STUDY TITLE:

Comments on EPA's Interpretation of the Phenothrin Rabbit Developmental Toxicity Study and Discussion of Appropriate Toxicologic Endpoint for Risk Assessment

DATA REQUIREMENT:

Not Applicable

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STUDY COMPLETED ON:

April 30, 2008

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PROJECT IDENTIFICATION:

RS0809

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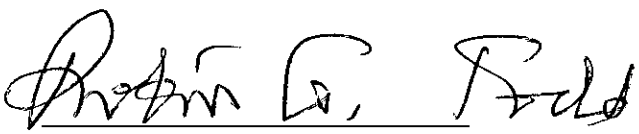
Signature: 

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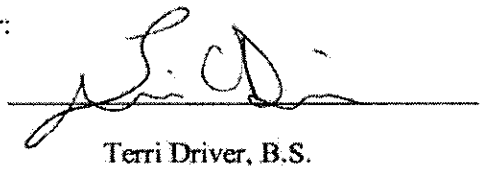
QUALITY ASSURANCE STATEMENT

REPORT TITLE: Comments on EPA's Interpretation of the Phenothrin Rabbit Developmental Toxicity Study and Discussion of Appropriate Toxicologic Endpoint for Risk Assessment

REPORT IDENTIFICATION: RS0809

This report was audited and reviewed with respect to the study data, data files, algorithms and data transformations used in the exposure/risk analysis. Data summary tables and analyses were derived using the electronic spreadsheet program, Microsoft Excel 2000®, Microsoft Corporation. The results of the formulae used in the spreadsheets were independently verified. The information in the report was representative of these tables, and the report contents accurately reflect the data.

Auditor: 

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Date: April 30, 2008

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1.0 ABSTRACT/SUMMARY

The weight of evidence strongly indicates that Phenothrin is not a developmental toxicant. Although U.S. EPA has cited limited evidence of developmental toxicity in rabbits, these data are not statistically significant. U.S. EPA's interpretation is not consistent with any known mechanism of action for Phenothrin or any pyrethroid. Other regulatory bodies have concluded that Phenothrin is not a developmental toxicant, despite the fact that it does produce toxicity in pregnant rabbits at high dosages. The uncertainty factor assigned by U.S. EPA is incongruent with the weight of evidence. The policy-driven uncertainty factor is not consistent with U.S. EPA's scientific review of the rabbit developmental toxicity study. The data indicate that an appropriate regulatory NOAEL would be 100 mg/kg from the rabbit developmental toxicity study, rather than 9.3 mg/kg from a subchronic dog study chosen by EPA. The nature of exposure to Phenothrin, as U.S. EPA acknowledges, is both short term (days and not months in duration) and intermittent. Consequently, it would be more appropriate to apply a moving average for the exposure estimate to be used in the risk assessment process.

2.0 FIRST ISSUE: DEVELOPMENTAL TOXICITY

US EPA has interpreted the Rabbit Developmental Toxicity study (Nemec, 1989a) as indicating that Phenothrin (Sumithrin) causes terata at doses below the maternal NOAEL (Daiss, 2006, 2007). Thus, according to this interpretation, Phenothrin is a reproductive toxicant. Consequently, the uncertainty derived from not having an acceptable rat teratology study, and certain other neurotoxicity studies, would lead U.S. EPA (under FQPA) to require an extra safety factor of 10 in the risk assessment.

The Data Evaluation Record (DER) from U.S. EPA indicates that in their initial review of the Rabbit Developmental Toxicity Study the maternal NOAEL was set at 100 mg/kg-day (increased clinical signs and abortions), and the fetal NOAEL (hydrocephaly) was set at 300 mg/kg-day (Hurley, 1991). The original U.S. EPA reviewer's opinion was apparently overruled in generating the RED (Daiss, 2007), using the following logic: First, there were 3 litters with hydrocephaly at the high dose (500 mg/kg). Second, there was one pup in one 1 litter with an instance of spina bifida at a mid dose (100 mg/kg), and one pup in 1 litter with an instance of microphthalmia at a different mid dose (300 mg/kg). All of these terata were reportedly very rare (hydrocephaly 4/15,000 fetuses; spina bifida 1/14,000 fetuses; and microphthalmia 3/15,000 fetuses). The basis for these incidence rates (http://hcd.org/search/abnormality.asp) was historical control data derived from Charles River and Covance, not from the laboratory where the study was conducted (WIL laboratories). Apparently, EPA's regulatory hypothesis was that the terata were all part of a spectrum of effects due to the compound's neurotoxicity. Consequently, U.S. EPA adopted the lowest dose at which terata do not occur as the fetal NOAEL (30 mg/kg-day), over-riding the primary reviewer who set the fetal NOAEL ten times higher.

Rebuttal of the Developmental Toxicity NOAEL and Its Basis:

U.S. EPA's regulatory conclusions, expressed in the RED, regarding the rabbit developmental toxicity study are flawed for a number of reasons. The bases for rebutting the conclusions regarding the developmental toxicity study in rabbits as expressed in U.S. EPA's RED and supporting documentation (Daiss, 2006, 2007) are as follows. (**1**) Both the DER from U.S. EPA (Hurley, 1991), and the review reported in the Toxicology Summary and Data Review Sheets of the California Department of Pesticide Regulation (CDPR, 1996) identified the same toxicological endpoints. The maternal NOAELs were set by both reviewers at 100 mg/kg-day for clinical signs, decrement in body weight gain, decrement in food consumption, and as part of a spectrum of effects, at the highest dose there was an increased level of abortions. Although the number of abortions at the highest dose tested (500 mg/kg) was not statistically significant, the CDPR reviewer linked it to the significantly increased rates of abortion noted at the higher dosages used in the range-finding study (Nemec, 1989b). The incidence of 3/20 dam abortions at a lower dosage (100 mg/kg-day) in the definitive study was high, but not unusual. Historical control data from WIL laboratories (Appendix E in Nemec, 1989a) showed that the highest incidence of abortions in control rabbits in any study was 6/16 dam abortions. The developmental NOAEL was set by the primary U.S. EPA reviewer and the CDPR reviewer at 300 mg/kg-day for hydrocephaly. The CDPR reviewer attributed the incidence of hydrocephaly at the high dose to "demonstrated maternal toxicity". (**2**) Historical control data for laboratory

animals should be derived from the laboratory in which the studies are performed in order to insure that the same strains of animals, housing environments, and treatment regimes are matched (U.S. EPA, 1998a). In addition, the incidence rate should be expressed on a per litter basis, not per fetus basis, as it is the dams that are being dosed (U.S. EPA, 1998a). The historical control data from WIL laboratories for the incidence of fetal malformations in New Zealand White rabbits, presented in Appendix E (Nemec, 1989a), is presented in Table 1 below and is different from the incidence rates iterated in the RED.

Table 1: Historical Control Data-Incidence of External Malformations in New Zealand White Rabbits (1980-1987) from Studies Conducted at WIL Laboratories

External Malformation	Litter Incidence	Total Litters Examined	Fetal Incidence	Total Fetuses Examined
Spina bifida	3	774	3	5,438
Microphthalmia	1	774	1	5,438
Hydrocephaly	1	774	4	5,438

The actual incidence rates of malformation in the WIL rabbit developmental toxicity study are shown in the last table of Appendix A (p 18) of this document.

Additional incidence rate data in the rabbit historical control data available from WIL Laboratories (WIL, 1996) from 1982 to 1996 were: spina bifida, 7/1460 litters; microphthalmia, 3/1460 litters; and hydrocephaly, 2/1460 litters. These incidence rates in the historical control data from WIL Laboratories indicate that the occurrences of spina bifida, microphthalmia, and hydrocephaly are unusual, but not so unusual as to suggest a possible spectrum of effects linking the terata. (**3**) There were no dose responses for either microphthalmia or spina bifida, indicating that the events were not chemical related. (**4**) Neither microphthalmia nor spina bifida were associated with any concomitant indications of chemical induced fetal toxicity in either the same litters or in other litters at the same dosages. (**5**) Microphthalmia may be caused by chemicals that prevent complete closure of the embryonic fissure and allow the escape of the vitreous substance as the eye forms (Coulombre, 1977). Such an action has nothing to do with neurotoxicity, especially from a chemical that did not cause neuropathological changes in any study, even at the limit dose (U.S. EPA, 1998b,c,d). (**6**) Spina bifida and hydrocephaly arise from neural tube defects at opposite ends of the tube (Leck, 1977), a different mechanism than that which causes microphthalmia. In addition, it is known that spina bifida results from delayed dorsal closure of the neural tube, while hydrocephaly producing in dome shape is not. Thus, they do not appear to be related effects. (**7**) As noted by both the U.S. EPA and CDPR reviewers, there were no reductions of litter size, fetal growth, nor remarkable changes in developmental patterns, such as skeletal developmental delays at any dose. Thus, indications of the mechanisms necessary for chemical causation of the terata were not present. (**8**) The World Health Organization Task Group on environmental health criteria for d-Phenothrin concluded, "Neither teratogenicity nor embryotoxicity was observed in fetuses of rabbits and mice orally administered d-Phenothrin up to 1,000 and 3,000 mg/kg body weight, respectively" (WHO, 1990). (**9**) The extensive *in vitro* mutagenicity studies on Phenothrin were all negative suggesting that there is no genetic mutation mechanism that could be responsible for developmental toxicity. (**10**) A 1974 developmental toxicity study in rabbits dosed with Phenothrin in corn oil did not describe any unusual malformations. Although this study was incompletely reported, the effects attributed to Phenothrin in the 1983 study (spina bifida, microphthalmia and hydrocephaly) are

externally obvious effects and would most certainly have been reported if they had occurred in that study. (**11**) The rat developmental toxicity study, determined to be unacceptable to EPA [although CDPR found it to be a core guideline study (DPR, 1996)], was conducted using oral gavage with corn oil as a carrier. That study produced no evidence of developmental toxicity in rats, even though the high dose was a limit dose (U,S, EPA, 1998a). Similarly, no terata were observed in the rat reproductive toxicity study (Hoberman, 1995) (**12**) A literature search for "pyrethroid" and "malformation" or "pyrethroid" and any of the 3 specific malformations found in the rabbit developmental toxicity study reveals no published evidence of any such association. Many of the pyrethroids have structural moieties identical to either the acid or alcohol moiety of d-Phenothrin, so one would expect that if the effects observed were in fact compound related, they would be observed with compounds that are structurally similar. (**13**) As noted above, there was no evidence of histopathological effects on the nervous system in any study. More specifically, in an acute neurotoxicity study (Okuno and Kadota, 1978), a single, limit dose of 5,000 mg/kg-day administered to rats for 5 consecutive days produced clear signs of systemic toxicity including urinary incontinence and piloerection, but no effect on axon or myelin sheath of the sciatic nerve. [A new acute neurotoxicity study is underway, and this study should provide more definitive data on the dose at which clinical signs are noted, and whether Phenothrin administration causes histopathological changes in the nervous system.] (**14**) U.S. EPA's argument that the bioavailability of the dose in the developmental toxicity study was reduced due to use of an aqueous suspension rather than a corn oil solution is specious. The only data U.S. EPA cites is for a behavioral study with rats given deltamethrin (Crofton *et al*., 1995). Because deltamethrin is so much more lipophilic than Phenothrin and much more bioactive than Phenothrin, such a comparison cannot be made. There is a rich literature on the effect of vehicle on toxicity of chlorinated hydrocarbons, and none of that has been cited. One particularly sanguine quote follows: "Many rodent bioassays have been conducted using oral gavage for delivery of test chemicals. Highly lipophilic compounds are generally administered to rodents dissolved in corn oil, a dosing vehicle shown to influence xenobiotic toxicity, carcinogenicity and pharmacokinetics by altering chemical absorption processes." (Semino *et al*., 1997). Another interesting observation is that a lethal intraperitoneal dose of a chlorinated hydrocarbon can be made non lethal by subsequently dosing rats orally with corn oil.

3.0 SECOND ISSUE: REGULATORY TOXICOLOGICAL ENDPOINTS

The selection of a regulatory endpoint is predicated on the applicability of a toxicologic effect to the exposure of concern. A key criterion in choosing regulatory endpoints is matching the length of exposure in the toxicology study (or time to effect) with the typical duration of exposure experienced by humans. For example, it would not be appropriate to apply an effect seen at an interim sacrifice in a chronic study to an exposure that lasts a few days. In the case of Phenothrin, it appears that a subchronic toxicological endpoint is being applied to an exposure lasting a few days. A second important criterion is selecting the most sensitive laboratory species with the lowest NOAEL contingent on the first criterion. A third consideration is the applicability of the endpoint to the appropriate subgroup of the exposed human population. The U.S. EPA regulatory endpoints used for Phenothrin are summarized in Table 7 of the RED, and reproduced for reference here.

Summary of Toxicological Doses and Endpoints for Use in Phenothrin Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (general population)	An acute RfD for the general population or any population subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.		
Acute Dietary (females 13-49)	Dose for risk assessment = 30 mg/kg UF_A=10 UF_H = 10 UF_{DB} = 10 Acute RfD = 0.30 mg/kg	**aPAD** = acute RfD / FQPA SF = 0.030 mg/kg/day	Developmental Toxicity Study – rabbit Developmental LOAEL = 100 mg/kg/day based on spina bifida
Chronic Dietary (all populations)	Dose for risk assessment = 7.1 mg/kg/day UF_A=10 UF_H = 10 UF_{DB} = 10 Chronic RfD = 0.007	**cPAD** = chronic RfD / FQPA SF = 0.007 mg/kg/d	Chronic Toxicity study in dogs Chronic toxicity LOAEL = 26.7 mg/kg/d based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes.
Incidental Oral Short-Term (1 - 30 days) and Intermediate-Term (1-6 months)	Systemic toxicity NOAEL = 9.3 mg/kg/d	Residential LOC for MOE = 1000 UF_A=10 UF_H = 10 UF_{DB} = 10 Occupational = N/A	26 week oral toxicity study in dogs LOAEL = 32 mg/kg/d based on increased alkaline phosphatase and increased liver weight (absolute and relative) in both sexes
Dermal Short/Intermediate-Term (1 - 30 days/1-6 months)	Dermal toxicity systemic LOAEL = not established 21/28 Dermal toxicity study in rats dermal toxicity systemic LOAEL not established up to 1000 mg/kg/d (HDT)		
Inhalation Short-, Intermediate-Term (1 - 30 days, 1-6 months)	Systemic toxicity NOAEL = 9.3 mg/kg/d	Residential LOC for MOE = 1000 Occupational LOC for MOE = 1000 UF_A=10 UF_H = 10 UF_{DB} = 10	26 week oral toxicity study in dogs LOAEL = 32 mg/kg/d based on increased alkaline phosphatase and increased liver weight (absolute and relative) in both sexes

Summary of Toxicological Doses and Endpoints for Use in Phenothrin Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Classification: not likely to be carcinogenic to humans		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

Rebuttal of Endpoint Selection for Dietary Risk:

In the U.S. EPA HED section on the Acute Reference Dose (dietary), the NOAEL proposed was 30 mg/kg-day from the Rabbit developmental toxicity study for females 13-49 years of age. The acute RfD was thus 0.3 mg/kg-d, and the aPAD was 0.03 mg/kg-d because of the application of an uncertainty factor of 1000 (which includes the extra 10x uncertainty factor-FQPA-for the lack of an acceptable rat developmental toxicity study). As noted above, the available data and virtually all of the reviews indicate that the lowest NOAEL from the rabbit developmental toxicity study was 100 mg/kg-day for maternal toxicity. Thus, the RfD should be 1, and the aPAD would be 0.1 if an FQPA safety factor of 10 were applied. These values would be applicable to all population subgroups for acute dietary exposure.

Rebuttal of Endpoint Selection for Non-Dietary Exposures - Short Term:

For short term (1-30 days), non-dietary oral exposure and inhalation exposure, a NOAEL of 9.3 mg/kg-day (increased alkaline phosphatase and increased liver weight [absolute and relative] in both sexes) from a 26 week oral toxicity study in dogs was used (Hazleton Laboratories, 1981). It should be noted that the duration of the study does not match the stated duration of human exposure. Twenty-six weeks is 180 days, not the 30 day limit on the definition of short-term exposure (Daiss, 2006, 2007). Moreover, statistical significance in the effect of concern (increased alkaline phosphatase levels in the blood) was not achieved until week 8 (60 days), which doesn't fit the short term exposure definition, either. It would be more consistent with U.S. EPA's definition of "short term" to use an adverse endpoint derived from a study of 30 days or less. The 12-day NOAEL of 100 mg/kg-day (increased clinical signs, decreased food consumption, decreased body weight gain) for maternal toxicity from the rabbit developmental toxicity study (Nemec, 1989a) would be appropriate for the short-term non-dietary oral and inhalation NOAELs. The results from the rat developmental toxicity study indicate that rats may be less sensitive to Phenothrin than rabbits. Consequently, when the acute neurotoxicity study in rats is completed, the NOAEL from that study is likely to be greater than NOAEL of 100 mg/kg-day in the rabbit developmental toxicity study.

Rebuttal of Endpoint Selection for Non-Dietary Exposures - Intermediate Term:

For intermediate term (1-6 months), non-dietary oral exposure and inhalation exposure, U.S. EPA used the same NOAEL of 9.3 mg/kg-day (increased alkaline phosphatase and increased liver weight [absolute and relative] in both sexes) from the 26 week oral toxicity study in dogs. Actually, both of these effects are indicative of exposure, and should be considered

compensatory or adaptive in nature, not truly adverse (Moslen, 1996). It is not until dogs were dosed daily for an additional 6 months that histopathological effects were seen in the liver and adrenals (Cox, 1987). Yet, both of the U.S. EPA documents (Daiss, 2006; p6: Daiss, 2007; p3) state: *"Only short-term, intermittent occupational and residential exposures are expected based on the use pattern and expected exposures."*

U.S. EPA's rationale for using an intermediate-term NOAEL (6 months) requires closer examination. Haber's "law" states that the toxic effect level of a chemical in an organism is related to the product of the dosage (concentration = C) of the chemical and the duration (time = T) of exposure to it (Haber, 1924). As Haber examined irritation responses to high concentrations of gas over extremely short durations, the C x T relationship was dominated by concentration over brief durations. However, Haber's "law" has been extended to characterize long-term exposures on the basis of potential accumulation of a chemical or damage that it has caused. An examination of these toxicological issues associated with extending the C x T metric to long-term exposures was explored in a symposium conducted by U.S. EPA (U.S. EPA, 1998e; Witschi, 1999). The participants generally agreed that these two factors, chemical accumulation and/or cumulative damage, appear to be paramount in deciding whether the C x T metric will obtain for long-term exposures. In the case of Phenothrin, there is neither chemical accumulation nor cumulative damage. If, in U.S. EPA's words, only short term, intermittent exposures are expected, then only a short term endpoint should be used to gauge the risks of those exposures.

For either short term (or intermediate term exposure, if it actually exists), the exposures are intermittent, meaning that they occur sporadically perhaps for a few days at a time. Under these exposure conditions, it is appropriate to use a moving average for calculating exposure. If the rabbit developmental toxicity study were used as a regulatory endpoint, averaging would still be appropriate, since the rabbit does were dosed each day over a 12 day period.

A tabular summary of the toxicological endpoints for d-Phenothrin is included below.

Summary of toxicological endpoint data for Phenothrin (Sumithrin).

Study	Duration	Species and No./dose group	LOEL	NOEL	Reference
Combined Toxicity	2 yrs	Rat	**500 mg/kg-d** decreased BW, thin appearance, increased liver wt, panicinar hepatocytic hypertrophy, elevated alkaline phosphatase, gamma glutamyl transpeptidase, and leucine amino transpeptidase	50 mg/kg-d	Aughton, 1995
Combined Toxicity	2 yrs	Rat	**150 mg/kg-d** decrease in BW, increase in relative liver wt., panicinar hepatocytic hypertrophy	50 mg/kg-d	Martin, 1987
Oncogenicity	1 1/2 yrs	Mouse	**150 mg/kg-d** Body wt. decrease Minor dose-related increase in liver wt. Panicinar hepatocytic hypertrophy w/ increased eosinophilia at 1 yr.	45 mg/kg-d	Amyes, 1987
Chronic	1yr	Dog	**26.7mg/kg-d** focal degeneration of adrenal cortex; diffuse hepatocellular diffusion	9.3 mg/kg-d	Cox, 1987
Subchronic	26 wk	Dog`	**26.7 mg/kg-d** slight elevation of alkaline phosphatase; increase in absolute/relative liver wt.	9.3 mg/kg-d	Hazleton, 1981
Reproduction	29-30 wk	Rat	**177 mg/kg-d** decreased BW, decreased food consumption, increased liver wt., hepatocellular hypertrophy	59 mg/kg-d	Hoberman, 1995
Developmental	12 days	Rabbit	**300 mg/kg-d** decreased BW gain, decreased food consumption, clinical signs (hair loss in inguinal area)	100 mg/kg-d	Nemec, 1989a
Developmental	10 days	Rat	**3,000 mg/kg-d** decreased BW gain, decreased food consumption	1,000 mg/kg-d	Tesh *et al*., 1983

4.0 CONCLUSIONS

The weight of evidence strongly indicates that Phenothrin is not a developmental toxicant. U.S. EPA has cited limited data as evidence for developmental toxicity in rabbits. U.S. EPA's interpretation of these data is not consistent with any known mechanism of action for Phenothrin or any pyrethroid. Further, there is no dose-response for the malformations observed. Other regulatory bodies, both within the US and in the EU have concluded that Phenothrin is not a developmental toxicant, although it does produce toxicity in pregnant rabbits at high dosages. The uncertainty factor assigned by U.S. EPA is incongruent with the weight of evidence. The policy-driven uncertainty factor is not consistent with U.S. EPA's scientific review of the rabbit developmental toxicity study. The data indicate that an appropriate regulatory short-term NOAEL is 100 mg/kg from the rabbit developmental toxicity study rather than 9.3 mg/kg from a subchronic dog study chosen by U.S. EPA. This is because the nature of exposure to Phenothrin, as U.S. EPA acknowledges, is both short-term (days and not months in duration) and intermittent. As a result, it would be appropriate to apply a moving average to the exposure estimate used in the risk assessment process.

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APPENDIX A

Rabbit Developmental Toxicity

A range-finding, developmental toxicity study was conducted in rabbits (Nemec, 1989b). Five groups of 7 artificially inseminated New Zealand White rabbits were dosed on gestation days 7 through 19 with sumithrin (94.1 % purity) at 0, 500, 1,000, 2,000, or 3,000 mg/kg-day dissolved in 0.5% aqueous methyl cellulose. Food consumption was significantly (P<0.01) less in all treated groups, as was body weight gain (P<0.01). Clinical signs, predominantly green staining in the anogenital area, decreased defecation, and swelling in the urogenital region were noted at all dose levels. The table below summarizes maternal food consumption, body weight gain, clinical signs, abortions, and mortality results.

Parameter	0 **mg/kg-day**	500 **mg/kg-day**	1,000 **mg/kg-day**	2,000 **mg/kg-day**	3,000 **mg/kg-day**
Food Consumption (compared to control)		P<0.01	P<0.01	P<0.01	P<0.01
Body wt. gain (compared to control)		P<0.01	P<0.01	P<0.01	P<0.01
Clinical signs		+	+	+	+
Abortions	1/7	4/7	5/5	1/2	1/1
Deaths	0/7	0/7	2/7	5/7	6/7

Tarsal flexure (one incidence at 2,000 mg/kg-day) was the only malformation noted in the fetuses of the treated dams. Two other fetuses in the same litter had subcutaneous hemorrhaging.

A developmental toxicity study was conducted in rabbits (Nemec, 1989a). Five groups of 20 artificially inseminated New Zealand White rabbits were dosed on gestation days 7 through 19 with sumithrin (94.1 % purity) at nominal doses of 0, 30, 100, 300, or 500 mg/kg-day dissolved in 0.5% aqueous methyl cellulose.

Maternal effects.

Parameter	Treatment Levels				
	0 mg/kg-d	30 mg/kg-d	100 mg/kg-d	300 mg/kg-d	500 mg/kg-d
Mean Food Consumption (7-20d; g/animal-d)	136	147	136	114	106
Mean Food Consumption (20-29d; g/animal-d)	87	84	56	99	74
Mean Body Weight Gain (7-19d; mg/kg-d)	85	116	59	3	-72*
Mean Body Weight Gain (20-29d; mg/kg-d)	48	23	138	64	-56
Deaths or terminated moribund	1/20	0/20	0/20	1/20	0/20
Abortions	1/18	0/20	3/17	1/18	4/16
Live litters	12/18	18/20	14/17	16/18	11/16
Decreased Defecation (occurrence/dams affected)	18/8	27/9	58/11	26/9	90/15
Decreased Urination	5/3	4/3	15/5	10/5	21/8
Hair loss-ventral abdominal	4/2	0/0	2/1	1/1	25/4
Hair loss-right inguinal area	0/0	7/1	0/0	21/3	45/4
Hair loss- left inguinal area	0/0	0/0	9/1	10/2	48/5

Mean body weight gain between days 7-19 is significantly reduced ($P<0.05$ by a one-tailed Dunnett's test) at the high dose (500 mg/kg-d). Food intake, at the high dose, also appears to be reduced during this period. In addition, there appears to be an increase in the number of abortions, and clinical signs (decreased defecation, urination, increased hair loss) at the high dose. At 300 mg/kg-day, there seems to be reduced mean body weight gain (days 7-19) and mean food consumption (days7-20), though not as marked as at the high dose. Similarly, clinical signs were reduced, so that only hair loss in the inguinal area might be attributed to the chemical. Taking the clinical signs and other effects noted in the pilot study at higher doses into account, the maternal NOEL for clinical signs, decrement in mean body weight gain, and food consumption would be 100 mg/kg-day.

Fetal effects

Parameter	Treatment Levels				
	0 mg/kg-d	30 mg/kg-d	100 mg/kg-d	300 mg/kg-d	500 mg/kg-d
Mean Litter size (live)	6.8	7.0	7.9	7.1	6.4
Mean Fetal weight (g)	41.6	43.7	36.6	42.4	40.3
Litters w/malformations Hydrocephaly	0/12	0/18	0/14	0/16	3/11
Litters w/ malformations Microphthalmia	0/12	0/18	0/14	1/16	0/11
Litters w/ malformations Spina Bifida	0/12	0/18	1/14	0/16	0/11
Litters w/ malformations Umbilical herniation	0/12	0/18	0/14	0/16	1/11
Litters w/ malformations Tarsal and/or carpal flexure	0/12	0/18	1/14	1/16	0/11

There was an increased incidence of abortions at the highest dose. However, there was no effect of the chemical on mean litter size or fetal weight. There was an increased level of hydrocephaly at 500 mg/kg-day. A single incidence of microphthalmia, a very rare event, was noted at 300 mg/kg-day. A single incidence of spina bifida, another rare event, was noted at 100 mg/kg-day. Also, single incidences of tarsal and carpal flexure were noted at 100 and 300 mg/kg-day. Although the latter flexures were associated with much higher doses of Phenothrin in the range-finding test, there was no dose-response for these malformations. Nor were there any other fetal effects that correlated with the single incidences. At the high dose, it was clear that the dams were stressed by the chemical, suffering clinical signs, abortions, and decrements in body weight gain. Consequently, the developmental NOEL was considered to be 300 mg/kg-day for hydrocephaly, usually accompanied by a domed head.