Abortion[b]	0	0	1	1	3
Body Wt gain (ges. Day 7-20), kg	0.03	-0.02	0.04	-0.06[c]	-0.28[c]
Viable fetus/liter	6.31	6.75	7.38	6.50	2.70*
Viability Index (live fetus/implantation)	0.91	0.91	0.93	0.98	0.35*
Mean fetal body wt, kg	0.0465	0.0454	0.0430	0.0453	0.0375

a/ A total of 18 rabbits per group.

b/ The first value was the number of animals with the specific observations; the value in parenthesis was the total number of time the effects were scored within the dose group during the gestation day 8 to day 29.

c/ The maternal weight was statistically different from the control on gestation day 11. The body weight gain was inhibited throughout the treatment period and resumed one day after the termination of treatment (day 20).

* statistically significantly different ($p<0.05$) from the controls

5.6. Illness Report

Data from California illness surveillance program (DPR, 1988-1998) showed that in the 10 years after the registration of myclobutanil for grapes, there were more than 160 cases of illnesses among California agricultural workers that could possibly be attributed to myclobutanil and its use. In a majority of cases, the possibility of concomitant exposure to other pesticides complicated the determination of a clear association of illnesses to a specific pesticide. The most prevalent effects reported for a possible exposure to myclobutanil included: skin rash, allergic dermatitis and itchiness, nausea, headaches, diarrhea, abdominal pain, vomiting, nosebleed, and eye irritation. The skin hypersensitivity is consistent with the positive results of hypersensitivity testing in guinea pigs for the technical grade myclobutanil (see: Section 5.2). Unfortunately, the database lack information for estimating the possible exposure level for these illnesses.

6. DOSE RESPONSE ASSESSMENT

Table 5 presents a list of NOELs and LOELs that are pertinent for establishing toxicity thresholds for assessing the risk of dietary exposures.

6.1. Acute NOEL

Toxicological studies which reported clinical and toxicological findings occurring within a few days of dosing were reviewed for establishing an acute NOEL for assessing the risk of dietary exposures. The focus of the database review was on oral studies. The database showed that teratology studies provided the lowest short-term LOELs. Since maternal clinical signs appeared within 2 to 5 days of dosing, and the possibility that developmental effects could occur from exposure at a narrow window of developmental stage, teratology studies are pertinent for establishing an acute NOEL.

The developmental NOEL of 31 mg/kg/day in rats was used in the 1988 RCD (CDFA, 1988) to characterize the risk of acute occupational exposures. This NOEL was based on the decreased fetal viability and increased skeletal variations at the LOEL of 93.8 mg/kg/day (Table 5). A maternal NOEL of 93.8 mg/kg/day was previously determined from the same study (CDFA, 1988) based on several clinical signs of toxicity (urogenital stain, alopecia, rough haircoat, disquamation, salivation). However, as discussed in Section 5.5, this NOEL could be considered insufficient for the protection of health since developmental effects (decreased viability index) and maternal effects (alopecia, increased total number of rats with clinical signs) occurred at the lowest tested dose of 31.3 mg/kg/day.

DPR review showed that the maternal NOEL in rabbits was 20.0 mg/kg/day based on the gestational body weight loss at the LOEL of 60.0 mg/kg/day. Without data to demonstrate which of the two tested species, rats or rabbits, are more sensitive, it is prudent to use the lower NOEL of 20.0 mg/kg/day from the rabbit study to characterize the potential risk of acute

Table 5. List of NOELs and LOELs of myclobutanil pertinent for the selection of toxicity thresholds for risk assessment.

Study	Toxicity endpoints	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref
Teratology rats	Maternal: alopecia; # of rats with clinical signs	-	31.3	1
	Maternal: rough hair coat	31.3	93.8	1
	Maternal: several clinical signs, high incidences	93.8	312.6	1
	Fetal: viability	-	31.3	1
	Fetal: viability, skeletal variant	31.3	93.8	1
Teratology rabbits	Maternal: abortion	-	20.0	2
	Maternal: loss of weight	20.0	60.0	2
	Fetal: viability	60.0	200	2
3-month rats	Elevated MFO	5.2	19.7	3
	Overt toxicity in liver, kidney	52	197	3
3-month dogs	Liver hypertrophy	0.34	7.9	4
1-year dogs	Liver hypertrophy, AKP	3.91	15.7	5
	Cholesterol, liver weight	0.41	3.91	5
2-gen reproduction	Liver wt, hypertrophy, testicular hypertrophy	2.5	10	6

MFO: mixed function oxidase; AKP: serum alkaline phosphatase.
Ref: 1) Costlow and Kane, 1984a; 2) Costlow and Kane, 1984b; 3) O'Hara and Didonato, 1984; 4) McLaughlin and DiDonato, 1984; 5) Goldman et al., 1986; 6) Costlow and Harris, 1985.

dietary exposures. It should be noted that, abortion (Table 4) occurred in one out of the 18 rabbits at this NOEL (Table 5; Section 5.5 discussion). Since abortion was one of the consistent endpoint in all treatment groups of this study, considerations should be given in determining an acceptable level of MOEs calculated from this NOEL (see Section 9 for further discussion).

6.2. Chronic NOEL

A chronic NOEL of 2.5 mg/kg/day (50 ppm in the diet) from the rat reproductive toxicity study was used in the 1988 RCD (CDFA, 1988; Costlow and Harris, 1985) to characterize the risk of chronic exposures. This NOEL was based on increased liver weight and centrilobular hepatocyte hypertrophy, and testicular atrophy at the LOEL of 10 mg/kg/day (200 ppm in the diet). This same NOEL was used by USPEA (USEPA, 2000; Table 1) in the recent evaluation of tolerances for myclobutanil. No new data on chronic toxicity of myclobutanil has been reported since the 1988 RCD. Therefore, the same NOEL of 2.5 mg/kg/day is used in this assessment for characterizing the chronic dietary exposure of myclobutanil. However, it should be noted that the subchronic and chronic dog studies (Table 5; Sections 5.3 and 5.4 discussions) indicated that a NOEL for liver effects may be closer to 0.41 mg/kg/day. This is approximately 6-fold below the NOEL of 2.5 mg/kg/day for testicular effects.

Negative evidence from the oncogenicity studies in rats and mice, and the genotoxicity studies formed the basis of USEPA's classifying myclobutanil as Group E, no evidence for oncogenicity in humans (USEPA, 2000). Therefore, no cancer risk assessment is performed for this assessment.

7. DIETARY EXPOSURE ASSESSMENT

Residues of myclobutanil has been detected in a few commodities under USDA Pesticide Data Program (PDP) and in DPR 1997 Priority Pesticide Program (PPP) targeting grapes. The highest residue levels detected under these two programs during 1995-98 are given in Table 6. In general, the level of residue detected was substantially below the tolerance, with the exception that the 1998 PDP program detected a maximum residue in strawberries that exceeded the tolerance published in May, 2000 (USEPA, 2000). In the 1995-98 PDP database, the percentage of residue detection were below 10% for all commodities, with the exception that residue was detected in 25% of grape samples and 15-20% of strawberry samples.

Dietary exposure assessment for various population subgroups was conducted using DEEM® software (version 7.705) from Novigen Sciences Inc. Dietary exposures were estimated for a total of 27 population subgroups that accounted for the 5 U.S. regions (Northeast, Midwest, Southern, Western, Pacific), and the various combinations of gender, age, and physiological statuses (e.g., pregnancy, nursing). The food consumption data were based on the 1989-1992 Continuing Surveys of Food Intakes by Individuals (CSFII) conducted by USDA. Although this

Table 6. The highest residue level (in ppm) detected in 1995-98 USDA and 1997 DPR commodity monitoring programs[a].

	Tolerance	USDA PDP				DPR PPP
		1995	1996	1997	1998	1997
Apples	0.5	0.033	0.025	-	-	-
Apple Juice	0.5	-	≤ 0.046	≤ 0.045	≤ 0.045	-
Cantaloupe	0.2	-	-	-	≤ 0.045	-
Carrots	0.03	0.014	≤ 0.046	-	-	-
Grapes	1.0	0.44	0.54	-	-	0.29
Grape Juice	1.0	-	-	-	≤ 0.045	-
Green Beans	0.03	-	≤ 0.046	≤ 0.045	-	-
Green Beans, C&F	0.03	-	-	-	≤ 0.045	-
Peaches	2.0	0.10	0.095	0.025	-	-
Pears	0.5	-	-	≤ 0.045	≤ 0.057	-
Spinach, fresh	0.03	-	≤ 0.057	≤ 0.076	-	-
Spinach, canned	0.03	-	-	≤ 0.076	≤ 0.083	-
Strawberries, fresh	0.5	-	-	-	0.55	-
Strawberries, frozen	0.5	-	-	-	0.14	-
Sweet Corn	0.03	-	≤ 0.046	-	-	-
Sweet Peas	0.03	-	≤ 0.046	-	-	-
Sweet potatoes	0.03	-	≤ 0.046	≤ 0.045	≤ 0.045	-
Tomatoes	0.3	-	0.025	0.040	0.16	-
Winter Squash, fresh	0.2	-	-	0.013	0.013	-
Winter Squash, frozen	0.2	-	-	≤ 0.045	≤ 0.045	-

a/ USDA: Pesticide Data Program; DPR: Priority Pesticide Program. The highest detection limits were given when residues were not detected in a commodity. The percentage of sample with detected residue was generally below 10%, except in grapes (~25%) and strawberries (15- to 20%).

assessment is for evaluating the tolerance of myclobutanil and its metabolite in strawberries and asparagus, all commodities with a valid tolerance (as listed under Section 2, Current Tolerance) are included in the exposure analysis. This accounts for the possibility of concomitant exposure through eating foods other than strawberries and asparagus. The large number of commodities included in the dietary results in nearly identical profile of acute exposure for "eaters" (those who consumed at least one commodity included in the analysis) and "non-eaters" (those who did not consume any commodities in the analysis).

The assessment followed a tier approach. In the initial screening tier assessment, the assumption for the acute exposure was that all commodities contained residues at the tolerance. The screening assessment for chronic exposures assumed that all commodities contained residues at one-half of the tolerance. Although these assumptions present a highly unlikely scenario, further refining assessment will not be necessary if the results show a MOE that is greater than the level generally considered protective for human health (i.e., MOE of at least 100).

The results of this screening analysis for representative population subgroups are presented in Table 6 for both the acute exposure at the 95^{th} and 99^{th} percentiles, and the chronic exposure. Chronic exposure represented the mean exposure of the each population subgroup. Of all the population subgroups, infants (≤ 1 year old) and children 1 – 6 years old had the highest exposures. No further refinement of dietary exposure to reflect a more realistic exposure scenario was conducted beyond this screening analysis. The rationale for this decision is presented in Section 9 (Risk Appraisal).

8. RISK CHARACTERIZATION

The potential risk of myclobutanil dietary exposure was characterized in terms of MOE for non-oncogenic effects. The MOE is the ratio of the NOEL to the exposure. The lower the exposure the higher the MOE, showing a greater margin from the NOEL. The MOEs for the 95^{th} and 99^{th} percentile of acute exposure and the chronic exposure are presented in Table 7.

When calculated from a NOEL determined in laboratory animals, a MOE exceeding 100 is generally considered as sufficiently large for the protection of human health. This MOE of 100 is a multiplication of two factors of 10. A MOE of 100 allows for a possibility that humans could be as much as 10-fold more sensitive than laboratory animals, and that there can be as much as 10-fold difference in sensitivity within a human population.

8.1. Acute Risk

The screening level MOEs corresponding to a 95^{th} percentile of exposure for the population subgroups having the highest exposures were: 270 – 520 for infants (≤ 1 year old) and 410 for

Table 7. Dietary exposure to myclobutanil and its metabolite from all crops at tolerances and the corresponding MOEs.[a]

Population Subgroups	Exposure (mg/kg/day)			MOE[b]		
	Acute (percentile)		Chronic[c]	Acute (percentile)		Chronic
	95th	99th	Ave	95th	99th	Ave
U.S. Population (total)	0.018	0.041	0.0108	1,100	490	920
Western region	0.021	0.044	0.0118	960	450	860
Infants (all)	0.065	0.097	0.0350	310	210	280
Infants – Nursing	0.039	0.072	0.0150	520	280	660
Infants – non nursing	0.074	0.106	0.0434	270	190	240
Children 1–6 yrs	0.049	0.081	0.0338	410	250	300
Children 7–12 yrs	0.022	0.034	0.0160	910	700	620
Females 13–19, non-pregnant/nursing	0.011	0.017	0.0070	1,760	1,200	1,440
Females 20+, non-pregnant/nursing	0.011	0.019	0.0072	1,750	1,100	1,400
Females 13-50 yrs	0.011	0.018	0.0066	1,820	1,120	1,500
Females 13+, pregant/not nursing	0.014	0.021	0.0092	1,460	940	1,100
Females 13+, nursing	0.019	0.041	0.0126	1,050	490	800
Males 13-19 yrs	0.013	0.022	0.0084	1,550	930	1,200
Males 20+ yrs	0.010	0.017	0.0064	1,980	1,190	1,540
Seniors 55+ yrs	0.012	0.021	0.0086	1,620	950	1,160

a/ The exposure was estimated using DEEM software (version 7.705) from Nogiven Sciences Inc. The consumption data was based on USDA 1989-92 Continuing Surveys of Food Intakes by Individuals. Residue levels were assumed to be at the tolerance in the acute exposure assessment, and at one-half of tolerance in the chronic exposure assessment.

b/ MOE: Margin of exposure, calculated as the ratio of the NOEL to the exposure. The acute NOEL was 20 mg/kg/day. The chronic NOEL was 2.5 mg/kg/day.

c/ Chronic exposure represented the average exposure of each population subgroup.

children 1 – 6 years old. The MOEs for other population subgroups were above 900. The MOEs for infants are approximately 3-fold above the MOE of 100 generally considered sufficient for the protection of human health.

8.2. Chronic Risk

The screening level MOEs corresponding to the population subgroups having the highest exposures were 240 – 660 for infants (≤ 1 year old) and 300 for children 1 – 6 years old. The MOE for Children 7 – 12 years old was also within the comparable range (MOE at 620). The MOEs for other population subgroups were at or above 800. The MOEs for infants and children 1 – 6 years old were approximately 2.5- to 3-fold above the MOE of 100.

9. RISK APPRAISAL

The MOEs presented in the preceding section and in Table 7 were screening levels of dietary risk to myclobutanil. The uncertainties associated with these analyses are presented in this section.

9.1. Toxicity Assessment

Studies in laboratory animals consistently showed toxicities of myclobutanil in the liver, the testes, and in the survival and development of fetuses. However, uncertainties exists in the determination of NOELs for the most sensitive endpoints for use in characterizing the risk of potential dietary exposures.

The acute NOEL of 20 mg/kg/day used in this assessment was based on the loss of body weight in pregnant rabbits that received oral dosing of myclobutanil at 60 mg/kg/day (Table 4). The body weight gain resumed one day after the cessation of treatment, indicating that the treatment effect was acute in nature. Moreover, lower body weight had been a consistent endpoint reported in laboratory animals exposed to myclobutanil. Therefore, it is an appropriate endpoint for assessing the risk of all population subgroups, not just for women of child-bearing age. However, some degree of uncertain existed in the delineation of the NOEL. As shown in Table 4, abortion occurred in one of the 18 rabbits at 20 mg/kg/day. Abortion was a consistent endpoint in all treatment groups in this study. The flat dose-response curve between the 20 and 60 mg/kg/day (Table 4) presented some degree of uncertainty in terms of whether the NOEL could be below or above 20 mg/kg/day.

The chronic NOEL of 2.5 mg/kg/day in rats were used in this assessment was based not only on testicular effects but also liver effects (liver weight increase and hypertrophy). Thus, the NOEL is pertinent for assessing the risk of all population subgroups. Some uncertainty existed in the adequacy of this NOEL for protection against liver toxicities. Based on the studies in dogs (3-month and 1-year studies), the NOEL for liver toxicity could be as much as 6-fold lower than the NOEL of 2.5 mg/kg/day (see: Section 6.2 discussions).

9.2. Dietary Exposure Estimates

The screening level assessment assumed that, in a person's single day diet, all commodities that have current tolerances for myclobutanil all contained residues at the tolerance. This assumption would likely result in an over-estimation of a single day exposure, especially in light of the large number of crops included in the analysis. Similarly, in the chronic exposure assessment, assuming that all commodities all containing residues at one-half of tolerance throughout every day of a person's diet would likely result in an over-estimation of a long-term or lifetime of dietary exposure. These views regarding the over-estimation of exposure is supported by the profile of low and infrequent residue detection shown in the monitoring programs (Table 6; Section 7).

This assessment included all crops with valid tolerances in the analysis. Because of the large number of commodities involed, the distribution pattern for acute exposures is expected to be similar for "eaters" (people who eat at least one commodity in the entire list) and "non-eaters" (people who do not eat any of the analyzed commodities). However, this exposure distribution pattern is expected to be different from the pattern for each individual commodity. Thus, for a thorough analysis for all myclobutanil tolerances, it is prudent to also evaluate each tolerance individually, especially for commodities with higher exposure (e.g., commonly consumed at higher rate and with high tolerances) and commodities favorably consumed by only a small segment of the population (e.g., few people but with high consumption). According to the critical exposure contribution (CEC) analysis, apples, grapes, peaches, plums, and beans would tend to have higher exposures in infants and children when the residue was assumed to be at the tolerance.

9.3. Risk Characterization

The lowest MOEs for both acute and chronic dietary exposures were approximately 250, for non-nursing infants, or approximately 300 for all infants. This is 3-fold higher than the MOE of 100 generally considered as adequate for the protection of health. However, the overall consideration of the adequacy of the MOE should take into account the uncertainties in both the toxicity and the exposure components. On the one hand, the chronic NOEL could be as much as 6-fold lower for a different endpoint (see: section 6.2, 9.1), albeit with much associated uncertainties. On the other hand, it is expected that a dietary exposure using more realistic residue levels instead of the tolerances would be lower than the screen level exposure used for the MOE calculation. Taken both considerations together, it is unlikely that the overall dietary risk will reach a level of concern for human health. Nevertheless, a firm conclusion cannot be made until more time is given for conducting a more refined assessment.

Data are not available for determining the potential for a higher sensitivity in infants and children. The current default of a 10-fold inter-individual variation in sensitivity is assumed to be adequate for protecting all population subgroups, including the young.

USEPA conducted a refined chronic dietary exposure assessment (USEPA, 2000). The estimated percentages of crop treated (PCT) data were used to adjust the residue levels for 8 major fruit crops and cotton, while all other commodities remained at the tolerance level. Using the same chronic NOEL of 2.5 mg/kg/day, USEPA estimated that the exposure would occupy approximately 50% of the population adjusted dose (PAD) or reference concentration (RfD) for infants and children (USEPA). Since POD (or RfD) was calculated as the NOEL divided by the target MOE of 100, USEPA's assessment could be translated to mean a MOE of approximately 200 for infants and children. It is interesting to note that the USEPA refining assessment resulted in a higher exposure (i.e., lower MOE) than the screening level exposure presented in this document. It appears that, in this case, assuming all residues at one-half of tolerances (as presented in this document) would have a greater impact on the overall exposure than using PCT data for the 8 fruit crops and cotton while holding all other commodities at tolerance.

The expeditious nature of this assessment does not allow for an assessment of exposure through pathways other than dietary. As a support for the recent actions to establish tolerances for many crops, USEPA evaluated the concomitant exposures to myclobutanil and its break down product through other exposure routes and pathways such as drinking water and residential uses (USEPA, 2000). These considerations were required under the Food Quality Protection Act (FQPA) of 1996 (see the following section).

9.4. FQPA Issues

A very brief summary of USEPA's evaluation of myclobutanil tolerances (USEPA, 2000) is presented below regarding the three key aspect of risk assessment required under FQPA.

Children Safety Factor

USEPA determined that the additional safety factor of 10 is not needed to account for the potentially higher sensitivity in infants and children (USPEA, 2000). This decision was based on the consideration that the submission of toxicological data was complete and that there was no evidence showing higher sensitivity in pre- and post-natal exposures. Furthermore, USEPA was confident that their exposure assessment would not under-estimate the aggregate exposure (see the next subsection).

It should be noted that developmental effects were identified in the teratology studies. Myclobutanil is also listed under California Proposition 65 as a chemical known to the State to cause reproductive and development effects. Moreover, USEPA's assessment did not include an evaluation of acute dietary exposure for infants and children for the lack of toxicological endpoints and thresholds that were deemed pertinent for this population subgroup (USEPA, 2000). The acute NOEL of 60 mg/kg/day based on maternal and fetal toxicity was used to assess only the risk for females 13 to 50 years old (child-bearing age).

Aggregate Exposure

For the lack of drinking water monitoring data, screening level models were used to determine the estimated environmental concentrations (EECs) of myclobutanil in surface and ground waters. These screening level concentrations were not included in the DEEM® analysis. Instead, USEPA concluded that adding the drinking water component would not result in an unacceptable level of aggregate risk since the EECs were lower than the DWLOC (drinking water levels of concern). DWLOC was calculated as the allowable chronic water exposure that represented the remainder of the "risk cup" after accounting for dietary and residential exposures. USEPA will reassess the potential impact of drinking water exposure when new uses of myclobutanil are added (USEPA, 2000).

Currently registered non-residential use of myclobutanil included turf, roses, flowers, shrubs, and trees (USEPA, 2000). USEPA assessed the exposure of residential handler and post application exposures. Pesticide Handers Exposure Database (PHED, version 1.1) was used to estimate the residential handler's exposure. A registrant submitted study on dislodgeable foliar residue, coupled with residential activity pattern, was used to estimate post-application exposures. Residential exposure through the dermal route was not added to the dietary exposure due to differences in route-specific toxicity endpoints (USEPA, 2000). Again, USEPA did not assess the risk of infants and children through post-application residential ingestion exposure due to the lack of acute toxicity endpoints (USEPA, 2000).

Cumulative Risk

USEPA did not evaluate the potential cumulative risk from exposures to substances that have a common mechanism of toxicity as myclobutanil. Data were lacking for determining whether myclobutanil has a common mechanism of toxicity with other substances (USEPA, 2000).

10. CONCLUSIONS

A screening level dietary exposure assessment was conducted for the evaluation of tolerances of myclobutanil in strawberries and asparagus. The potential risk was characterized as margin of exposure (MOE) based on non-oncogenic endpoints of toxicity. MOE is the ratio of the NOEL to the exposure. Therefore, with an established NOEL, a lower exposure will result in a higher MOE.

The assumption used in the exposure assessment was that all commodities that have existing tolerances, not just strawberries and asparagus, contained residue either at the tolerance (for acute exposures) or at one-half of the tolerance (chronic exposures). Of all population subgroups, infants and children 1 – 6 years old have the highest potential exposure. Based on the acute NOEL of 20 mg/kg/day determined in rabbits for body weight reduction, the acute MOEs were 270 – 520 for infants (≤1 year old) and 410 for children 1 – 6 years old. Based on the chronic NOEL of 2.5 mg/kg/day determined in rats for liver toxicity and testicular atrophy, the chronic MOEs were 240 – 660 for infants (≤ 1 year old) and 300 for children 1 – 6 years old. These MOEs were higher than the minimum level of 100 generally required for the protection of

human health. The uncertainties associated with these MOEs were presented. It is concluded that the existing tolerances would likely not pose a risk level of concern.

As a part of the evaluation of tolerances for strawberries and asparagus, all commodities with valid tolerances were included in the analysis. However, for other crops with either high exposures or those that are favored by fewer individuals in a population (i.e., high exposure for fewer "eaters"), it is prudent to also evaluate the tolerances for these crops individually since their patterns of exposure distributions are expected to be different from the pattern presented in this document.

The expeditious nature of this assessment does not allow for an assessment of exposure through pathways other than dietary. The reader is referred to USEPA's evaluation of tolerances published in May, 2000 (USEPA, 2000) for issues required to be addressed under FQPA.

11. REFERENCES

Anderson, D. M., G. P. O'Hara, and W. R. Brown. 1993. RH-3866: Dietary oncogenicity study in female mice. Rohm and Haas Co. Report No. 89R-261. CDPR Vol. 51315 - 139-140, #122368-9.

California Department of Food and Agriculture (CDFA), 1988. Myclobutanil Risk Assessment. Division of Pest Management, Environmental Protection, and Worker Safety, California Department of Food and Agriculture. August 16, 1988.

California Department of Pesticide Regulation (DPR), 1988-1998. Case reports received by the California pesticide illness surveillance program. DPR, California Environmental Protection Agency. 830 K Street, Sacramento, CA.

Code of Federal Regulations (CFR), 1999. CFR 40, Part 180.443. Myclobutanil; tolerances for residues.

Costlow, R. D. and J. C. Harris. 1985. RH53-866: Two generation reproduction study in rats. Rohm and Haas Co. Report No. 84R-117. DPR Vol. 51315-078, #51888.

Costlow, R. D. and W. W. Kane. 1984a. Teratology study with RH-53,866 in rats. Rohm and Haas Co. Report No. 83R-024. DPR Vol. 51315-077, #51887.

Coatlow, R. D., and W. W. Kane. 1984b. Teratology study with RH-53,866 in rabbits. Rohm and Haas Co. Report No. 83R-217. CDPR Vol. 51315-75, #51885.

Goldman, P. R. and J. C. Harris. 1986. RH-3866: A three-month dietary toxicity study in mice. Rohm and Haas Co. Report No. 83R-136. DPR Vol. 51315-056, #51866

Goldman, P. R., J. C. Harris, and J. D. Frantz. 1986. RH-3866: One year dietary study in beagle dogs. Rohm and Haas Co., Report No. 84R-078. CDPR Vol. 51315-072-073, #51882, 51883.

McLaughlin, J. E. and L. J. DiDonato. 1984. RH-3866: A three-month dietary study in dogs. Rohm and Haas Co. Report No. 83R-204. DPR Vol. 51315-052, #51862; -053, #51863.

McLeod, P. L. and K. L. McCarthy. 1984. RH-3866 in vivo cytogenetic study in mice. Rohm and Haas Co. Report No. 84R-074. DPR Vol.51315-079, #51890.

O'Hara, G. P. and L. J. DiDonato. 1984. RH-3866: Three month dietary toxicity study in rats. Rohm and Haas Co. Report No. 83R-068. DPR Vol. 51315-054, #51864; -055, #51865

Rohm and Haas Co. 1985. Toxicity Report, Report No. 85R-0107 (Acute range finding study for oral LD_{50}). DPR Vol. 51315-104, #64981.

Wolfe, G. W. 1993. RH-3866 technical myclobutanil: 104-Week dietary oncogenicity study in rats. Hazelton Washington. Rohm and Haas Co. Report No. 89RC-260. CDPR Vol. 51315-135, #12363; Vol. 51315-137, 138, #122366-7.

U.S. Environmental Protection Agency (USEPA), 2000. Myclobutanil; Pesticide Tolerances. Federal register 65(91):29963-29973. http://www.epa.gov/fedrgstr/EPA-PEST/2000/May/Day-10/p11571.htm.