United States
Environmental Protection Agency
Office of Prevention, Pesticides and Toxic Substances
(7505P)

Pesticide Fact Sheet

Name of Chemical: **Metofluthrin**
Reason for Issuance: **New Chemical Nonfood Use**
Date Issued: **September 2006**

Description of Chemical

IUPAC name:	2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (EZ)-(1RS,3RS;1RS,3SR)-2,2-dimethyl-3-prop-1-enylcyclopropanecarboxylate
CAS name:	[2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl 2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate
Common Name:	Metofluthrin
Empirical Formula:	$C_{18}H_{20}F_4O_3$
EPA Chemical Code:	109709
Chemical Abstracts Service (CAS) Number:	240494-70-6
Chemical Class:	Pyrethroid ester
Registration Status:	New Chemical, nonfood use
Pesticide Type:	Insecticide repellent not applied to human skin

U.S.Technical Registrant : Sumitomo Chemical Company, LTD.
1330 Dillon Hghts. Ave.
Baltimore, MD 21228

Use Pattern and Formulations

Currently there are two end use products being proposed for metofluthrin.
DeckMate ™ Mosquito Repellent Strip is an impregnated paper strip (~3,528 cm2) containing 1.82 percent metofluthrin as the active ingredient. The product also contains Bitrex ™ to discourage oral exposure to children or animals. The product is for use on patios, campsites, decks, cabanas, and other outdoor areas. One strip is applied per 10 ft × 10 ft outdoor area. Indoors the application rate is two strips per 50 m^3. There are approximately 200 mg of metofluthrin initially in the strip. The strips can provide up to one week of protection Metofluthrin evaporates readily and therefore requires no external heat.

Norm 1- is a personal outdoor insect repellent product consisting of a holder containing a replaceable cartridge insert coated with up to 50 mg of metofluthrin. The product is activated by turning on a battery powered fan to release the metofluthrin into the air surrounding the individual. The device can be worn by adults or children for up to 12 hours although a specific time is not presented on the proposed label. A time of 12 hours was used in the exposure study and was used by the Agency. There are no label restrictions on who can use the products or the use frequency.

There are no proposed agricultural or occupational uses for metofluthrin.

Science Findings

Available product chemistry data supporting the use of flufenoxuron are summarized below in Tables 1 and 2.

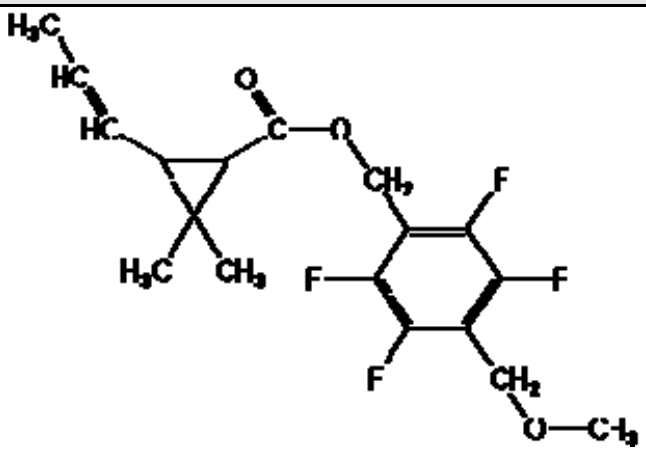
TABLE 1 Nomenclature and Physiochemical Properties of Metofluthrin	
Chemical Structure	
Empirical Formula	$C_{18}H_{20}F_4O_3$
Common name	Metofluthrin
Company experimental name	S-1264
IUPAC name	2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (*EZ*)-(1*RS*,3*RS*;1*RS*,3*SR*)-2,2-dimethyl-3-prop-1-enylcyclopropanecarboxylate
CAS name	[2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl 2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate
CAS Registry Number	240494-70-6
End-use product/EP	SumiOne®, Eminence®
Chemical Class	Pyrethroid ester

TABLE 2 Physiochemical Properties of Technical Grade Metofluthrin	
Molecular Weight	360.34
Melting point/range	NA
pH	5.24 at 25°C (1% aqueous solution)
Density	1.21 at 20°C
Water solubility (20°C)	0.67 mg/L (20°C) for (S-1264RTE) 0.50 mg/L (20°C) for (S-1264RTZ)
Solvent solubility (20°C to 25°C) (g/L)	Acetone 303.4, methanol 312.2, ethyl acetate 307.6, toluene 326.9, n-hexanes 328.7, dichloromethane 318.9, n-octanol 325.1, isopropyl alcohol 313.2
Vapor pressure (25°C)	1.47×10^{-5} Torr
Dissociation constant, pKa	Could not be measured
Octanol/water partition coefficient, $\log P_{OW}$ (25°C)	5.03 (S-RTE) 4.97 (S-RTZ)
UV/visible absorption spectrum	In 100% methanol: peak maximum = 273 nm, extinction coefficient = 1670 $M^{-1}cm^{-1}$, band width 23 nm

TOXICOLOGY SUMMARY

The Registrant submitted the studies listed in Tables 3 and 4, which include a number of

toxicity studies. These include the usual acute studies for metofluthrin technical. The Registrant has also submitted oral, dermal and inhalation studies as well as chronic, carcinogenicity and developmental studies as shown in Table 4.

TABLE 3 Acute Toxicity Profile – Test Substance

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	46406719	LD_{50} > 2000 mg/kg	III
870.1200 Acute dermal toxicity	46406721	LD_{50} >= 2000 mg/kg	III
870.1300 Acute inhalation toxicity	46406723	LC_{50} > 1.08 and < 1.96 mg/L	III
870.2400 Acute eye irritation	46406724	Not an eye irritant	IV
870.2500 Acute dermal irritation	46406724	Mildly irritating to the skin (PDI = 0.8)	IV
870.2600 Skin sensitization	46406726	Not a dermal sensitizer	-

Table 4 Subchronic, Chronic, and Other Toxicity Profile

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rats (Wistar rats)	46454109 (2003) Acceptable/Guideline 0, 100, 300, 1000, or 2500 ppm M: 0, 6.8, 20.6, 70.4, or 183.6 mg/kg/day F: 0, 7.5, 21.6, 73.0, or 185.6 mg/kg/day	NOAEL = 20.6/21.6 mg/kg/day LOAEL = 70.4/73.0 mg/kg/day, based on increased absolute and relative liver weights in both sexes; increased serum total cholesterol and phospholipids levels in males, and increased incidences of enlarged livers, hepatocellular hypertrophy, and basophilia in males; and decreased body weight gain in females.
870.3100 Subchronic (6-month) oral toxicity rats (Sprague-Dawley rats)	46406733 (2002) Acceptable/Guideline 0, 100, 300, 1000, or 3000 ppm M: 0, 5.3, 16.0, 54.1, 164.6 mg/kg/day F: 0, 6.4, 19.0, 65.4, 191.4 mg/kg/day	NOAEL = 16.0/19.0 mg/kg/day LOAEL = 54.1/65.4 mg/kg/day, based on increased relative liver weights, serum phospholipids, and total cholesterol levels in males; increased incidences of dark, enlarged livers and hepatocellular hypertrophy in both sexes; and an increased incidence of slight focal hepatic necrosis in females.

Table 4 Subchronic, Chronic, and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity in mice (CD-1 mice)	46454108 (2004) Acceptable/Guideline 0, 100, 1500, 2500, or 3500 ppm M: 0, 13.7, 20.9, 35.7, or 48.7 mg/kg/day F: 0, 17.2, 25.2, 43.9, or 58.7 mg/kg/day	NOAEL = 35.7/43.9 mg/kg/day LOAEL = 48.7/58.7 mg/kg/day, based on findings indicative of hepatotoxicity including increased absolute and relative liver weights in both sexes; increased serum total cholesterol, phospholipids, and triglycerides in females; and minimal degeneration/necrosis of the liver and minimal to moderate hepatocellular hypertrophy in both sexes, and increased Kupffer cells in males.
870.3150 90-Day oral toxicity in dogs (Beagles)	46406734 (2002) Acceptable/Guideline 0, 10, 30, or 100 mg/kg/day	NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day, based on tremor and vomiting observed in both sexes
870.3250 90-Day dermal toxicity in rats (Sprague-Dawley)	46556101 (2004) Acceptable/Guideline 0, 30, 100, 300, or 1000 mg/kg/day	Systemic NOAEL = 300 mg/kg/day Systemic LOAEL = 1000 mg/kg/day, based on mortality and clinical signs (tremor and salivation) Dermal NOAEL = not determined Dermal LOAEL = 30 mg/kg/day, based on hyperactivity and vocalization in the females during the daily exposure period
870.3465 Subchronic inhalation study in rats (Sprague-Dawley)	46406736 (2002) Acceptable/Guideline 0, 10, 50, 100, or 200 mg/m^3 0, 0.01, 0.051, 0.099, or 0.196 mg/L) M: 4 hrs/day, 28 days F: 4 hrs/day, 29 days	NOAEL = 0.099 mg/L LOAEL = 0.196 mg/L, based on mortality and clinical signs including tremors, hypersensitivity, ataxic gait, tiptoe gait, lateral position, clonic convulsion, and hypothermia in both sexes. Clinical signs began on days 1-4 and occurred consistently in the males and transiently in females thereafter.
870.3700a Prenatal developmental in rats (Sprague-Dawley)	46454111 (2002) Acceptable/Guideline 0, 5, 15, or 30 mg/kg/day from GD6 – GD19	Maternal NOAEL = 15 mg/kg/day Maternal LOAEL = 30 based on increased incidence of tremor Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = not observed
Prenatal developmental in rats (Sprague-Dawley)	46454112 (2002) Acceptable/Non-Guideline M: 0, 10, or 20 mg/kg/day beginning 2 weeks prior to mating through necropsy (57 days) F: 0, 10, 20, or 40 mg/kg/day beginning 2 weeks prior to mating through GD7	Parental NOAEL = 20 mg/kg/day (both sexes) Parental LOAEL = 40 mg/kg/day, based on mortality and incidences of tremors and salivation in females. Reproduction NOAEL = 20/40 mg/kg/day M/F Developmental NOAEL = 40 mg/kg/day in females Developmental LOAEL = not observed
Prenatal developmental in rats (Sprague-Dawley	46454113 (2002) Acceptable/Non-guideline 0, 5, 15, or 30 mg/kg/day from GD6 through LD20	Maternal NOAEL = 15 mg/kg/day Maternal LOAEL = 30 mg/kg/day, based on mortality and increased incidences of tremors and salivation. Reproductive NOAEL = 30 mg/kg/day Reproductive LOAEL = not observed Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = not observed

Table 4 Subchronic, Chronic, and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal developmental in rabbits (New Zealand White)	46454114 (2002) Acceptable/Guideline 0, 25, 125, or 250 mg/kg/day from GD6 – GD27	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 125 mg/kg/day, based on mortality Developmental NOAEL = 250 mg/kg/day Developmental LOAEL = not observed
870.4100a Chronic toxicity rodents (Wistar rats)	46611301 (2005) Acceptable/Guideline 0, 20, 200, 900, or 1800 ppm M: 0, 0.8, 8.2, 38.1, or 77.8 mg/kg/day F: 0, 1.0, 10.1, 47.4, or 96.1 mg/kg/day	NOAEL = 8.2/10.1 mg/kg/day LOAEL – 38.1/47.4 mg/kg/day, based on decreased body weights and body weight gains in both sexes; increased incidence of hepatic clear cell foci in both sexes; increased fatty liver change, and kidney lesions (including interstitial fibrosis, lipofuscin, mononuclear foci, and glomerulosclerosis) in males; increased centrilobular hepatocellular hypertrophy in females
870.4100b Chronic toxicity dogs (Beagle)	46454110 (2004) Acceptable/Guideline 0, 10, 30, or 100 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day, based on increased incidence of tremor in males.
870.4300 Carcinogenicity mice (CD-1 mice)	46611302 (2005) Acceptable/Guideline 0, 100, 1000, or 1750/2500 ppm M: 0, 12, 116, or 209 mg/kg/day F: 0, 15, 155, or 277 mg/kg/day	NOAEL = 116/155 mg/kg/day LOAEL = 209/277 mg/kg/day, based on decreased body weight gain in both sexes.
Gene Mutation 870.5100 Bacterial Reverse Gene Mutation Assay	46406742 (2002) Acceptable/Guideline 0, 156, 313, 625, 1250, 2500, or 5000 µg/plate +/- S9 in *S. typhimurium* TA98, TA100, TA1535 and TA1537 and *E. Coli* WP2 uvrA	There was no evidence of induced mutant colonies over background levels.
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation Assay	46454115 (2004) Acceptable/Guideline Trial 1 (-S9): 4.88, 9.77, 19.5, 39.1, 78.1, or 156 µg/plate strains TA100, TA1535 Trial 2 (+S9): 19.5, 39.1, 78.1, 156, 313, or 625 µg/plate strains TA100, TA1535, and TA1537 Trial 3 (+/-S9): 156, 313, 625, 1250, 2500, or 5000 µg/plate strains TA98 and WP2*uvrA*	There was no evidence of induced mutant colonies over background levels.

Table 4 Subchronic, Chronic, and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenics (Chromosomal Aberration Assay in Chinese Hamster Lung Fibroblasts)	46406744 (2002) Acceptable/Guideline Trial 1 (-S9): 50, 70, 90, 110, or 130 µg/mL Trial 1 (+S9): 50, 100, 150, 200, or 250 µg/mL Trial 2 (-S9) 20, 50, 80, or 110 µg/mL Trial 2 (+S9): 100, 150, 200, or 250 µg/mL	There was no evidence of chromosome aberration induced over background in the presence or absence of S9-activation.
Other Effects 870.5395 *In vivo* Mammalian Cytogenetics – Erythrocyte Micronucleus Assay in Mice	46406745 (2002) Acceptable/Guideline 0, 12.5, 25, or 50 mg/kg	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.
870.6200a Acute neurotoxicity screening battery (Sprague-Dawley)	46406728 (2004) Acceptable/Guideline 0, 20, 50, or 100 mg/kg	NOAEL = 50 mg/kg LOAEL = 100 mg/kg, based on mortality, adverse clinical signs, FOB (unusual behavior, limb twitches/tremors, and abnormal respiration) effects, and increased motor activity in both sexes.
870.6200b Subchronic neurotoxicity screening battery (Sprague-Dawley)	46406729 (2004) Acceptable/Guideline 0, 300, 1000, or 3000 ppm M: 0, 18.3, 59.8, or 178.8 mg/kg/day F: 0, 20.9, 68.8, 206.0 mg/kg/day	Systemic NOAEL = 59.8/68.8 mg/kg/day Systemic LOAEL = 178.8/206.0 mg/kg/day, based on mortality (females only); clinical signs (soft/liquid feces and scant feces in the males and tremors and twitches in the females); decreased body weight, body weight gain, and absolute and relative food consumption in both sexes. Neurotoxicity NOAEL = 59.8/68.8 mg/kg/day Neurotoxicity LOAEL = 178.8/206.0 mg/kg/day, based on the clinical signs of tremors and twitches in the females
870.7485 Metabolism and pharmacokinetics	46406746, 46406747, 46406748, 46414002, and 46414003 (2004) Acceptable/Guideline 1 or 20 mg/kg for single dose studies 1 mg/kg for 21 day studies	Overall recoveries were 95-97% for both dose groups. Absorption was rapid (detectable plasma residues within 30 minutes, T_{max} 3.3-8.0 hours) and thorough (>80% absorption). Absorption was not dose limited. At 168 hours post dosing, urinary and fecal excretion accounted for 29-71% and 25-66% of the total administered dose, respectively. Radioactivity increased above plasma levels in both liver and kidney, but dissipated 12 hours post-dose. 46 metabolites were identified, including all major metabolites.
Non-Guideline An evaluation of the human relevance of the metofluthrin-induced liver tumors in rats based on mode of action	46756304 (2006) Acceptable/Nonguideline	Summary of proposed MOA and weight of the evidence. The MOA for metofluthrin-induced liver tumors is postulated to involve liver cytochrome P450 enzyme induction leading to stimulation of increased cellular proliferation. MOA not accepted by CARC due to insufficient data.

Table 4 Subchronic, Chronic, and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Non-Guideline Study for the mode of action of S-1264 for liver tumor promotion in rats (Wistar rats)	46581501 (2005) Acceptable/Nonguideline 0, 900, 1800, or 3600 ppm in the diet for 7 days Concurrent recovery group fed basal diet for 7 days following treatment period	Liver morphology and enzyme induction were affected in at 900 ppm and above, as evidenced by increased liver weights, hepatocellular hypertrophy, replicative DNA synthesis in the hepatocytes, induction of CYP 2B and 3A mRNA, and increased expression of CYP 2B. All of these findings were reversible on cessation of treatment.
Non-Guideline The 2nd study of mode of action of S-1264 for liver tumor promotion in rats	46756301 (2006) Acceptable/Nonguideline 0, 200, 900, 1800, or 3600 ppm in diet for 7 days	Metofluthrin inhibited gap junction interactions (as evidenced by decreased dye transfer) and induced oxidative stress (measured by lipid oxidation and GSH levels).
Non-guideline Study for mode of action of S-1264 for liver tumor promotion in rats (in vitro effects of S-1264 on cytochrome P450 activity and mRNA levels)	46756302 (2006) Acceptable/Nonguideline Rat, mouse, and human hepatocytes were exposed 50 μM metofluthrin for 3 days, and comparative metabolic profiles were examined.	Metofluthrin induced CYP 2B mRNA and 7-pentoxyresorufin O-dependentylase activity in rat and human hepatocytes, but not in mouse hepatocytes, but the induction level was less than that of phenobarbital induction in human hepatocytes.
Non-Guideline Gene expression profiling analysis of early phase treatment in the liver from S-1264 treated rats	46756303 (2006) Acceptable/Nonguideline Wistar rats were exposed to 1800 ppm metofluthrin for 1 week. DNA microarray was used to evaluate gene expression.	The majority of genes upregulated by metofluthrin were GSTs, CYPs, and UDPGTs. In general, this resembled the upregulation of Phenobarbital, only to a lesser degree.

HAZARD CHARACTERIZATION/ASSESSMENT

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations." http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf

Human Testing: This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

Hazard and Dose-Response Characterization

The toxicology database for metofluthrin is complete for the proposed use pattern. Although metofluthrin is a neurotoxicant, a developmental neurotoxicity (DNT) study is not necessary at this time. However, if new uses are proposed, the need for a DNT study

will need to be re-evaluated. The risk assessment team is confidant that risk to pregnant women and children will not be underestimated due to: 1) regulatory endpoints are based on neurotoxicity, 2) no neuropathy or changes in morphometrics were observed in the acute and subchronic neurotoxicity studies, and 3) for pyrethroids where DNT studies are available for endpoint consideration, the regulatory endpoints are generally based on neurotoxicity to dogs because dogs are more sensitive to pyrethroids than rats (it is unlikely that a DNT in rats would produce a lower neurotoxicity NOAEL than the NOAEL from the chronic dog study).

Summary and Discussion of Dose Related Effects

Metofluthrin, like other pyrethroids, is neurotoxic in rats, rabbits, and dogs; both sexes were equally sensitive to metofluthrin. Clinical signs include tremor (all species), vomiting (dog only), and increased salivation (rats and dogs). Clinical signs appeared within 206 hours post-dosing and generally disappeared by the dosing period the following day. All routes of exposure (oral, dermal, and inhalation) elicited neurotoxic effects in rats. Rats appeared to be most sensitive via the inhalation route, based on clinical signs including ataxic gait, tremors, tip-toe gait, lateral position, clonic convulsion, hypothermia, and mortality in both sexes. In the acute neurotoxicity battery, neurotoxic effects were seen in rats following a single dose of 100 mg/kg/day including mortality, tremors/twitches, abnormal respiration, and increased motor activity (acute NOAEL = 50 mg/kg/day). Dermal exposure to 10 mg/kg/day in rats produced increased vocalization during the daily application period, which subsided after the removal of the chemical. There were no systemic effects resulting from dermal exposure. In subchronic exposures in rats (based on the subchronic and developmental studies, NOAELs ranged 15-20 mg/kg/day) the LOAELs range from 30-54.1 mg/kg/day, based on liver effects and neurotoxicity. Neurotoxicity was not noted in the chronic studies. The dose-response curve for neurotoxicity is steep with mortality occurring frequently at the LOAEL; death was preceded by tremor, convulsion, salivation, and prostration.

Metofluthrin also targeted the liver in rats and mice, producing increased absolute and relative liver weights, hepatocellular hypertrophy, and increase incidence of enlarged, discolored livers. Hepatocellular toxicity was present at or above 48.7 mg/kg/day in mice and 54.1 mg/kg/day in rats in the subchronic studies. In the chronic rat study, exposure to metofluthrin was connected to increased incidence of hepatocellular adenomas, carcinomas, and combined tumor types at doses greater than or equal to 38.1 mg/kg/day. The registrant submitted a proposed mitogenic mode of action (MOA) for hepatocellular tumor induction. While these studies did suggest a mitogenic MOA was plausible, the studies did not provide enough information for the Agency to accept their proposed MOA. Metofluthrin is not mutagenic or cytotoxic; it does not induce peroxisomal proliferation. The Agency classified this chemical as “likely to be carcinogenic to humans” and generated a Q1* of 1.62x10-2, based on the increased liver tumors in female rats.

In utero and/or post-natal exposure to metofluthrin did not produce any evidence of increased qualitative or quantitative susceptibility in fetuses or pups. Four acceptable developmental studies in rats and rabbits were submitted for metofluthrin. Maternal toxicity was seen at or above 30 mg/kg/day in rats (tremor, salivation, and mortality) and 125 mg/kg/day in rabbits (mortality, preceded by tremor/convulsion). These doses did

not produce any developmental effects on the fetuses or pups. A developmental toxicity study is not being requested at this time for the following reasons: 1) neurotoxicity is well defined within the toxicology database, 2) regulatory endpoints are based on the neurotoxicity, and 3) there were no pathology findings or changes in morphometrics noted in either the acute or subchronic neurtoxicity studies. The FQPA safety factor has been reduced to 1x.

Considerations for Infants and Children

The toxicity database for this chemical is complete for the purposes of this risk assessment. Acceptable neurotoxicity and developmental studies have been submitted for review. Though not required for a non-food use registration, a 2-generation rat reproduction study is being conducted. The Agency has received preliminary results in a 6(a)(2) document, but the final study report has not been submitted at this time**.**

Neurotoxicity

Evidence of neurotoxicity exists throughout the entire toxicology database via the oral route of exposure in three species (rats, rabbits, and dogs) and via dermal and inhalation routes of exposure in rats.

In the acute neurotoxicity study in rats, a single dose of 100 mg/kg produced tremors, twitches, abnormal respiration, increased motor activity, and mortality. The animals found dead or in extremis 24 hours post-dosing (7 out of 20 animals) exhibited signs of clonic convulsions, hyperpnea, prostration, lost righting reflex, soft or liquid feces, tonic extensor convulsions, salivation, chromorhinorrhea, and chromodachyorrhea. In the subchronic neurotoxicity study, the LOAEL (59.8/68.8 M/F, respectively) was based on mortality in the females; clinical signs including tremors and twitches (in females); decreased body weight and body weight gain, and absolute and relative food consumption in both sexes. Neither study indicated neuropathy.

In a subchronic oral study in rats, all animals exhibited signs of tremor 2-6 hours post-dosing during Week 1 of treatment at doses above 164.6 mg/kg/day; 0-2 animals/sex exhibited transient tremors throughout Weeks 2-3. No clinical signs were observed after Week 3. At 100 mg/kg/day in the subchronic dog study, 5/6 males showed signs of tremor (1-7 incidences/animal) beginning on Day 23 and 5/6 females showed signs of tremor (1-5 incidences/animal) beginning on Day 10. Mild repetitive jerks or tremors of the head, limb or body were seen in 1 animal/sex at Weeks 12-13 (male) and Weeks 11 and 13 (female); these effects were evidenced during cage-side and table top observations. Three developmental rat studies were performed for metofluthrin; all three maternal LOAELs were based on tremor and salivation and two maternal LOAELs included mortality.

In the subchronic dermal study in rats, two females were found dead on Day 2 in the 1000 mg/kg/day dose group. One female, before being found dead, displayed tremors prior to dosing and salivation 3-5 hours post-dosing. Hyperactivity and vocalization were transiently observed in the >= 30 mg/kg/day females and >= 100 mg/kg/day males during the daily application period on Days 1-4. There were no treatment-related clinical signs outside of the daily dosing period.

In the 28-day inhalation toxicity study in rats, 7/10 males and 3/10 females in the 0.196 mg/L dose group died. At this concentration, tremors of the tail and body were observed during the treatment period; tremor, hypersensitivity, ataxic gait, tiptoe gait, lateral position, clonic convulsion, and hypothermia were observed. Onset occurred on Days 1-4, and clinical signs were transiently seen until Day 26 in males and less frequently in the females until Day 24.

No evidence of neurotoxicity was recorded in either the rat or the mouse chronic/carcinogenicity studies. Increased incidence of tremor was observed in males at 30 mg/kg/day in the chronic dog study. Tremor was observed in the head, limbs, or body of all males beginning on Day 96 (1-5 incidences/dog except one male with 46 incidences) and in only one female and only on Day 289. Tremors were observed 2-6 hours post-dosing and disappeared by the time of observation the next morning.

Developmental Toxicity

Acceptable guideline developmental toxicity studies in rats and rabbits have been submitted for review, along with two acceptable non-guideline developmental studies in rats. In the three rat studies (MRID 46454111, 46454112, 46454113) maternal toxicity was observed in the form of neurotoxicity (tremors and salivation) and death. Neurotoxic effects were observed 2-3 hours post dosing and disappeared by the following day. The maternal NOAELs ranged from 15-20 mg/kg/day, and the maternal LOAELs ranged from 30-40 mg/kg/day. No developmental effects were seen in the rat studies up to 40 mg/kg/day. In one non-guideline study (MRID 46454112) males and females were dosed during the premating and mating periods all the way through gestation day (GD)7 for females. No reproductive effects were noted in either the males or females up to 20/40 mg/kg/day (males/females, respectively, highest dose tested). In the other non-guideline study (MRID 46454113), the female rats were dosed from GD6 (implantation) through lactation day (LD)20. Reproductive effects were not observed in the P or F1 generations. There were no offspring effects noted with regard to FOB results, sensory reflexes, clinical signs, developmental landmarks, body weights, or gross pathology up to the highest dose tested of 30 mg/kg/day.

In the rabbit developmental study, one female in the 125 mg/kg/day group exhibited sneezing and convulsions before death on GD23. One female in the 250 mg/kg/day dose group was found dead on GD14. These deaths were considered treatment related because another female was found dead with convulsions preceding death in the range finding study at 200 mg/kg/day. There were no other mortalities or clinical signs; the LOAEL was determined to be 125 mg/kg/day. The maternal NOAEL is 25 mg/kg/day. There were no treatment-related effects on developing fetuses; the developmental LOAEL was not observed. The developmental NOAEL was determined to be 250 mg/kg/day, the highest dose tested.

Reproductive Toxicity

A reproductive study in rats has not been submitted to the EPA at this time. However, the Agency has received a 6(a)(2) document indicating that a 2-generation reproduction study in rats is being performed. Preliminary findings include neurotoxic effects (tremors, convulsions, and salivation) in the F1 and F2 generations. When the final study report is submitted, a full review of the data will be conducted.

Pre-and/or Postnatal Toxicity

There were no effects on fetal growth or development up to 40 mg/kg/day in rats or 250 mg/kg/day in rabbits; doses at which maternal toxicity was present. There were no treatment related effects on the numbers of litters, fetuses (live or dead), resorptions, sex ratio, or post-implantation loss. There were no effects on fetal body weights or skeletal ossification; and no external, visceral, or skeletal malformations or variations were observed.

Developmental Neurotoxicity

A DNT study is not being requested at this time; however, because this chemical is part of the pyrethroid class, the need for a DNT study will be re-evaluated for all future proposed uses

Summary of Toxicological Doses and Endpoints for Metofluthrin for Use in Human Risk Assessments

Table 3.4.2 Summary of Toxicological Doses and Endpoints for Metofluthrin for Use in Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short-Term (1-30 days)	NOAEL = 15 mg/kg/day	UF_A= 10x UF_H=10x	Residential LOC for MOE = 100	Developmental Rat Study LOAEL = 30 mg/kg/day based on increased incidence of tremor in maternal animals
Dermal Short-Term (1-30 days)	NOAEL= 300 mg/kg/day	UF_A= 10x UF_H= 10x	Residential LOC for MOE = 100	90-Day Dermal Rat Study LOAEL = 1000 mg/kg/day based on mortality and clinical signs
Inhalation Short-Term (ALL DURATIONS)	NOAEL = 16 mg/kg/day	UF_A= 10x UF_H =10x	Residential LOC for MOE = 100	28-Day Inhalation Study in Rats LOAEL = 32 mg/kg/day based on mortality and clinical signs including tremors, ataxia, hypersensitivity, ataxic gait, tiptoe gait, lateral position, clonic convulsion, and hypothermia in both sexes
Cancer (oral, dermal, inhalation)	Likely to be a human carcinogen	Q_1* = $1.62x10^{-2}$ $(mg/kg/day)^{-1}$ Dermal absorption factor = 17%		Based on female rat liver combined adenoma and carcinoma tumor rates

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Public Health and Pesticide Epidemiology Data
Metofluthrin is a new active ingredient; therefore, no epidemiological data is available at this time.

Dietary Exposure/Risk Characterization
There are no proposed agricultural uses for metofluthrin at this time; therefore dietary exposure is not expected.

Residential (Non-Occupational) Exposure/Risk Pathway
The aggregate exposure assessment is based solely on residential use patterns. Due to the seasonal nature of insect repellents, only short-term exposure scenarios were considered. The incidental oral endpoint for children was based on maternal neurotoxicity in the rat developmental study (NOAEL = 15 mg/kg/day). This endpoint was selected because of the appropriate time period in which the maternal neurotoxic effects were seen. The short-term dermal endpoint for adults and children (15 mg/kg/day) was selected from the same developmental rat study based on neurtoxic effects because no systemic toxicity was present in the 90-day dermal study. A dermal penetration study in rats was submitted for metofluthrin, which suggests a 17% dermal absorption rate. This 17% dermal absorption rate was applied to all dermal exposure scenarios. The 28-day inhalation study in rats provided a sensitive inhalation endpoint (0.099 mg/L) based on mortality and neurotoxic effects (including tremors, hypersensitivity, ataxic gait, tip-toe gait, clonic convulsion, and hypothermia. The default absorption value of 100% was applied to the inhalation exposure assessment. All levels of concern are set at 100, based on a 10x interspecies extrapolation safety factor and 10x intraspecies variability safety factor. The FQPA safety factor was reduced to 1x.

As a part of every pesticide risk assessment, the Agency considers a large variety of consumer subgroups according to well-established procedures. The Agency estimates risks to population subgroups from pesticide exposure that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, the Agency is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as the Agency has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific populations.

Estimated Cancer Risk
The Q1* for metofluthrin was based on female hepatocellular adenomas, carcinomas, and

combined adenomas/carcinomas in rats. The Q1* is 1.62 x 10-2 (mg/kg/day) -¹. This cancer assessment is conservative in assuming that the product will be used 12 times per year for 50 years out of a 70 year lifespan.

A high-end worst case inhalation cancer assessment was performed for the metofluthrin products (DeckMate and NORM-1). The saturation concentration of 0.28 mg/ m3 was used, with a 12 hour / day exposure time (half a day). An adult breathes 20 m3 of air per day. The use frequency was 12 applications per year from the use survey conducted by the Residential Exposure Joint Venture (REJV). The users are expected to use the products over a 50 year period in their 70 year lifetime. This results in a Lifetime Average Daily Dose (LADD) of 0.000939 mg/kg/day. The LADD is multiplied by the Q1*, which results in an estimated cancer risk of 1.5 x 10-5.

Aggregate Exposure Assessment
Metofluthrin is proposed for residential use only at this time. No food uses exist. Residues in water are unlikely. An aggregate exposure assessment is not needed at this time.

Cumulative Risk Characterization/Assessment
Metofluthrin is a member of the pyrethroid class of pesticides. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. Although all pyrethroids interact with sodium channels, there are multiple types of sodium channels and it is currently unknown whether the pyrethroids have similar effects on all channels. Nor do we have a clear understanding of effects on key downstream neuronal function e.g., nerve excitability, nor do we understand how these key events interact to produce their compound specific patterns of neurotoxicity. There is ongoing research by the EPA's Office of Research and Development and pyrethroid registrants to evaluate the differential biochemical and physiological actions of pyrethroids in mammals. This research is expected to be completed by 2007. When available, the Agency will consider this research and make a determination of common mechanism as a basis for assessing cumulative risk. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Occupational Exposure/Risk Pathway
Only residential uses are proposed for metofluthrin at this time; dietary and occupational risk assessments are not necessary at this time.

ENVIRONMENTAL FATE AND EFFECTS SUMMARY

Metofluthrin, like other synthetic pyrethroids, is practically non-toxic to mammals and birds, but it is highly to very highly toxic to aquatic animals and insects. Its repellency power is related to its insecticidal character. The published literature supports its character both as a repellent and as an insecticide. No Level of Concern was exceeded, but the insecticidal properties of metofluthrin imply that it will pose a risk to non-target

insects and to species federally listed as endangered or threatened by the United States government.

Since there is no geographic restriction on metofluthrin's use, it will be used in every place where there are mosquitoes. The proposed use is not expected to stress aquatic or terrestrial vertebrates or aquatic invertebrates even though it is toxic to them, because it is not expected to have a high aquatic concentration.

Environmental Effects

The registrant has submitted adequate effects and fate data needed to complete a Tier 1 Risk Assessment. A summary of all submitted studies are shown in Table 5 and 6 below. Metofluthrin's effect on aquatic organisms is estimated from acute, subacute and chronic laboratory studies submitted to the Agency. The registrant has submitted acute and chronic studies on aquatic vertebrates and invertebrates. Freshwater fish, e.g., bluegill sunfish (Lepomis macrochirus), rainbow trout (Oncorhynchus mykiss) and fathead minnow (Pimephales promelas) are used as surrogates for all freshwater fish species. Freshwater fish are used as surrogates for aquatic-phase amphibians. No acute bluegill sunfish (§72-1a) was submitted. A common carp study was ruled "supplemental," because it is not a standard species. The Agency shall require confirmatory data to satisfy the acute bluegill sunfish data requirement.

The effect of metofluthrin on all bird species is estimated from acute, subacute and chronic studies on two species, bobwhite quail (Colinus virginianus) and mallard duck (Anas platyrhynchos). These species also act as surrogates for reptiles and terrestrial-phase amphibians. Effects on mammals are estimated from acute and chronic rat studies submitted to and reviewed by the Agency.

No studies have been submitted that address toxicity to insects. The registrants have requested a waiver for a study on beneficial insects (bees), but this has not been granted. There are no published field surveys or monitoring data. Published information (Kawada, et al.) found that metofluthrin kills insects (mosquitoes) in a cage. All experimental mosquitoes directly under a paper strip were killed within 24-hours. This was not quantified nor was a measure of toxicity (LD50, etc.) calculated. The Agency shall require confirmatory data to satisfy this data requirement.

TABLE 5 Measures of Envrionmental Effects of metofluthrin

Guidelines	Data Requirements	Measures Of Effect
71-1(a)	Acute Avian Oral Quail or Duck	LD_{50} >2250 mg/kg-bw.
71-2(a)	Avian Dietary/Quail	LC_{50} >5760 mg/kg-bw
71-2(b)	Avian Dietary/Duck	LC_{50} >5760 mg/kg-bw.
OPPTS 870.1100	Rat Acute Oral LD50	LD50 >2,000 mg/kg

Non-guideline	Rat reproductive development study	NOAEL = 20 mg/kg bw/day dose based on maternal mortality during the 57 days of dosing
72-1	Fish Toxicity- Common carp	LC_{50} = 2.61
72-1(c)	Fish Toxicity Rainbow Trout	LC_{50} = 1.2
72-2(a)	Invertebrate Toxicity, Daphnid	48-hr LC_{50} = 4.7 ppb

Table 5. Environmental Fate properties of metofluthrin.

PARAMETER	VALUE(S)	SOURCE
Solubility in water (20 °C)	0.50 mg/L (*Z-isomer*) 0.67 mg/L (*E-isomer*)	MRID 46406754
Vapor Pressure (20 °C)	1.47 x 10^{-5} mmHg	MRID 46402005
Henry's Law Constant (20 °C)	1.5 x 10^{-5} atm m^3/mol (*Z-isomer*) 1.1 x 10^{-5} atm m^3/mol (*E-isomer*)	Estimated from vapor pressure & solubility[1]
Hydrolysis Half-life (25 °C)	*pH 4 & 7*: Stable *pH 9*: 33 days	MRID 46406750
Aqueous Photolysis Half-life (pH 4)	6 days	MRID 46406754 (Based on 12-hour light/12-hour dark cycle with Xe lamp)
Aerobic Soil Metabolism Half-life	*MS sandy loam*: DT_{50} = 3-8 days *CA sandy loam*: DT_{50} = 1-3 days	MRID 46406751
Soil Partition Coefficient (K_d)	57.5, 75.8, 85.3, 163 mL/g	MRID 46406753 (calculated, based on submitted data)
Organic Carbon Partition Coefficient (K_{oc})	3704, 4489, 5414, 7187 mL/g_{oc}	MRID 46406753 (Calculated, based on calculated K_d)

[1] Estimated as Hg = vapor pressure (atm) ÷ solubility (mol/L)

Contact Person at USEPA

Mailing address:

Mark Suarez
Product Manager (10)
Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7505P)
Insecticide Branch
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

Office location and telephone number:

Room S-7246, One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202
703-305-0120

APPENDIX I

GLOSSARY OF TERMS AND ABBREVIATIONS

ADNT	Acute delayed neurotoxicity
a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
ARI	Aggregate Risk Index
BCF	Bioconcentration Factor
CAS	Chemical Abstracts Service
ChE	Cholinesterase
ChEI	Cholinesterase inhibition
cPAD	Chronic Population Adjusted Dose
%CT	Percent crop treated
DAT	Days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model - Food Consumption Intake Database
DNA	Deoxyribonucleic acid
DNT	Developmental neurotoxicity
DIT	Developmental immunotoxicity
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
GLC	Gas Liquid Chromatography
GLN	Guideline Number
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOAEL	Lowest Observed Adverse Effect Level
LOAEC	Lowest Observed Adverse Effect Concentration
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of Quantitation
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure

MRID	Master Record Identification (number), EPA's system of recording and tracking studies submitted
MTD	Maximum tolerated dose
NA	Not Applicable
NOEC	No Observable Effect Concentration
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NPDES	National Pollutant Discharge Elimination System
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
TGAI	Technical Grade Active Ingredient
UF	Uncertainty Factor
µg	micrograms
µg/L	Micrograms Per Liter
µL/g	Microliter per gram
USDA	United States Department of Agriculture
WPS	Worker Protection Standard

APPENDIX II

Citations Considered to be Part of the Data Base Supporting the Registration of Metofluthrin.

MRID	Citation	Receipt Date
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