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OFFICE OF
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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DATE: September 12, 2007 **TXR NO. 0050424**

MEMORANDUM

SUBJECT: **PP# 6080 Deltamethrin** Updating the Toxicology Data Base for Deltamethrin *in preparation* for the Toxicology Chapter of the Human Health Risk Assessment for Deltamethrin on Various Crops

TO: Risk Assessor - Deltamethrin
Reregistration Branch 2
Health Effects Division (7509P)

Christina Swartz, Branch Chief
Registration Action Branch 2
Health Effects Division (7509P)

and

William Sproat
Product Manager
Registration Division (7505P)

FROM: Nancy E. McCarroll, Toxicologist
Toxicology Branch (TB)
Health Effects Division (7509P)

THRU: Marion Copley, DVM, DABT
SIMB, Health Effects Division (7509P)

Registrant: Aventis Environmental Science USA
Chemical: Deltamethrin PC Code: 097805
DP Barcode: D283537 (Parent DP# 247310)

I. ACTION: Review and prepare Data Evaluation Reports (DER) and/or revised Executive Summaries for the appropriate studies in the toxicology data base for deltamethrin in preparation for writing the Toxicology Chapter for the Human Health Risk Assessment of Deltamethrin on Various Crops.

II. CONCLUSIONS: In preparation for writing the Toxicology Chapter, the DERs in the toxicology data base for deltamethrin were reevaluated by TB and reviews were updated as needed. All upgraded DERs (new DERs prepared to conform to current toxicology review formats) and Supplemental DERs providing Executive Summaries to earlier reviews that did not need upgrading are attached to this memorandum. In addition, complete new DERs for nine studies are included.

III. COMMENTS: Executive Summaries for all studies are provided in Section IV. DISCUSSION of this memorandum. Table 1 summarizes the toxicity studies submitted for deltamethrin. The data base for deltamethrin is not complete; however, it does provide adequate information to characterize toxicity and establish doses and endpoints for the risk assessments . Identified data gaps include: a developmental study in rabbits, a 28-day inhalation toxicity study in rats and a developmental neurotoxicity test (with special protocol).

TABLE 1: SUMMARY OF NEW AND REEVALUATED TOXICOLOGY STUDIES FOR DELTAMETHRIN

OPPTS No. (Guideline No.)/Study type	MRID	Type of DER	Classification
Acute Toxicity Studies			
870.1100 (§81-1) Acute oral toxicity, rat	41651019	Executive Summary	Acceptable
870.1200 (§81-2) Acute dermal toxicity, rabbit	41651020	Executive Summary	Acceptable
870.1300 (§81-3) Acute inhalation toxicity, rat	41651021	Executive Summary	Acceptable
870.2400 (§81-4) Primary ocular irritation, rabbit	41651022	Executive Summary	Acceptable
870.2500 (§81-5) Primary dermal irritation, rabbit	41651023	Executive Summary	Acceptable
870.2600 (§81-6) Dermal sensitization potential, guinea pig	41654124	Executive Summary	Acceptable
870.1100 (§81-1) Acute oral toxicity, rat	00060714	Full DER	Acceptable
870.1100 (§81-1) Acute oral toxicity, mice	00098078	Full DER	Acceptable
870.1100 (§81-1) Acute oral toxicity, dogs	00098079	Full DER	Acceptable
Subchronic Toxicity Studies			
870.3100 (§82-1a) Subchronic oral toxicity, rat	00098103	Updated DER	Unacceptable
870.3150 (§82-1b) Subchronic oral toxicity, dog	00098104	Updated DER	Unacceptable
870.3200 (§82-2) 21- Day dermal toxicity, rat	42773901	Executive Summary	Acceptable
871.xxxx 3- Week, 14 exposure inhalation toxicity, rat	00098089	Updated DER	Unacceptable
Chronic Toxicity Studies			

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OPPTS No. (Guideline No.)/Study type	MRID	Type of DER	Classification
870.4100b (§83-1b) Chronic oral toxicity, dog	44372601	Full DER	Acceptable
870.4200b (§83-2b) Carcinogenicity, mouse	44372602	Full DER	Acceptable
870.4300 (§83-5) Combined chronic oral toxicity/carcinogenicity, rat	00098105	Executive Summary	Uacceptable
870.4300 (§83-5) Combined chronic oral toxicity/carcinogenicity, rat	44398102	Full DER	Acceptable
Developmental and Reproductive Toxicity Studies			
870.3700a (§83-3a) Developmental toxicity, rat	41651025	Executive Summary	Acceptable
870.3700b (§83-3b) Developmental toxicity, rabbit	41651026	Executive Summary	Acceptable
Nonguideline Developmental toxicity, multiple species	00098092 00098091	Executive Summary	Unacceptable
870.3800 (§83-4) Two-generation reproductive toxicity, rat	44398101	Full DER	Acceptable
Genetic Toxicology Studies			
870.5100 (§84-2a) Bacterial reverse gene mutation	42475902	Executive Summary	Acceptable
870.5375 (§84-2b) Chinese Hamster ovary cell cytogenetic assay	41651027	Executive Summary	Acceptable
870.5550 (§84-4) Unscheduled DNA synthesis	41651028	Executive Summary	Acceptable
Neurotoxicity			
870.6200 (§81-8) Neurotoxicity Screening Battery, rat	44557901	Full DER	Acceptable
870.6200 (§82-5) Subchronic (13 weeks) Neurotoxicity Study, rat	44557902	Full DER	Acceptable
Metabolism			
870.7485 (§85-1) Metabolism, rat	41677401	Executive Summary	Acceptable

III. DISCUSSION

ACUTE STUDIES

Acute Oral Toxicity - Rat; OPPTS 870.1100 [§81-1]; OECD 401.

CITATION: Myer, J.R. (1989) Acute Oral Toxicity Test of Deltamethrin in Rats. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-122, May 4, 1989. MRID 41651019. Unpublished.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 41651019), groups of 8 week old Sprague-Dawley rats (5/sex) were given a single oral dose (10 mL/kg) of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) in 1% methylcellulose at a dose of 5000 mg/kg (limit test) and observed for 13 days.

Oral LD_{50} Males >5000 mg/kg
Females >5000 mg/kg
Combined >5000 mg/kg

No mortality was observed during this limit test. Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category IV** based on the LD_{50} observed in males and females.

There were no treatment related clinical signs, necropsy findings, or changes in body weight.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the rat.

Acute Dermal Toxicity Study - Rabbits; OPPTS 870.1200 [§81-2]; OECD 402.

CITATION: Myer, J.R. (1989) Acute Dermal Toxicity Study of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-123, May 4, 1989. MRID 41651020. Unpublished.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 41651020), a 50% (w/v) suspension of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) in 1% methylcellulose was applied to the shaved intact skin (15 % of body surface) of young adult New Zealand White rabbits (5/sex) for 24 hours at a dose of 2000 mg/kg (limit test). Animals then were observed for 14 days.

Dermal LD_{50} Males >2000 mg/kg
Females >2000 mg/kg
Combined >2000 mg/kg

No mortality was observed during this limit test. Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category III** based on the LD_{50} observed in males and females.

There were no treatment related clinical signs, necropsy findings, or changes in body weight.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1200; OECD 402) for an acute dermal toxicity study in the rabbit.

Acute Inhalation Toxicity - Rats; OPPTS 870.1300 [§81-3]; OECD 403.

CITATION: Ulrich, C.E. (1990) Acute Inhalation Toxicity Evaluation of Deltamethrin in Rats. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-121, June 9, 1990. MRID 41651021. Unpublished.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 41651021), groups of young adult Sprague-Dawley rats (5/sex) were exposed by whole-body inhalation to Deltamethrin (purity not reported, Batch/Lot# 8N 0701 B2) for 4 hours at gravimetrically determined concentrations of 1.0, 1.8, or 2.3 mg/L. Animals then were observed for up to 14 days.

Inhalation LC_{50} Combined = 2.2 mg/L (with 95% C.I. of 1.5-3.3 mg/L)

Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category IV** based on the LC_{50} in males and females combined.

The mass median aerodynamic diameter (MMAD) was < 5 μm; averages [± geometric standard deviations (GSD)] were 4.4 ± 1.9, 3.5 ± 1.85 and 3.1 ± 1.87 for the high, mid and low dose, respectively.
Mortality occurred throughout the study (Days 0-14) at 1.0 (1/5 females), 1.8 (2/5 males and 2/5 females), and 2.3 (2/5 males and 3/5 females) mg/L. Clinical signs observed at all doses included labored breathing, impaired hindlimb function, ataxia, loss of righting reflex, decreased activity, and material around nose and/or eyes. Overall (Day 0-14) body weight gain was decreased in all groups. At necropsy, the 1.8 and 2.3 mg/L animals showed enlarged inguinal and mandibular lymph nodes, pulmonary congestion, and skin discoloration.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1300; OECD 403) for an acute inhalation toxicity study in the rat. Although test article purity data were not provided, mortality was observed at all doses.

Primary Eye Irritation - Rabbit; OPPTS 870.2400 [§81-4]; OECD 405.

CITATION: Myer, J.R. (1989) Eye Irritation Study of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-125, April 17, 1989. MRID 41651022. Unpublished.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 41651022), approximately 87 mg of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) was instilled into the conjunctival sac of the right eye of young adult New Zealand White rabbits (3/sex). The eyes were not washed at anytime after instillation. Animals then were observed at 1, 24, 48, and 72 hours for signs of ocular irritation. Irritation was scored by the method of Draize.

Signs of irritation including moderate to marked conjunctival redness, slight to marked discharge (clear), slight swelling, and slight iridial irritation were observed at one hour post-instillation. All signs of irritation cleared by 72 hours post-instillation. In this study, **Deltamethrin is mildly irritating to the eye**, and is classified as **EPA Toxicity Category III** based on the degree of irritation that cleared by 72 hours post-instillation.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2400; OECD 405) for a primary eye irritation study in the rabbit.

Primary Dermal Irritation - Rabbits; OPPTS 870.2500 [§81-5]; OECD 404.

CITATION: Myer, J.R. (1989) Primary Dermal Irritation Test of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-124, April 17, 1989. MRID 41651023. Unpublished.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 41651023), young adult New Zealand White rabbits (3/sex) were dermally exposed to 0.5 g of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) moistened with 1% methylcellulose for 4 hours. Animals were observed for up to 3 days post-exposure. Irritation was scored by the method of Draize.

No signs of dermal irritation were observed at any time point. In this study, Deltamethrin is not a dermal irritant, and classified as **EPA Toxicity Category IV** based on the lack of dermal irritation.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2500; OECD 404) for a primary dermal irritation study in the rabbit.

Skin Sensitization - Guinea Pigs; OPPTS 870.2600 [§81-6]: OECD 406.

CITATION: Myer, J.R. (1989) Dermal Sensitization Study of Deltamethrin in the Albino Guinea Pig (Buehler Test). International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-126, September 7, 1989. MRID 41651024. Unpublished.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 41651024) young adult Hartley Guinea pigs (10/sex) were dermally exposed to 0.4 gm of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) moistened with 1% methylcellulose, using the Buehler method. The test consisted of three induction treatments (Days 0, 7, and 14) followed by a challenge phase on Day 28. Additionally, groups of 5 animals/sex were used as positive controls (0.4 mL of 0.01% 2,4-dinitrochlorobenzene) or untreated controls.

No dermal effects were induced by the test article. **In this study, Deltamethrin is not a dermal sensitizer.**

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2600; OECD 406) for a dermal sensitization study in the Guinea pig.

Acute Oral Toxicity - Rat; OPPTS 870.1100 [§81-1]; OECD 401.

CITATION: Glomont, R. and B. Chevalier (1976) RU22974: Acute Toxicity in the Mouse - Rat by Oral Route. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: TOX 76810, March 30, 1976. MRID 00060714. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00060714), groups of Sprague-Dawley (CD_1) rats (10/sex) were given a single oral dose (10 mL/kg) of RU22974 (Deltamethrin; purity not reported, Batch/Lot# not reported) in either polyethylene glycol 200 (PEG 200) at doses of 29.65, 44.50, 66.70, 100.0, or 150.0 mg/kg or in sesame oil at doses of 66.7, 100.0, 150.0, 225.0, or 337.5 mg/kg, and observed for 8 days.

In PEG 200: Oral LD_{50}	**Males = 66.7 mg/kg (with 95% C.I. of 53.0-83.9 mg/kg)** **Females = 86.0 mg/kg (with 95% C.I. of 70.6-106.2 mg/kg)**
In sesame oil: Oral LD_{50}	**Males = 128.5 mg/kg (with 95% C.I. of 104.9-156.5 mg/kg)** **Females = 138.7 mg/kg (with 95% C.I. of 114.2-168.2 mg/kg)**

Mortality occurred on Days 1-4 at doses ≥44.5 mg/kg (PEG 200) and ≥100.0 mg/kg (sesame oil). RU22974 is considered to be of **Moderate Toxicity** and is classified as **EPA Toxicity Category II** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. In the highest doses shortly after administration, motor uncoordination, convulsions, and respiratory defects were observed. At 24 and 48 hours after administration hypomotility and convulsions were observed. All surviving animals appeared normal by Day 3.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the rat. Test article purity and batch/lot# were not provided; however, treatment-related clinical signs and mortality were observed. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

Acute Oral Toxicity - Mouse; OPPTS 870.1100 [§81-1]; OECD 401.

CITATION: Glomont, R. and B. Chevalier (1976) RU22974: Acute Toxicity in the Mouse - Rat by Oral Route. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: TOX 76810, March 30, 1976. MRID 00098078. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00098078), groups of albino Swiss CD_1 mice (10/sex) were given a single oral dose of RU22974 (Deltamethrin; purity not reported, Batch/Lot# not reported) in either polyethylene glycol 200 (PEG 200;10 mL/kg) at doses of 9.1, 12.8, 17.9, 25.0, or 35.0 mg/kg or in sesame oil (20 mL/kg) at doses of 12.8, 17.9, 25.0, 35.0, 49.0, or 68.6 mg/kg, and observed for 8 days.

In PEG 200: Oral LD_{50}	**Males = 20.6 mg/kg (with 95% C.I. of 17.3-24.8 mg/kg)** **Females = 18.7 mg/kg (with 95% C.I. of 15.7-22.4 mg/kg)**
In sesame oil: Oral LD_{50}	**Males = 33.1 mg/kg (with 95% C.I. of 27.2-40.8 mg/kg)** **Females = 34.4 mg/kg (with 95% C.I. of 28.4-42.0 mg/kg)**

Mortality occurred on Days 1-2 at doses ≥12.8 mg/kg (PEG 200) and ≥17.9 mg/kg (sesame oil). RU22974 is considered to be of **High Toxicity** and is classified as **EPA Toxicity Category I** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. It was stated that the following signs were observed: (i) in all doses shortly after administration, hypomotility, stereotypic movements of the head, tachychardia, and cyanosis; (ii) at 1 hour post-dosing, muscular stiffening and at the highest doses, clonic-tonic convulsions; and (iii) at 24 hours post-dosing, hypomotility, stereotypic movements of the head, tachychardia, hypertonicity of the tail, and transient convulsions. All surviving animals appeared normal by 48 hours.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the mouse. Test article purity and batch/lot# were not provided; however, treatment-related clinical signs and mortality were observed. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

Acute Oral Toxicity - Dog; OPPTS 870.1100 [§81-1]; OECD 401.

CITATION: Glomont, R., B. Chevalier, E. Collas, et al. (1977) RU22974: Acute Toxicity by Oral Route in Male and Female Beagle Dogs. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: 77804/JL-5, March 17, 1977. MRID 00098079. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00098079), groups of fasted Beagle dogs (2-3/sex) were given a single gavage dose (5 mL/kg) of RU22974 (Deltamethrin; purity not reported, Batch/Lot# 18) in polyethylene glycol 200 (PEG 200) at doses of 0 or 300 mg/kg and observed for 15 days. Additional groups of dogs (3/sex) received the test material in capsules at doses of 100 or 300 mg/kg.

Oral LD_{50} **Males >300 mg/kg**
Females >300 mg/kg

No mortality was observed during the study. RU22974 is considered to be of **Moderate Toxicity** and is classified as **EPA Toxicity Category II** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in males and females, and included: stiffness of the hind legs, vomiting, akinesia, and slight diarrhea All animals appeared normal by 72 hours.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the dog. Test article purity was not provided; however, treatment-related clinical signs were observed in most animals. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

SUBCHRONIC STUDIES

90-Day Oral Toxicity gavage - rat with 4 week Recovery Period. OPPTS 870.3100 [§82-1a] (rodent); OECD 408.

CITATION: Hunter, B., Jordan, J., Heywood, R., et al. (1977) RU22974 - Assessment of toxicity to rats by oral administration for 13 weeks (followed by a 4-week withdrawal period). Huntingdon Research Centre (Cambridgeshire, England). Laboratory report number RSL254/76938/A3, March 21, 1977. MRID 00098103. Unpublished.

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00098103) RU 22974 (purity not reported, Lot 17) was administered daily by gavage to 20 CD Sprague-Dawley rats/sex/dose at doses of 0, 0.1, 1.0, 2.5, or 10 mg/kg bw/day. The RU 22974 was suspended in polyethylene glycol and administered to the animals initially at the rate of 5 ml/kg, later reduced to 2.5 ml/kg because of gavage trauma to the animals. A recovery group of 5 animals/sex/group was followed during post-treatment weeks 14 to 17.

The animals were observed daily for toxicity. Body weights and food consumption were measured weekly. Eye examinations, hematology and clinical chemistry determinations were carried out initially and during treatment weeks 6 and 13; urinalyses carried out during weeks 6 and 12. Neurological examinations were carried out on control and high dose animals, prior to treatment and during weeks 6 and 13. Neurological examinations included a) "segmental" responses (flexor, extensor and patellar reflexes); b) Postural assessments including righting, placing and grip reflexes and extensor thrust; c) locomotion and muscle strength; and d) behavior changes and responses to noise. At termination of the treatment phase, the animals in the control and high dose groups were subjected to gross necropsy and histopathology. Recovery groups were observed daily for clinical signs and weighed weekly during weeks 14 to 17.

There were no animal deaths due to the treatment with RU 22974. Several animals died secondary to gavage trauma during the first few weeks of the study. These animals were replaced. Except for neurological effects, there were no treatment-related signs of systemic toxicity or effects on the eyes, hematology, or clinical chemistry. Toxic signs included slightly increased hypersensitivity to sound in 9 of 10 high dose males and 3 of 10 high dose females during week 6, but these signs cleared by week 13. Body weight gains in the 2.5 and 10.0 mg/kg/day group males were slightly lower throughout the treatment period, being 97 and 94%, respectively, of the controls during weeks 1 to 4; 90 and 88%, respectively, during weeks 5 to 8; and 81 and 87%, respectively, during weeks 9 to 12. For the entire treatment period, the overall weight gains of the 2.5 and 10.0 mg/kg/day group males were significantly reduced to 92 and 91%, respectively, of the controls. No significant changes in weight gain were found in treated female rats.

Post treatment animals regained body weights at rates greater than the treated animals to the extent and there were no significant differences among the treated groups and the control animals. There were no gross pathology findings and no treatment-related histological lesions found.

The LOAEL for deltamethrin (RU22794) in male rats is 2.5 mg/kg/day based on decreased body weight gains during the 90 day treatment period. The LOAEL for female rats is not established. The NOAEL is 1.0 mg/kg/day for male rats and 10.0 mg/kg/day for females.

This 90-day oral toxicity study in the rat is **Unacceptable/Nonguideline**. The study was conducted prior to establishment of EPA guidelines and GLP practicies, but does not meet the intent of these. The stability and purity of the test material were not provided. The dose levels selected did not produce sufficient toxicity, other than weight loss, to effectively assess the toxicity of RU 22974.

90 Day Subchronic Oral Toxicity Study (Capsule) with 20 week Recovery Period. [OPPTS 870.3150 (§82-1b)] (Dog); OECD 409.

CITATION: Chesterman, H., Heywood, R., Perkin, C.J., et. al. (1977) Oral toxicity study in Beagle dogs. Huntingdon Research Centre. (Report Number RSL 253/77251), June 9, 1977. MRID 00098104. Unpublished.

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID00098104), deltamethrin (purity not reported, Lot #17) was dissolved in polyethylene glycol 200 and administered by capsules daily to beagle dogs (3/sex/group) at 0, 0.1, 1.0, 2.5, and 10 mg/kg body wt/day. Additional dogs (2/sex/group) were included in the 1.0, 2.5. and 10 mg/kg main treatment groups which were observed for an additional 20 weeks after the 90 day treatment period as a recovery study group

All animals were observed daily for toxicity throughout the treatment and recovery periods. Body weights, food consumption and water consumption were measured weekly. Neurological examinations were performed prior to treatment, during weeks 6 and 12 (main treatment groups) and during weeks 5, 8, 15 and 18 of the recovery period. The neurological examinations consisted of the assessments of pupillary reflex, blink reflex, corneal reflex, gag reflex, flexor reflex, crossed extensor reflex, extensor reflex, patellar reflex, tonic neck reflex, extensor postural thrust, righting reactions, placing reactions, and hopping reactions. EEGs were performed on each animal initially and during treatment week 12 and during post treatment weeks 5 and 17. Ophthalmological examinations were done initially, during weeks 5 and 12 (main treatment groups) and during 5 and 18 weeks (recovery groups). Hematology, clinical chemistry and urinalyses were carried out at the start of treatment, during treatment weeks 5 and 12 and post treatment weeks 5 and 16. Gross pathology, organ weights and histopathology were performed on the main treatment groups during week 13. Necropsy of the recovery animals after 20 weeks post-treatment was limited to observations on the nervous and muscular systems.

There were no mortality or treatment-related effects on clinical chemistry, hematology, urinalysis or ophthalmology. Mild to moderate CNS toxicity was observed 1 to 7 hours after dosing in both male and female dogs of the two highest dose groups. These effects declined in severity over the 13-week study period. Clinical signs of toxicity seen only in the high dose group (10 mg/kg) were excessive salivation, unsteadiness, tremors, and jerking movements. Pupil dilation was observed sporadically in the 2.5 mg/kg/day group, but more routinely at 10 mg/kg/day groups. Male and female dogs receiving 2.5 mg/kg/day and 10 mg/kg/day test material had significantly increased incidences of vomiting and diarrhea which decreased after first two weeks of treatment. Significant decreases in body weight relative to controls were observed in the female dogs at the three highest doses. Food consumption was significantly decreased in the high dose males and females during the first two weeks on treatment but not thereafter. Food consumption was normal during the first two weeks of dosing bu decreased for males and females in the 1 mg/kg/day during the 3-13 week periods.

Results of the neurology tests were mixed relative to dose-response characteristics. After 5 weeks of treatment, abnormalities in patellar reflex (either exaggeration or depression) were observed from 6/10 dogs in the 10 mg/kg, 5/10 from the 2.5 mg/kg/day group, 1/10 from the 1 mg/kg/day group, and from 1/6 control dogs after 5 weeks of treatment. After 12 weeks of treatment, abnormalities were also noted for 2/10 dogs in 10 mg/kg/day group, 7/10 dogs from the 2.5 mg/kg/day group, 3/10 dogs from the 1 mg/kg/day group, and 1/6 control dogs. By the end of the 20-week recovery period, 2/4 dogs from the 1 mg/kg/day group and 1/4 dogs from the 2.5 mg/kg/day were still showing abnormalities in this reflex, while none of the dogs at 10 mg/kg/day showed abnormalities after 8 weeks of recovery. One of the four high dose dogs (10 mg/kg/day) observed for 20 weeks after the treatment period showed evidence of sustained neurological effects. No control dogs were available

for comparisons during the recovery period. No other abnormal findings in the neurology testing were remarkable due to their occurrence in controls animals, their sporadic nature or the lack of dose-response presentation.

EEG recordings made after 12 weeks of dosing were normal for control dogs, but showed abnormalities in the occipital region of one female dog in the 2.5 mg/kg/day dose group, and in one female and two males at the 10 mg/kg/day dose level. No histopathologic correlates for abnormal EEG recordings were found. After 5 weeks of recovery 1/4 dogs (a female) in the 10 mg/kg/day dose group was still exhibiting EEG abnormalities which persisted into the last EEG testing conducted during Week 17 of the 20-week recovery period. All other dogs held for the recovery period showed normal EEGs at both post-treatment recording intervals.

No treatment-related effects were found for the main treatment groups or for the recovery groups at necropsy or during histopathological assessment.

The LOAEL for RU 22974 is 2.5 mg/kg/day based on CNS effects, vomiting, diarrhea, and decreased body weight gains of treated male and female dogs. The NOAEL is 1.0 mg/kg/day.

This 90-day oral toxicity study in the dog is **Unacceptable/Nonguideline** and does not satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs. The study was conducted prior to establishment of guideline requirements and GLP procedures, but meets the intent. The purity of the test agent was not provided. The numbers of animals used were too few and the number of the required observations for subchronic testing were lacking.

21-Day Dermal Toxicity Study - Rats; OPPTS 870.3200 [§82-2]; OECD 410.

CITATION: Siglin, J.C. (1993) 21-Day Dermal Toxicity Study in Rats with Deltamethrin Technical - Springborn Laboratories, Spencerville, Ohio; Study No.: 3207.28; April 9, 1993. MRID 42773901. Unpublished.

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 42773901), groups of five male and five female Sprague Dawley Crl:CD BR VAF/Plus rats received dermal applications of deltamethrin (99.6% a.i., Batch/Lot# 2NO398B2) in polyethlene glycol 400 at 0, 100, 300 or 1000 mg/kg/day (limit dose). On the day prior to application, a section of the dorsal-lumbar region was clipped and the test material was applied at a rate of 6 mL/kg. Applied doses were kept in contact with the skin for ≈6 hours using occlusive dressings secured with tape. At the end of the contact period, the dressings were removed and the area wiped with gauze and water. Animals were observed twice daily for death or clinical signs; body weight and food consumption were recorded weekly. At termination, rats were sacrificed and samples were taken for hematology and clinical chemistry; necropsies were performed; selected organ weights were determined and selected tissue were examined histologically.

There were no treatment- related deaths, clinical signs of toxicity, gross pathology or changes in hematology, clinical chemistry or organ weights. Body weight gain differences, seen only in the males, were considered minimal and of no toxicological concern. Dermal irritation was noted at all

dose levels at the site of application and was characterized as eschar and eschar exfoliation at the low dose and as slight erythema, slight desquamation and thickening of the skin at higher doses. Microscopically, several conditions of the skin (abscesses, chronic dermatitis, exudate, mononuclear cell foci in the dermis, epidermal necrosis, parakeratosis, ulcers and epidermal vesiculation) were noted in the treated animals that were not found in the controls. The lesions were localized primarily on the lateral side (away from the center of test material application and were possibly due to scratching) of the test site. None of these showed a dose response with respect to frequency or intensity, but their absence in the control group implied that they were related to treatment with deltamethrin.

At the Hazard Identification Assessment Review Committee (HIARC) meeting held on August 8, 2002, the study was revisited and it was determined that there were no treatment-related deaths, clinical signs of toxicity, gross pathology, or changes in hematology, clinical chemistry, or organ weights noted at any level. The NOAEL for males and females is >1000 mg/kg/day (limit dose). Signs of local dermal irritation at the site of application were noted for all deltamethrin dose levels. The localization of these lesions suggested that they were self-induced by the animals through scratching. This response is typical of the "pyrethroid reaction", also know as paresthesia which is induced by Type II pyrethroids and considered to be a localized rather than a systemic effect.

3 Week (14 exposure) inhalation toxicity study in rats (nonguideline)

CITATION: Coombs, D.W., Clark, G.C., Street, A.E., et. al. (1978) Inhalation toxicity study in rats, 14 x 6 hour exposures, 5 days per week over 3 weeks. Huntingdon Research Centre, Huntingdon, England. (Report Number RSL 318/78638), October 19, 1978. MRID 00098089. Unpublished

SPONSOR: Centre de Recherches Roussel Uclaf, Dept. Toxicology, 102, Route de Naisy, BP No. 9, 93230, Romainville, France.

EXECUTIVE SUMMARY: In a 21 day inhalation toxicity study (MRID 00098089), rats of the CD strain (8/sex/group) were exposed in whole body exposure chambers to deltamethrin [RU 22974 (purity not reported)] at concentrations of 0, 3.0, 9.6, and 56.3 mg/m^3. The exposures were for six hours per day for five days a week for a total of 14 exposures. Clinical observations, body weights, food and water consumption were made daily. Selected hematology, clinical chemistry and urinalyses were carried out on exposure day 19. Complete gross necropsy and organ weights were carried out on day 22. Histopathology was limited to trachea, lungs, liver and nasal turbinates and other organs with gross pathology in the control and high dose groups.

No rats died as a result of the exposures. Toxic signs were limited to skin irritation (washing and scratching of the face) and nervous system stimulation were noted in the high-dose groups were seen in all treated animals. Nervous system effects included hunched posture, peripheral vasodilation, minimal aggressive behavior, hypersensitivity to noise. Individual observational data were not provided.

Total weight gain of male rats in the mid- and high-dose groups was decreased 14-24% for male rats and 12-14% for female rats. The serum sodium of both male and female rats was increased in a dose-related manner, however the increase in males was not biologically significant while that of females borders on significance. The toxicological significance of the increased sodium is unclear as no changes were found with potassium or calcium and serum chloride and CO_2 analyses were not done. No histological correlates were found in the kidney. Gross findings were limited to scarring of the ears (presumed related to irritative properties of the test material). Other than scarred ears for high-dose male and female rats, no macro- or microscopic lesions were found in any of the examined organs and tissues.

The LOAEL for RU 22974 is 9.6 mg/m^3 based on clinical signs of irritative effects during exposure and on the >10% decreased weight gain of male and female rats during the study. The NOAEL is 3.0 mg/m^3.

This 21-day inhalation toxicity study in the rat is **Unacceptable/Nonguideline** not usable for inhalation risk. Deltamethrin was identified as a significant irritant yet there were no toxic effects seen in the pulmonary system. The lack of pulmonary adverse effects may be due to inadequate distribution of the deltamethrin aerosol within the chamber and to the fact that the particle sizes were too large to be inhaled by the test animals. Although the LOAEL of 9.6 mg/m^3 reflects severe toxicity, deltamethrin may be even more highly toxic if the testing was carried out using more current testing requirements.

This study was classified as **acceptable/Guideline**. Several organs were, however, not assessed for weight as recommended in the series 82-2 guidelines. Histopathology was limited to liver, kidneys, and skin only. These deviations did not alter the outcome of the study. No other data were required.

CHRONIC STUDIES

Chronic Oral Toxicity in Dogs; OPPTS 870.4100 §83-1b: OECD 452.

CITATION: Ryle, Buist, Crook, Rao, and Gopinath. (1993), Deltamethrin: Toxicity to Dogs by Repeated Oral Administration for 52 Weeks. Huntington Research Centre, Ltd. Huntington, Cambridgeshire, England. Laboratory Project ID RSL 816/920929. October 21, 1993. MRID 44372601. Unpublished.

EXECUTIVE SUMMARY: In this chronic toxicity study (MRID 44372601), deltamethrin (98.9% a.i.) was administered via gelatin capsule to purebred 4 beagle dogs/sex/group at doses of 0, 1, 10, or 50 mg/kg/day for 52 weeks. Dose level selection was based on the results of a previous 13-week study in which the test substance was administered to dogs at doses of 0, 2, 10, or 50 mg/kg/day.

No treatment-related findings were observed in the 1 mg/kg/day groups. Mortality, food consumption, organ weights, ophthalmoscopic observations, hematology parameters, clinical chemistry findings, urinalysis parameters, and gross and histopatholgical findings were unaffected by the test substance.

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Dose-related decreases in male body weight gains were seen at 1, 10 and 50 mg/kg/day, respectively. For weeks 0-52, significant decreases were seen (↓37, 37 and 49%) at 1, 10 and 50 mg/kg/day, respectively. There were also nonsignificant decreases in body weight gain (↓33, 35 and 42%) during weeks 0-26 at 1, 10 and 50mg/kg/day, respectively. However, the growth of dogs, particularly in the 1 mg/kg/day group were within expected limits and, therefore, not related to treatment.

Early clinical signs were seen at 10 mg/kg/day and included chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30).

At 50 mg/kg/day, chewing of extremities was observed in 4 males (69 incidences) and 4 females (102 incidences); liquid feces was reported during weeks 1-13, weeks 14 to 23 and sporadically, thereafter. Abnormal gait was noted in all animals (8/8 treated) during clinical examinations. During neurological examinations at week 26, the following signs were observed: (i) slight trembling in males (1/4 treated); (ii) generalized trembling with splayed digits (fore and hindlimb) in females (1/4 treated); and (iii) alterations in gait (slight high-stepping) in females (1/4 treated). At week 52, neurological observations included the following: (i) slight trembling during the physical examination (males- 1/4 treated, females 2/4 treated); (ii) general slight unsteadiness of gait in males (1/4 treated); (iii) high-stepping in males (2/4 treated); (iv) splayed digits and slight high-stepping in females (1/4 treated); (v) trembling during wheelbarrowing, thoracic hopping, and pelvic hopping in males (1/4, each); and (vi) splayed digits and slight high-stepping of limbs during wheelbarrowing and hopping in females (1/4, each).

The chewing of extremities was observed in 4 males (30 incidences) and 3 females (4 incidences) in the mid-dose group, in the high-dose group in 4 males (69 incidences) and 4 females (102 incidences), and observed in none or 1/sex in control and low-dose groups.

The LOAEL for this study is 10 mg/kg/day, based on the ≥35% reduction in body weight gain over weeks 0 to 26, which was significant over weeks 0 to 52, in conjunction with the reported clinical signs (i.e., chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30) during the early segment of the study. The NOAEL for this study is 1 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.4100/OPP 83-1[b])** and does satisfy the guideline requirements for a chronic toxicity study dogs.

<u>Carcinogenicity Study in Mice, 870.4200 §83-2 (b), OECD 451</u>

<u>CITATION</u>: Richard, J. (1995) Deltamethrin: 97-Week Carcinogenicity Study by Oral Route (Dietary Admixture) in Mice. Centre International de Toxicologie (C.I.T.) Miserey, Evreux, France. Project No. 7347TCS. December 26, 1995. MRID 44372602. Unpublished.

EXECUTIVE SUMMARY: In this oncogenicity study (MRID 44372602), deltamethrin (98% a.i.) was administered for 97 weeks to 50 Crl:CD-1(ICR)BR mice/sex/dose at dietary concentrations of 0, 10, 100, 1000, or 2000 ppm (equivalent to [M/F] 0, 1.5/2.0, 15.7/19.6, 155.4/189.3 or 314.8/395.1 mg/kg/day). The animals were examined daily throughout the dosing period and palpated for tumors every two weeks after 6 months of treatment. Body weights and food consumption were determined weekly. Routine hematological analyses were determined at weeks 52, 78 and 97. Organ weights, gross pathology and histopathology were assessed at necropsy after the 97 week treatment period.

No clinical toxicity or palpable masses were found during the study. Survival at 52 weeks ranged from 94% to 100% for males and females. Male survival exceeded female survival ranging from 54% to 64% for males and 44% to 56% for females. There were no dose related survival changes due to the treatments with deltamethrin. Body weight gains were not dose related however high dose males had significant ($p>0.05$) decreases of 5%-7% over control males and females had significant decreases (3%-6%) over control females. Food consumption differences were not significant or related to treatment levels.

There were no significant dose related effects on hematological findings. Necropsy at the termination of the study was negative for organ weight differences, gross organ findings and for histopathological effect related to treatment with deltamethrin. An increased incidence of bronchoalveolar carcinoma was found in high-dose females (10% treated vs. 2% controls); however, it was stated that this finding is within the normal range (0-24%) for mice of this strain and age. Under the conditions of this study, there was no evidence of carcinogenic potential of deltamethrin.

The dose levels employed in this study were assumed to be adequate to characterize the carcinogenic potential of deltamethrin in both sexes of Crl:CD-1(ICR)BR mice based on a previous 12-week toxicity study in mice (CIT/Study No. 5566TSS) in which deltamethrin was administered at 0, 30, 300, 3000, or 6000 ppm. At 6000 ppm, 14/15 males and 13/15 females died by day 8; clinical signs were convulsions. At 3000 ppm, 3/10 males and 1/10 females died during the study, and body weights differed from controls by ↓13%.

The NOAEL for this study is ≥2000 ppm (equivalent to 314.8 mg/kg/day in males and 395.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable (§83-2(b))** and satisfies the guideline requirements for an oncogenicity study in mice.

Combined Chronic Toxicity/Carcinogenicity [Feeding] in Rats; OPPTS 870.4300 [§83-5]; OECD 453.

CITATION: Goldenthal, E.I, A.C. Kahn III, R.J. Arceo, et al. (1980) Two-year oral toxicity and carcinogenicity study in rats. International Research and Development Corporation. Laboratory Report No.: IRDC 406-002/A4, May 6, 1980. MRID 00098105. Unpublished.

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 00098105), decamethrin (deltamethrin; purity not reported; Lot 22) was administered daily in the

diet to 90 CD rats/sex/dose at dose levels of 0, 2, 20, or 50 ppm (approximately equivalent to 0, 0.1, 1.0, or 2.5 mg/kg/day, calculated by Agency reviewers) for 24 months. An additional 60 rats/sex were included as a second control group. Ten rats/sex/dose were sacrificed at Months 6, 12, and 18, and the remaining rats were sacrificed during Month 24.

There were no treatment-related adverse effects on mortality, clinical signs, ophthalmology, body weights, body weight gains, food consumption, hematology, clinical chemistry, urinalysis, or gross and histological (including tumors) pathology.

The LOAEL was not determined. The NOAEL for this study is >50 ppm (approximately equivalent to >2.5 mg/kg/day, calculated by the Agency reviewers).

Under the conditions of this study, the carcinogenic potential of decamethrin is considered negative. Dosing was considered inadequate. An adverse effect was not observed, and the limit dose was not tested.

At the August 2002 meeting of the Hazard Identification Assessment Review Committee (HIARC), it was determined that there were no adverse effects on body weight or body weight gain. Data showed significant (p<0.01 or <0.05) body weight reductions for males but these decreases ranged from -3 to -7% of control for both sexes. Additionally, body weight gain differences ranged from a 5 to an 8% decrease for males and a 4 to 8% decrease for the females. Since neither parameter exceeded a ≥10% difference from the vehicle control group, the Committee concluded that differences were not biologically relevant. Accordingly, the NOAEL has been revised from 1.0 mg/kg/day to >2.5 mg/kg/day and the LOAEL from 2.5 mg/kg/day to "not determined".

This study is **unacceptable (not upgradable)/guideline** and does not satisfy the guideline requirement for a chronic/ carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

Combined Chronic/Carcinogenicity in Rats; 870.4300 §83-5a; OECD 453

CITATION: Ryle, P.R. (1995). Deltamethrin: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats. Huntington Research Centre, Ltd. Huntington, Cambridgeshire, England. Laboratory Project ID RSL814, December 11, 1995. MRID 44398102. Unpublished.

EXECUTIVE SUMMARY: In this combined chronic/oncogenicity study (MRID 44398102), deltamethrin was administered continuously in the diet to 50 Crl:CD(SD)BR rats/sex/group (main group) at nominal dose levels of 0, 25, 125, 500, or 800 ppm (equivalent to [M/F] 0, 1.1/1.5, 5.4/7.3, 22.2/29.5, or 35.9/47.1 mg/kg/day) for approximately 104 weeks. An additional 20 rats/sex/dose (satellite group) were designated for toxicological evaluation, including blood sampling. At week 52, 10 rats/sex/dose in the satellite group were terminated for interim study.

No treatment-related findings were observed in any treated group. Mortality, clinical observations, body weight, body weight gain, food consumption and efficiency, water consumption,

ophthalmoscopic observations, hematological parameters, clinical chemistry findings, urinalysis parameters, organ weights, and gross and microscopic pathological findings were all unaffected by the test substance. In addition, no treatment-related neoplastic tissue was observed in any treated group.

According to the sponsor's dose rationale, the dose levels employed in this study were adequate to characterize the carcinogenic potential of deltamethrin in both sexes of Crl:CD(SD)BR rats.

Under the conditions of this study, there was no treatment-related effect on the incidence of tumors in animals.

The NOAEL for chronic toxicity is 800 ppm (equivalent to 35.9 mg/kg/day in males and 47.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable** (**§83-5[a]**) and does satisfy the guideline requirements for a combined chronic toxicity/oncogenicity study in rats.

Developmental and Reproductive Toxicity Studies

Prenatal Developmental Toxicity Study in Rats; OPPTS 870.3700a [§83-3a]; OECD 414.

CITATION: Schardein, J.L. (1990) Developmental toxicity study of deltamethrin in rats. International Research and Development Corporation, Mattawan, MI. Laboratory Study No.: 327-120, July 6, 1990. MRID 41651025. Unpublished.

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41651025), deltamethrin (>99% a.i., Lot/Batch# 8B 0153 B3 and 8N 0701 B2) in corn oil was administered to pregnant Crl:CD VAF/Plus rats (25/dose) via gavage in a dosing volume of 1 mL/kg at concentrations of 0, 1.0, 3.3, 7.0, or 11.0 mg/kg/day on gestation days (GDs) 6 through 15. All dams were sacrificed on GD 21 and their uterine contents examined.

When compared to concurrent controls, there were no effects of treatment on maternal gross pathology, gravid uterine weights, numbers of live fetuses, dead fetuses, early or late resorptions, post-implantation loss, sex ratio, or fetal weight.

At 7 mg/kg, one dam was sacrificed following convulsions after dose administration. Additionally, increased salivation and body surface staining were noted. Maternal body weights were decreased ($p<0.05$) on GD 0, 9, 12, and 16; and body weight gains were decreased during the dosing period (decr. 16%; $p<0.01$).

At 11 mg/kg, 14/25 (56%) dams were either sacrificed *in extremis* or found dead. Convulsions, anogenital staining, sensitivity to external stimuli, and body surface staining were observed in the maternal animals. Body weight gains were decreased during the dosing period (decr. 16%; $p<0.05$);

and body weight gains, corrected for gravid uterine weight, were decreased (decr. 22%; not significant) for the entire (days 0-20) gestation period.

The maternal LOAEL is 7 mg/kg/day based on decreased body weights and body weight gains and on clinical signs of toxicity. The maternal NOAEL is 3.3 mg/kg/day.

There were no effects of treatment on fetal malformations or variations.

The developmental LOAEL was not observed. The developmental NOAEL is >11 mg/kg/day.

This developmental toxicity study is classified **acceptable/guideline (OPPTS 870.3700; §83-3[a])** and satisfies the requirement for a developmental toxicity study in the rat.

Prenatal Developmental Toxicity Study in Rabbits; OPPTS 870.3700b [§83-3b]; OECD 414.

CITATION: Schardein, J.L. (1990) Developmental toxicity study of deltamethrin in New Zealand white rabbits. International Research and Development Corporation, Mattawan, MI. Laboratory Study No.: 327-112, May 7, 1990. MRID 41651026. Unpublished.

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41651026), deltamethrin (99.4% a.i., Lot/Batch# 8N 0701 B2) in 0.5% carboxymethylcellulose (CMC) was administered to pregnant New Zealand White rabbits (16/dose) via gavage in a dosing volume of 3 mL/kg at concentrations of 0, 10, 25, or 100 mg/kg/day on gestation days (GDs) 7 through 19. All does were sacrificed on GD 29 and their uterine contents examined.

When compared to concurrent controls, there were no effects of treatment on maternal body weight gains, gross pathology, gravid uterine weight, numbers of resorptions (early and late), numbers of fetuses (live and dead), post-implantation loss, sex ratio, or fetal weight.

At 10, 25, and 100 mg/kg, an increased incidence of clinical signs of toxicity (anogenital staining, no stool, decreased defecation, and excessive lacrimation) was observed. The number (%) of animals exhibiting one or more of these signs was 8 (50%), 12 (75%), 13 (81%), and 14 (88%) in the control, 10, 25, and 100 mg/kg groups, respectively. However, in the absence of corroborating evidence of an effect of treatment, the toxicological relevance of these findings is uncertain. Additionally at 100 mg/kg, one pregnant doe died on GD 27; necropsy revealed congestion of the lungs. It was uncertain whether this death was due to the test substance or gavage error.

The maternal LOAEL was not established. The maternal NOAEL is 100 mg/kg/day.

At 100 mg/kg, dose-related increases in fetal and/or litter incidences of selected variations (>12 full pairs of ribs and 27 pre-sacral vertebrae) were observed. Additionally at this dose, increased fetal and/or litter incidences of non-ossification of the hyoid body, sternebrae (#5 and/or #6), pubic bones, and tail bone were observed.

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The developmental LOAEL is 100 mg/kg/day based on increases in the incidences of delayed ossification and skeletal variations (>12 pairs of full ribs and 27 pre-sacral vertebrae). The developmental NOAEL is 25 mg/kg/day.

At the August 2002 meeting of the Hazard Identification Assessment Review Committee (HIARC), it was determined that the study was Unacceptable. The study can, however, be upgraded if the sponsor can justify the used of the aqueous vehicle (CMC) since there are results in the submitted data base and the published literature indicating that deltamethrin is less toxic when delivered orally in aqueous vehicles such as CMC.

Accordingly, this developmental toxicity study is classified **unacceptable (OPPTS 870.3700; §83-3[b])** and does not satisfy the requirement for a developmental toxicity study in the rabbit.

Prenatal Developmental Toxicity Study - (Multiple Species)

CITATION: Glomot, R. and Vannier, B. (1977). RU 22974: Teratological Study in Mouse–Rat–Rabbit. Roussel Uclaf, France; Reference No. 76534–7636/Z/A. Unpublished study received March 25, 1982; MRID 00098092, 00098091.

EXECUTIVE SUMMARY: In three different developmental toxicity studies (MRID 00098092, 00098091) deltamethrin as RU 2974 (% a.i. not indicated) was administered to 24 CD-1 mice/dose, 24 Sprague-Dawley rats/dose, and 15 New Zealand White rabbits/dose. Doses to rats and rabbits were prepared in sesame oil. Neither the route of administration nor the vehicle used for mice were specified, and the route(s) of administration for the rats or the rabbits were not indicated.

Mice: Mice were dosed at 0, 0.1, 1.0, or 10 mg/kg/day on gestational days 6-17 and were sacrificed on day 18. There was no maternal toxicity noted at any dose level. Body weight gains and conception rates were comparable between the control and treated groups and there was no treatment-related effect on mortality. **There was no maternal LOAEL observed. The maternal NOAEL is ≥10 mg/kg/day.** Developmental toxicity was demonstrated as significantly ($p<0.05$ = *) reduced average fetal weights at 1.0 and 10 mg/kg/day (controls 1.35g; low-dose 1.28g; mid-dose 1.26g*; high-dose 1.24g*). In addition, the incidences of delayed ossification of the sternebra and paws were statistically significantly higher in all dose groups. It is not indicated if the increases were seen in fetal and/or litter incidence for these variations. The study author stated that the frequency of these findings was within normal variation for this strain of mouse. **The developmental LOAEL is 1.0 mg/kg/day based on increase incidence (fetal and/or litter) of delayed ossification of the sternebrae and paws together with decreased fetal body weights. The developmental NOAEL is 0.1 mg/kg/day.**

Rats: Rats were dosed at 0, 0.1, 1.0, or 10 mg/kg/day on days 6-18 of gestation and were sacrificed on day 21. Maternal toxicity was demonstrated at 10 mg/kg/day as slightly reduced body weights (approximately 10%, individual body weights were not reported in the registrant's submission). There were no deaths or clinical signs of toxicity at any dose level and conception rates were comparable between the control and treated groups. **The maternal LOAEL is 10 mg/kg/day based on slightly reduced body weights. The maternal NOAEL is 1.0 mg/kg/day.** Developmental toxicity was suggested at 10 mg/kg/day as a statistically significant increase in delayed ossification of the sternebrae. It is not indicated if the increase was in the fetal and/or litter incidence for this skeletal variation. Fetal losses were also increased at the high dose, however, the difference from controls was not reported to be statistically significant (2.19, 2.60, 2.71, and 3.97% average fetal loss for the control, low-, mid-, and high-dose groups). No treatment-related effects were noted in other fetal malformations or variations, fetal weights, gestation period, total number of living pups at birth, day 4, and day 21, or in the viability and lactation indices. **The developmental LOAEL is equivocally set at 10 mg/kg/day, based only on a statistically significant increased incidence (fetal and/or litter) of delayed ossification of the sternebrae. The developmental NOAEL is 1.0 mg/kg/day.**

Rabbits: Rabbits were dosed at 0, 1, 4, or 16 mg/kg/day on days 6-19 of gestation and were sacrificed on day 28; two separate groups of rabbits received 16 mg/kg/day. There was no maternal

toxicity noted at any dose level. There were no treatment-related changes in body weight gains or mortality. **The maternal NOAEL is ≥16 mg/kg/day. There was no maternal LOAEL observed.** Developmental toxicity was demonstrated at 16 mg/kg/day as an increase in fetal losses. The average fetal losses per group were 6.6, 18.5, 15.5, 10.2, and 27.4% for the control, low-dose, mid-dose, and two high-dose test groups, respectively. In addition, pup body weights were decreased by 8% and 4% for the low- and mid-dose groups relative to the control, and decreased by 14 and 13% for the two high-dose group. There was no evidence of teratogenic effects noted in the pups (details of the parameters examined were not given). **The developmental LOAEL is 16 mg/kg/day based on increased fetal losses and decreased fetal weights. The developmental NOAEL is 4 mg/kg/day.**

HIARC concluded that while these multiple species studies were unacceptable and did not provide a robust assessment of fetal sensitivity, the developmental effects seen in mice (i.e., delayed ossification and decreased fetal body weights), rats (i.e., delayed ossification) and rabbits (i.e., increased fetal loss or decreased fetal body weight) appeared to occur either in the absence of maternal toxicity (mice or rabbits) or the presence of mild maternal toxicity (slightly reduced maternal body weight in rats).

Reproduction and Fertility Effects Study in Rats OPPTS 870.3800 [§83-4]; OECD 416.

CITATION: Hoberman, A.M. (1992) Deltamethrin: Reproductive Effects of Deltamethrin Administered Orally in the Diet to Crl:CDBR VAF/Plus Rats for 2-Generations. Argus Research Laboratories, Inc., 905 Sheehy Drive, Horsham, PA 19044. Laboratory Project ID 818-001. AgrEvo Report Reference A70863, January 17, 1992 (Unpublished.). EPA MRID # 44398101.

EXECUTIVE SUMMARY: In a 2-generation reproduction toxicity study (MRID 44398101), deltamethrin (99.7% a.i.) was administered continuously in the diet to Sprague-Dawley rats (30/sex/dose) at dose levels of 0, 5, 20, 80, or 320 ppm (equivalent to 0, 0.3/0.4, 1.3/1.5, 5.4/6.1, or 21.2/23.5 mg/kg/day in the P animals [M/F] and 0, 0.4/0.4, 1.4/1.7, 5.8/6.7, or 24.9/27.2 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at approximately 6 weeks of age and lasted for at least 82 days prior to mating. F_1 pups selected (30/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents on postnatal day (PND) 21 and continuously throughout the rest of the study. F_1 animals were administered the test article for at least 86 days prior to mating to produce the F_2 litters. Mating to produce a second F_{2b} generation was not performed. Exposure of all animals to the test material was continuous throughout the study.

When compared to concurrent controls, there were no differences in food efficiency. There was no evidence of histopathological changes in the organs specified for examination. The brain was not examined. There were no differences of toxicological concern in organ weights.
In the high-dose, treatment-related mortality occurred in P females (1), F_1 males (17) and F_1 females (19). Clinical signs observed in these rats included: ataxia, impaired righting reflex, and stained abdomen, nose, mouth, neck, and chest, hyperactivity, splayed limbs, vocalization, and excess salivation. Necropsy findings included: black, red, and/or brown material in the gastrointestinal tract, stomach erosions, enlarged adrenals, cerebral congestion, and blood clots in the brain.

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Treatment-related clinical signs observed in the P males were lesions on the head, neck, or forelimbs (11/30 treated vs. 1/30 controls) and alopecia (8/30 treated vs. 2/30 controls). In the P females, clinical signs observed were limited to ataxia (22/25 treated vs. 0/25 controls) and hypersensitivity (3/25 treated vs. 0/25 controls) during lactation. In the F_1 males and females, clinical signs observed were ataxia (27-28/28 treated vs. 0/30 controls), impaired righting reflex (23-25/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (6-10/28 treated vs. 1/30 controls), hyperactivity (8-9/28 treated vs. 0/30 controls), splayed limbs (3-8/28 treated vs. 0/30 controls), vocalization (7/28 treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red or brown or yellow, wet or dried substance on nose, mouth, neck, chest, fur, and/or abdomen (13-14/28 vs. 0/30 treated). During gestation and lactation, F_1 females demonstrated lesions (1/9 treated vs. 0/25 controls), foot splay (6/8 treated vs. 0/20 controls), and ataxia (2/8 treated vs. 1/20 controls).

Body weights were decreased compared to concurrent controls throughout the premating period in P (decr 7-16%) and F_1 (decr 15-49%) males and females. Body weights were decreased in P females during gestation days (GDs) 0-15 and lactation days (LDs) 1-14 (decr 7-16%). In F_1 females, body weights were decreased throughout gestation and during LDs 1-14 (decr 11-15%). Body weight gains were decreased during premating 3-5/12-14 weeks in P males (decr 16-89%) and F_1(decr 26-81%) males and females and highly variable in P females (decr 30-incr.300%). Body weight gains for the overall premating periods (1-82 days for P; 1-99 days for F_1) were decreased in all high-dose groups (decr 20-24%). Absolute food consumption was decreased in high-dose groups throughout the premating period (decr 8-59%). The largest decrease in food consumption was observed during the first week of dosing in all groups (decr 34-59%), suggesting that the diet was unpalatable. During lactation, P dams and F_1 dams ate less (decr 16-26%) than controls at all intervals.

Treatment-related gross pathological findings were limited to the F_1 males and females that died during the study. These animals demonstrated cerebral congestion and/or blood clots (9-12/28 treated vs. 0/30 controls).

There were no treatment-related findings at any of the lower doses.

The LOAEL for parental systemic toxicity is 320 ppm in males and females (equivalent to 21.2/23.5 mg/kg/day [M/F]) based on increased mortality and clinical signs, decreased body weights, body weight gains, and absolute food consumption, and gross pathological findings in both sexes. The NOAEL is 80 ppm (equivalent to 5.4/6.1 mg/kg/day [M/F]).

There were no differences of toxicological concern in reproductive performance. Sexual maturation and developmental parameters were not measured.

The LOAEL for reproductive toxicity is greater than 320 ppm (equivalent to >21.2/23.5 mg/kg/day [M/F]). The NOAEL is equal to or greater than 320 ppm (equivalent to ≥24.9/27.2 mg/kg/day [M/F]).

No treatment-related differences in clinical signs were observed at any time in the F_1 and F_2 litters. There were no treatment-related findings of toxicological concern at necropsy of the F_1 or F_2 litters.

In the high-dose, an increase in mortality relative to concurrent controls in the F_1 pups (13/200 treated vs. 0/184 controls) from PND 8 to 14 caused a decrease in the lactation index (decr 8%) for this group. Body weights were decreased relative to concurrent controls in F_1 pups (decr 14-25%) for PNDs $4_{(precull)}$-21, and in F_2 pups (decr 12-24%) for PNDs 7-21. Overall body weight gains were reduced (decr 27-28%) for PNDs 1-21 in F_1 and F_2 pups.

There were no treatment-related findings at any of the lower doses.

The LOAEL for offspring systemic/developmental toxicity is 320 ppm (equivalent to 24.9/27.2 mg/kg/day [M/F] based on increased pup mortality and decreased body weights and body weight gains). The NOAEL is 80 ppm (equivalent to 5.8/6.7 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS# 870-3800; OECD# 416) for a multigenerational reproductive toxicity study in the rat.

At the August 2002 meeting of the Hazard Identification Assessment Review Committe (HIARC), it was noted that there was qualitative evidence of increased susceptibility at 320 ppm as indicated by effects on the F_1 generation which were not seen in the P generation or when the F_1 generation were pups but only when they were adults. These effects included increased death (P ♀: 1, 3% vs. F_1 ♂: 17, 61% and F1 ♀: 19, 68%; F_1 pups: 13/200, 7%), clinical findings not seen in the P generation or the F_1 or F_2 litters (i.e. impaired righting reflexes, hyperactivity, splayed limbs, vocalization, and excessive salivation) and cerebral congestion and/or blood clots [9/28 (F_1 ♂) 12/28 (F_1♀) at the highest dose tested vs. 0/30 in male or female controls or in the high dose-group of both sexes in the P adults).

GENETIC TOXICOLOGY STUDIES

***In vitro* Bacterial Gene Mutation (*Salmonella typhimurium*)/ Mammalian Activation Gene Mutation Assay; OPPTS 870.5100 [§84-2]; OECD 471 (formerly OECD 471 & 472). Other Genotoxicity: Bacterial DNA Damage in *Escherichia coli* (Pol A_1^-); OPPTS 870.5500 [§84-2]; OECD None**

CITATION: Chantot, J.F., R. Glomot, L. Penasse, et al. (1980) Detection of a mutagenic potency of decamethrin (RU22974) bacterial tests. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Report No.: RU/TOX/80.21.01/A, January 21, 1980. MRID 42475902. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In this study (MRID 42475902), two different bacterial assays were performed. In a DNA damage assay, *E. coli* strains W3110 (Pol A^+), WP2 ($uvrA^+$, $exrA^+$), p3478 (Pol A_1^-), and CM611 ($uvrA^-$, $exrA^-$) were exposed to deltamethrin (purity not reported; Lot/Batch #: not reported) in DMSO at concentrations of 0, 1250, 2500, or 5000 µg/mL for 18 hours. The well diffusion method was used. In a gene mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to deltamethrin (purity not reported;

Lot/Batch #: not reported) in DMSO at concentrations of 0, 2, 10, 50, 200, 500, 1000, or 5000 µg/plate in the presence and absence of S9-activation in an Ames assay. Acceptable strain specific positive controls were used.

In the DNA damage assay, deltamethrin was tested up to the limit dose (5000 µg/mL). No treatment-related increases in the difference between zones of inhibition were observed in any treatment group compared to the concurrent controls. The positive controls induced the appropriate response. **There was no evidence that DNA damage was induced.**

In the gene mutation assay, deltamethrin was tested up to the limit of solubility (>200 µg/plate +/- S9). No treatment-related increases in the number of revertants/plate were observed in any bacterial strain at any dose level in the presence or absence of S9-activation compared to solvent controls. The positive controls induced the appropriate response. **There was no evidence of induced mutant colonies over background in the presence of S9.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) and (OPPTS 870.5500) for other genotoxic mutagenicity (bacterial DNA damage) data. Although the test article purity was not reported, the technical compound was tested to the limit dose and/or the limit of solubility.

***In vitro* Mammalian Cytogenetics [Chromosome Aberration in CHO cells] OPPTS 870.5375 [§84-2]; OECD 473.**

CITATION: Putman, D.L. and M.J. Morris (1989) Chromosome aberration assay of deltamethrin in Chinese hamster ovary (CHO) cells. Microbiological Associates, Inc., Rockville, MD. Laboratory Study No.: T8418.337003, February 23, 1989. MRID 41651027. Unpublished.

EXECUTIVE SUMMARY: In a chromosome aberration assay (MRID 41651027), Chinese hamster ovary (CHO) cells were exposed to deltamethrin (99.2% a.i.; Lot/Batch #: 8B-0153B3) in acetone at concentrations of 0, 9.5, 19, 38, 75, or 150 µg/mL in the presence and absence of S9-activation for 16 (-S9) or 2 (+S9) hours. Cells were harvested at 18 hours (-S9) or 8 and 12 hours (+S9) after initiation of treatment.

Deltamethrin was tested up to the limit of solubility (≥75 µg/mL, +/-S9). Cytotoxicity was observed at ≥38 µg/mL (-S9) and at 150 µg/mL (+S9, 12 hr harvest). No statistically significant increases in aberration frequency were observed at any dose in the presence or absence of S9-activation compared to controls. Positive controls induced the appropriate response. **There was no evidence of chromosome aberration induced over background.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

Other Genotoxicity: Unscheduled DNA Synthesis in Primary Rat Hepatocytes/ Mammalian Cell Cultures; OPPTS 870.5550 [§84-2]; OECD 482

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CITATION: Curren, R.D. (1989) Unscheduled DNA synthesis of deltamethrin in rat primary hepatocytes. Microbiological Associates, Inc., Rockville, MD. Laboratory Study No.: T8418.380, March 13, 1989. MRID 41651028. Unpublished.

EXECUTIVE SUMMARY: In an unscheduled DNA synthesis assay (MRID 41651028), primary rat hepatocyte cultures were exposed to deltamethrin (99.2% a.i.; Lot/Batch #: 8B-0153B3) in acetone for 18-20 hours at concentrations of 0, 4.2, 13, 42, 130, 420, 1300, or 4200 µg/mL.

Deltamethrin was tested up to the limit of solubility (≥130 µg/mL). No cytotoxicity (as indicated by decreased lactate dehydrogenase activity) was observed at any dose. No treatment-related increases in mean net nuclear grains (NNG) or percent of cells under repair (≥ 5 grains/nuclei) were observed at any dose compared to controls. The positive controls induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.5550; OECD 482) for other genotoxic mutagenicity data.

NEUROTOXICITY STUDIES

Neurotoxicity Screening Battery in Rats, 870.6200; §81-8(a); OECD 424

CITATION: Nemec, M. (1998). An Acute Neurotoxicity Study of Deltamethrin in Rats. WIL Research Laboratories, Inc. Ashland, Ohio. Laboratory Study No. WIL-274002. March 18, 1998. MRID 44557901. Unpublished.

EXECUTIVE SUMMARY: In this acute neurotoxicity screening battery (MRID 44557901), deltamethrin (99.2% a.i.) was administered as a single dose by gavage to 12 Crl:CD (SD)BR rats/sex/dose at levels of 0, 5, 15, or 50 mg/kg. All animals were subjected to the functional observational battery (FOB) and motor activity measurements during the pretest interval and on study days 0 (≈3 hours after dosing), 7, and 14. Animals were checked twice daily for mortality and moribundity. All surviving animals were perfused *in situ* at study termination, and five animals/sex from the control and high-dose groups were subjected to neuropathological evaluation.

Body weight, body weight gains, brain weights, and neuropathological findings were unaffected by the test substance in all dose groups.

One male and one female in 50 mg/kg group died on day 0 (3-3.5 hours post-dosing). Pale lungs and red matting on external surfaces were observed in the male. Mottled lungs, ocular opacity, and red/yellow matting on external surfaces were observed in the female.

At 50 mg/kg, the following treatment-related clinical findings (total occurrences/number of animals) were observed on days 1, 2, and/or 3: (i) rocking, swaying, or lurching (males- 2/2, females- 3/2); (ii)

dried yellow staining on the ventral abdominal area (males- 3/3, females- 6/6); (iii) dried yellow staining on the urogenital area (females- 9/7); and (iv) dried tan staining around the mouth (males- 3/2).

Treatment-related effects were observed on day 0 during the home cage, handling, open field, sensory, neuromuscular, and physiological observations, and were mostly dominant in the high-dose groups.

At 50 mg/kg, significant (vs. controls) signs of toxicity noted during the **home cage observations** included altered posture, clonic convulsions, tonic convulsions, slight tremors, increased cage biting, and alterations palpebral closure were observed in both sexes. Statistical significant signs of toxicity noted during the **handling observations** included increase displayed freezing upon removal from the cage, reduced ease of handling in the hand, slight to severe salivation, slight lacrimation, and slightly soiled fur in males and females. Statistical significant signs of toxicity observed in both sexes during the **open field observations** included impaired mobility, alterations in gait, impaired gait score, clonic and tonic convulsions, low arousal and writhing, as well as decreased rearing, grooming, urination, and increased time-to-first step. Both sexes showed decreased rearing activity (100%) and increased time-to-first step (3240%). Signs of toxicity seen during the **sensory observations** included alterations in approach, touch, startle, and tail pinch responses, olfactory orientation, lack of forelimb and hindlimb extension, and air righting reflex. During the **neuromuscular observations**, the following significant decreases were observed in the animals: (i) forelimb grip strength (males-45%; females- 29%); (ii) hindlimb grip strength (males-38%; females-27%); (iii) rotarod performance (males-79%; females-87%); and (iv) hindlimb footsplay (males-32%). During the **physiological observations**, body temperatures were decreased in the males (7%) and females (8%). Catalepsy times were increased in the males (1080%) and in the females (2683%).

On days 7 and 14, observations in treated animals were similar to observations made for control animals with the exception of increased ($p<0.01$) hindlimb footsplay in 50 mg/kg males on day 7.

Several effects were observed in animals on day 0 at 15 mg/kg. This included slight salivation in one male and slightly soiled fur for one female during **handling observations**; slightly impaired mobility for one male during **open field observations**; and no reactions to approach response (2 females) and touch response (2 females) **during sensory observations**. None of these effects were observed in the control animals.

Under the conditions of this study, the NOAEL for male and female rats is 5 mg/kg. The LOAEL is 15 mg/kg based on salivation, soiled fur, impaired mobility, no reaction to approach and no reaction to touch response observed in the FOB.

This acute oral neurotoxicity study is classified as **Acceptable/ Guideline** and satisfies the guideline requirement for an acute oral neurotoxicity study [OPPTS 870.6200(§81-8)] in rats.

Subchronic Oral Neurotoxicity [Feeding] in Rats; 870.6200; §82-5, OEDC None

CITATION: Nemec, Mark. (1998) A Subchronic (13-week) Neurotoxicity Study of Deltamethrin in Rats. WIL Research Laboratories, Inc. Ashland, Ohio. Laboratory Study Number WIL-274003. March 19, 1998. MRID 44557902. Unpublished.

EXECUTIVE SUMMARY: In this subchronic neurotoxicity study (MRID 44557902), deltamethrin (Batch No.: 4N0397B, 99.2% purity) was administered to 10 Charles River (Crl:CD®[SD]BR) rats/sex/dose at dietary levels of 0, 50, 200, or 800 ppm for 13 weeks. Based on analytical measurements, doses were 0, 4, 14, and 54 mg/kg/day for males and 0, 4, 16, and 58 mg/kg/day for females. Body weights were recorded weekly and clinical observations were recorded daily. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all animals/sex/group pretreatment and once/week during weeks 3, 7, and 12. At study termination, all surviving animals were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5 rats/sex in the control and high-dose groups were subjected to histopathological evaluation of the central and peripheral nervous system tissues.

Brain weights and dimensions, motor activity, and neuropathological findings were unaffected by the test substance at all dose levels.

Three males (days 13, 25, and 47; 3/10 = 30%) and two females days (22 and 90; 2/10 = 20%) in the 800 ppm treatment group died before the end of the study, motility did not occur in other groups. Findings in these rats included emaciation (one male) dark red stomach and intestinal contents (two males and one female) gas-distended stomach (one male), enlarged lymph nodes (one male and one female), pale spleen (one male) and mottled lungs (one female). A third female appeared to have experienced mechanical trauma and was euthanized *in extremis* (day 91). This female had a broken incisor, an abrasion of the tongue, swollen gingiva, and red matting on the entire head, ventral surface, limbs and tail. No explanation of the mechanical trauma was given.

Clinical findings noted at the high-dose throughout the study included (i) rocking, swaying, or lurching, (ii) hypersensitivity to noise, (iii) impaired righting reflex, (iv) piloerection, (v) seizures, (vi) altered posture, (vii) convulsions, and (viii) soiled fur.

Significant decreases in body weights (males: 26-35% and females: 10-17%), body weight gains (males: 50-102% and females: 48-114%) and food consumption (males:18-45% and females: 11-25%) were observed at the high dose throughout the study.

Results of the FOB indicated no treatment-related findings during the home cage observations; however, treatment-related effects were noted at the high-dose (800 ppm) during the handling, open field, sensory, and neuromuscular observations. Findings noted during the **handling observations** included slightly soiled fur, altered palpebral closure, salivation, pale mucous membranes, pale eyes, and pale skin in the females. During the **open field observations**, animals showed impaired mobility, body drags or sways, splayed or dragging hindlimbs, impairment of gait score, side to side rocking, and gait alterations (ataxia, excessive sway), and walking on tiptoes. Signs of neurotoxicity were noted during the **sensory observations** such as slightly uncoordinated air righting reflex in the males and females, and landing on the side or back in females. During the **neuromuscular observations**, decreased forelimb and hindlimb grip strength were observed in the

males. Reduced hindlimb resistance (animal shows some weakness) was observed in the males and females, and an absence of hindlimb resistance was observed in the females.

At the low dose (500 ppm) there were no effects on body weight, FOB parameters or motor activity and there were no treatment-related lesions in the brain or central or peripheral nervous system tissues. At the mid dose (200 ppm) there were single incidences of effects in males as indicated by the FOB (soiled fur and impaired mobility), but no effects on body weight or motor activity and no treatment-related lesions in the brain or central or peripheral nervous system tissues.

The neurotoxicity LOAEL is 800 ppm (equivalent to 54 mg/kg/day in males and 58 mg/kg/day in females) based on mortality, clinical signs of toxicity, FOB findings, and decreased body weights, body weight gains, and food consumption. The neurotoxicity NOAEL is 200 ppm (equivalent to 14 mg/kg/day in males and 16 mg/kg/day in females).

The submitted study is classified as **Acceptable/Guideline (§82-7)** and satisfies the guideline requirements for a subchronic neurotoxicity screening battery in rats.

METABOLISM

Metabolism in Rats; OPPTS 870.7485 (§85-1); OECD 417.

CITATION: Bosch, A. (1990) Metabolism of ^{14}C-Deltamethrin in rats. Hazleton Laboratories America, Inc., Madison, WI. Laboratory Project No.: HLA 6187-108, July 9, 1990. MRID 41677401. Unpublished.

EXECUTIVE SUMMARY: In a rat metabolism study (MRID 41677401), [^{14}C-benzyl] deltamethrin (Lot no. X6819A, >95% radiochemical purity) in corn oil was administered as a single gavage dose at 0.55 or 5.50 mg/kg to 5 Crl:CD (SD) BR rats/sex/dose. [^{14}C-dimethyl] deltamethrin (Lot no. X7506A, >95% radiochemical purity) was administered similarly. Two control groups, each with a single male and female rat, received the vehicle (assumed by the reviewer). In addition, 5 rats/sex/dose for each radiolabeled compound received 14 days of non-radiolabeled compound (Lot No. 7B0235B, 99.3%) at 0.55 mg/kg followed by the labeled compound (0.55 mg/kg) on Day 15.

Absorption was ≥31.2% based on urinary excretion. Absorption was very rapid as excretion was virtually complete within 6 hours after dose administration (data not provided). Biliary duct canulation or i.v. injection were not performed to allow a more accurate estimation of absorption. Furthermore, blood kinetics were not reported. Differences in the excretion profile due to sex, treatment regime (single vs repeated), or radiolabel were slight or absent. Seven days following administration, 31.2-56.3% dose was recovered in the urine and 35.7-58.5% was excreted in the feces. Less than 2% dose was recovered in the tissues and carcass. Overall recovery of the dosed radioactivity was 84.2-96.2%.

Concentrations of radioactivity (ppm) in the tissues were <0.01 ppm at 0.55 mg/kg and <0.05 ppm at 5.50 mg/kg, except in the fat (concentration not reported). In general, the concentration in fat was proportional to the dose.

Metabolism of deltamethrin occurred through cleavage of the ester bond to form m-phenoxybenzoic acid (mPBA) and (1R-cis)-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane carboxylic acid (Br_2CA) and through hydroxylation at the 4' position of the mPBA moiety in the intact molecule or after cleavage. Glucuronidation and sulfation occurred during phase II metabolism.

The parent was found in the feces at 46% dose in the 5.50 mg/kg females treated with [^{14}C-benzyl] deltamethrin and 17-35% dose in both sexes and radiolabels at all doses. A minor metabolite, 4' hydroxy deltamethrin, was found (3-6% dose) in the feces of animals treated with [^{14}C-benzyl] deltamethrin. In the urine of animals treated with [^{14}C-benzyl] deltamethrin, the major metabolite was mPBA- 4'-sulfate (30-49% dose), and the minor metabolite was mPBA (2-4% dose). In the urine of animals treated with [^{14}C-dimethyl] deltamethrin, the major metabolites were Br_2CA (4-10% dose) and its glucuronide conjugate (22-38% dose). The amount of radioactivity that was isolated but not identified was 10.8-32.1% dose. Consequently, it is possible that major metabolites were not successfully isolated and characterized.

This study is classified **acceptable/guideline** and satisfies the requirements for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-1, Acute Oral Toxicity Study in Rats

Work Assignment No. 4-02-189A (MRID 41651019)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S. — Signature: David A. McEwen — Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez — Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez — Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D. — Signature: Steven Brecher — Date: 7/3/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E.M. Carroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** SWF
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100 [§81-1]; OECD 401.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Myer, J.R. (1989) Acute oral toxicity test of deltamethrin in rats. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-122, May 4, 1989. MRID 41651019. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 41651019), groups of 8 week old Sprague-Dawley rats (5/sex) were given a single oral dose (10 mL/kg) of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) in 1% methylcellulose at a dose of 5000 mg/kg (limit test) and observed for 13 days.

Oral LD_{50} Males >5000 mg/kg
Females >5000 mg/kg
Combined >5000 mg/kg

No mortality was observed during this limit test. Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category IV** based on the LD_{50} observed in males and females.

There were no treatment related clinical signs, necropsy findings, or changes in body weight.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the rat.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-2, Acute Dermal Toxicity Study in Rabbits

Work Assignment No. 4-02-189B (MRID 41651020)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 7/3/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. M. Carroll
Toxicology Branch, Health Effects Division (7509C) **Date** 10/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** [illegible]
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Acute Dermal Toxicity Study - Rabbits; OPPTS 870.1200 [§81-2]; OECD 402.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Myer, J.R. (1989) Acute Dermal Toxicity Study of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-123, May 4, 1989. MRID 41651020. Unpublished.

SPONSOR: Hoechst-Russell Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 41651020), a 50% (w/v) suspension of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) in 1% methylcellulose was applied to the shaved intact skin (15 % of body surface) of young adult New Zealand White rabbits (5/sex) for 24 hours at a dose of 2000 mg/kg (limit test). Animals then were observed for 14 days.

Dermal LD_{50} Males >2000 mg/kg
Females >2000 mg/kg
Combined >2000 mg/kg

No mortality was observed during this limit test. Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category III** based on the LD_{50} observed in males and females.

There were no treatment related clinical signs, necropsy findings, or changes in body weight.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1200; OECD 402) for an acute dermal toxicity study in the rabbit.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-3, Acute Inhalation Toxicity Study in Rats

Work Assignment No. 4-02-189C (MRID 41651021)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.
Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.
Signature: Steve Brecher
Date: 7/3/02

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EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 10/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Acute Inhalation Toxicity - Rats; OPPTS 870.1300 [§81-3]; OECD 403.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (purity not reported)

SYNONYMS: (S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Ulrich, C.E. (1990) Acute Inhalation Toxicity Evaluation of Deltamethrin in Rats. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-121, June 9, 1990. MRID 41651021. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 41651021), groups of young adult Sprague-Dawley rats (5/sex) were exposed by whole-body inhalation to Deltamethrin (purity not reported, Batch/Lot# 8N 0701 B2) for 4 hours at gravimetrically determined concentrations of 1.0, 1.8, or 2.3 mg/L. Animals then were observed for up to 14 days.

Inhalation LC_{50} Combined = 2.2 mg/L (with 95% C.I. of 1.5-3.3 mg/L)

Deltamethrin is considered to be of **Low Toxicity** and is classified as **EPA Toxicity Category IV** based on the LC_{50} in males and females combined.

The mass median aerodynamic diameter (MMAD) was < 5 µm; averages [± geometric standard deviations (GSD)] were 4.4 ± 1.9, 3.5 ± 1.85 and 3.1 ± 1.87 for the high, mid and low dose, respectively.

Mortality occurred throughout the study (Days 0-14) at 1.0 (1/5 females), 1.8 (2/5 males and 2/5 females), and 2.3 (2/5 males and 3/5 females) mg/L. Clinical signs observed at all doses included labored breathing, impaired hindlimb function, ataxia, loss of righting reflex, decreased

activity, and material around nose and/or eyes. Overall (Day 0-14) body weight gain was decreased in all groups. At necropsy, the 1.8 and 2.3 mg/L animals showed enlarged inguinal and mandibular lymph nodes, pulmonary congestion, and skin discoloration.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1300; OECD 403) for an acute inhalation toxicity study in the rat. Although test article purity data were not provided, mortality was observed at all doses.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-4, Primary Eye Irritation in Rabbits

Work Assignment No. 4-02-189D (MRID 41651022)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S. — Signature: David A. McEwen — Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez — Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez — Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D. — Signature: Steven Brecher — Date: 7/3/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400 [§81-4]; OECD 405.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Myer, J.R. (1989) Eye Irritation Study of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-125, April 17, 1989. MRID 41651022. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 41651022), approximately 87 mg of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) was instilled into the conjunctival sac of the right eye of young adult New Zealand White rabbits (3/sex). The eyes were not washed at anytime after instillation. Animals then were observed at 1, 24, 48, and 72 hours for signs of ocular irritation. Irritation was scored by the method of Draize.

Signs of irritation including moderate to marked conjunctival redness, slight to marked discharge (clear), slight swelling, and slight iridial irritation were observed at one hour post-instillation. All signs of irritation cleared by 72 hours post-instillation. In this study, **Deltamethrin is mildly irritating to the eye**, and is classified as **EPA Toxicity Category III** based on the degree of irritation that cleared by 72 hours post-instillation.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2400; OECD 405) for a primary eye irritation study in the rabbit.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-5, Primary Dermal Irritation Study in Rabbits

Work Assignment No. 4-02-189E (MRID 41651023)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 7/3/02

Disclaimer

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EPA Reviewer: Nancy McCarroll **Signature:** Nancy S. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Primary Dermal Irritation - Rabbits; OPPTS 870.2500 [§81-5]: OECD 404.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Myer, J.R. (1989) Primary Dermal Irritation Test of Deltamethrin in Rabbits. International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-124, April 17, 1989. MRID 41651023. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 41651023), young adult New Zealand White rabbits (3/sex) were dermally exposed to 0.5 g of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) moistened with 1% methylcellulose for 4 hours. Animals were observed for up to 3 days post-exposure. Irritation was scored by the method of Draize.

No signs of dermal irritation were observed at any time point. In this study, Deltamethrin is not a dermal irritant, and classified as **EPA Toxicity Category IV** based on the lack of dermal irritation.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2500; OECD 404) for a primary dermal irritation study in the rabbit.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §81-6, Skin Sensitization Study in Guinea Pigs

Work Assignment No. 4-02-189F (MRID 41651024)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steve Brecher
Date: 7/3/02

Disclaimer

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EPA Reviewer: Nancy McCarroll **Signature:** Nancy S. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** [illegible]
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Skin Sensitization - Guinea pigs; OPPTS 870.2600 [§81-6]; OECD 406.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Myer, J.R. (1989) Dermal Sensitization Study of Deltamethrin in the Albino Guinea Pig (Buehler Test). International Research and Development Corp., Mattawan, MI. Laboratory Study No.: 327-126, September 7, 1989. MRID 41651024. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 41651024) young adult Hartley Guinea pigs (10/sex) were dermally exposed to 0.4 gm of Deltamethrin (99.2% a.i., Batch/Lot# 8 B015 3B3) moistened with 1% methylcellulose, using the Buehler method. The test consisted of three induction treatments (Days 0, 7, and 14) followed by a challenge phase on Day 28. Additionally, groups of 5 animals/sex were used as positive controls (0.4 mL of 0.01% 2,4-dinitrochlorobenzene) or untreated controls.

No dermal effects were induced by the test article. **In this study, Deltamethrin is not a dermal sensitizer.**

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.2600; OECD 406) for a dermal sensitization study in the Guinea pig.

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DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §81-1, Acute Oral Toxicity Study in Rats

Work Assignment No. 4-02-189N (MRID 00060714)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 7/3/02

Disclaimer

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EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100 [§81-1]; OECD 401.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): RU22974 (Deltamethrin; purity not reported)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Glomont, R. and B. Chevalier (1976) RU22974: Acute Toxicity in the Mouse - Rat by Oral Route. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: TOX 76810, March 30, 1976. MRID 00060714. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00060714), groups of Sprague-Dawley (CD_1) rats (10/sex) were given a single oral dose (10 mL/kg) of RU22974 (Deltamethrin; purity not reported, Batch/Lot# not reported) in either polyethylene glycol 200 (PEG 200) at doses of 29.65, 44.50, 66.70, 100.0, or 150.0 mg/kg or in sesame oil at doses of 66.7, 100.0, 150.0, 225.0, or 337.5 mg/kg, and observed for 8 days.

In PEG 200: Oral LD_{50} Males = 66.7 mg/kg (with 95% C.I. of 53.0-83.9 mg/kg)
Females = 86.0 mg/kg (with 95% C.I. of 70.6-106.2 mg/kg)

In sesame oil: Oral LD_{50} Males = 128.5 mg/kg (with 95% C.I. of 104.9-156.5 mg/kg)
Females = 138.7 mg/kg (with 95% C.I. of 114.2-168.2 mg/kg)

Mortality occurred on Days 1-4 at doses ≥44.5 mg/kg (PEG 200) and ≥100.0 mg/kg (sesame oil). RU22974 is considered to be of **Moderate Toxicity** and is classified as **EPA Toxicity Category II** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. In the highest doses shortly after administration, motor uncoordination, convulsions, and

respiratory defects were observed. At 24 and 48 hours after administration hypomotility and convulsions were observed. All surviving animals appeared normal by Day 3.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the rat. Test article purity and batch/lot# were not provided; however, treatment-related clinical signs and mortality were observed. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided; however, the study was conducted prior to the adoption of GLP Standards [40 CFR 160].

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** RU22974 (Deltamethrin)
   Description: Not reported
   Lot/Batch #: Not reported
   Purity: Not reported
   CAS # of TGAI: 52918-63-5

2. **Vehicle:** Polyethylene glycol 200 or sesame oil

3. **Test animals**
   Species: Rat
   Strain: Sprague-Dawley (CD_1)
   Age/weight at dosing: Age not reported; mean weight 100-110 g.
   Source: Iffa-Credo (France)
   Housing: 5/sex in plastic cages (type not reported)
   Diet: Not reported, *ad libitum*, except for 6 hours prior to dosing.
   Water: Tap water, *ad libitum*
   Environmental conditions
   Temperature: Not reported
   Humidity: Not reported
   Air changes: Not reported
   Photoperiod: Not reported
   Acclimation period: Not reported

B. STUDY DESIGN and METHODS

1. **In life dates:** Not reported

2. **Animal assignment and treatment:** Animals were assigned to the test groups noted in Table 1. (Following a 6 hour fast), rats were given a single dose of RU22974 by gavage then observed for up to 8 days. Details of sacrifice were not reported. Gross necropsies were not performed.

Table 1. Study design and mortality. [a]

Dose (mg/kg)	Mortality (number dead/number of animals)		
	Males	Females	Combined
PEG 200			
29.65	0/10	0/10	0/20
44.50	3/10	0/10	3/20
66.70	5/10	3/10	8/20
100.0	7/10	7/10	14/20
150.0	10/10	9/10	19/20
Sesame oil			
66.70	0/10	0/10	0/10
100.0	3/10	2/10	5/20
150.0	7/10	6/10	13/20
225.0	9/10	9/10	18/20
337.5	10/10	10/10	20/20

a Data obtained from Study Report, pages 9 and 11.

3. **Statistics:** The oral LD_{50} was calculated using the method of Finney (probit analysis, 1962).

II. RESULTS AND DISCUSSION

A. MORTALITY: Given in Table 1. Mortality occurred on Days 1-4 in males and 2-3 in females.

In PEG 200, the oral LD_{50} (95% C.I.) for males is 66.7 mg/kg (53.0-83.9)
females is 86.0 mg/kg (70.6-106.2)

In sesame oil, the oral LD_{50} (95% C.I.) for males is 128.5 mg/kg (104.9-156.5)
females is 138.7 mg/kg (114.2-168.2)

B. CLINICAL OBSERVATIONS: Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. It was stated that in the highest doses shortly after administration, motor uncoordination, convulsions, and respiratory defects were observed. At 24 and 48 hours after administration hypomotility and convulsions were observed. All surviving animals appeared normal by Day 3. No tabular clinical signs data were provided.

C. BODY WEIGHT: Body weight data were not provided.

D. NECROPSY: Necropsies were not performed.

E. REVIEWER'S CONCLUSIONS: Although the test article purity was not reported, treatment-related clinical signs and mortality were observed during the study. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

F. DEFICIENCIES: The following deficiencies were noted, but do not alter the conclusions of this DER:

- Test article purity and Batch/Lot # were not provided.
- Individual and/or summary tabular clinical signs data were not provided.
- Body weights were not provided.
- Gross necropsies were not performed.
- Animal environmental conditions were not provided.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §81-1, Acute Oral Toxicity Study in Mice

Work Assignment No. 4-02-189O (MRID 00098078)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.
Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.
Signature: Steve Brecher
Date: 7/3/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy S. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/01/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** [illegible]
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Mouse; OPPTS 870.1100 [§81-1]; OECD 401.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): RU22974 (Deltamethrin; purity not reported)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Glomont, R. and B. Chevalier (1976) RU22974: Acute Toxicity in the Mouse - Rat by Oral Route. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: TOX 76810, March 30, 1976. MRID 00098078. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00098078), groups of albino Swiss CD_1 mice (10/sex) were given a single oral dose of RU22974 (Deltamethrin; purity not reported, Batch/Lot# not reported) in either polyethylene glycol 200 (PEG 200;10 mL/kg) at doses of 9.1, 12.8, 17.9, 25.0, or 35.0 mg/kg or in sesame oil (20 mL/kg) at doses of 12.8, 17.9, 25.0, 35.0, 49.0, or 68.6 mg/kg, and observed for 8 days.

In PEG 200: Oral LD_{50} Males = 20.6 mg/kg (with 95% C.I. of 17.3-24.8 mg/kg)
Females = 18.7 mg/kg (with 95% C.I. of 15.7-22.4 mg/kg)

In sesame oil: Oral LD_{50} Males = 33.1 mg/kg (with 95% C.I. of 27.2-40.8 mg/kg)
Females = 34.4 mg/kg (with 95% C.I. of 28.4-42.0 mg/kg)

Mortality occurred on Days 1-2 at doses ≥12.8 mg/kg (PEG 200) and ≥17.9 mg/kg (sesame oil). RU22974 is considered to be of **High Toxicity** and is classified as **EPA Toxicity Category I** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. It was stated that the following signs were observed: (i) in all doses shortly after administration,

hypomotility, stereotypic movements of the head, tachychardia, and cyanosis; (ii) at 1 hour post-dosing, muscular stiffening and at the highest doses, clonic-tonic convulsions; and (iii) at 24 hours post-dosing, hypomotility, stereotypic movements of the head, tachychardia, hypertonicity of the tail, and transient convulsions. All surviving animals appeared normal by 48 hours.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the mouse. Test article purity and batch/lot# were not provided; however, treatment-related clinical signs and mortality were observed. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided; however, the study was conducted prior to the adoption of GLP Standards [40 CFR 160].

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: RU22974 (Deltamethrin)
Description: Not reported
Lot/Batch #: Not reported
Purity: Not reported
CAS # of TGAI: 52918-63-5

2. Vehicle: Polyethylene glycol 200 or sesame oil

3. Test animals
Species: Mouse
Strain: Swiss CD_1
Age/weight at dosing: Age not reported; mean weight 19-21 g.
Source: Charles River (France)
Housing: 5/sex in plastic cages (type not reported)
Diet: Not reported, *ad libitum*, except for 6 hours prior to dosing.
Water: Tap water, *ad libitum*
Environmental conditions
Temperature: Not reported
Humidity: Not reported
Air changes: Not reported
Photoperiod: Not reported
Acclimation period: Not reported

B. STUDY DESIGN and METHODS

1. In life dates: Not reported

2. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 1. (Following a 6 hour fast), mice were given a single dose of RU22974 by gavage then observed for up to 8 days. Details of sacrifice were not reported. Gross necropsies were not performed.

Table 1. Study design and mortality. [a]

Dose (mg/kg)	Mortality (number dead/number of animals)		
	Males	Females	Combined
PEG 200			
9.1	0/10	0/10	0/20
12.8	1/10	1/10	2/20
17.9	3/10	5/10	8/20
25.0	8/10	9/10	17/20
35.0	9/10	9/10	18/20
Sesame oil			
12.8	0/10	0/10	0/20
17.9	1/10	0/10	1/20
25.0	2/10	3/10	5/20
35.0	7/10	6/10	13/20
49.0	8/10	8/10	16/20
68.6	9/10	9/10	18/20

a Data obtained from Study Report, pages 4 and 6.

3. **Statistics:** The oral LD_{50} was calculated using the method of Finney (probit analysis, 1962).

II. RESULTS AND DISCUSSION

A. MORTALITY: Given in Table 1. All mortality occurred on Days 1-2 in both sexes.

In PEG 200, the oral LD_{50} (95% C.I.) for males is 20.6 mg/kg (17.3-24.8)
females is 18.7 mg/kg (15.7-22.4)

In sesame oil, the oral LD_{50} (95% C.I.) for males is 33.1 mg/kg (27.2-40.8)
females is 34.4 mg/kg (28.4-42.0)

B. CLINICAL OBSERVATIONS: Clinical signs observed were similar in animals dosed using PEG 200 and sesame oil as vehicles. It was stated that the following signs were observed: (i) in all doses shortly after administration, hypomotility, stereotypic movements of the head, tachychardia, and cyanosis; (ii) at 1 hour post-dosing, muscular stiffening and at the highest doses, clonic-tonic convulsions; and (iii) at 24 hours post-dosing, hypomotility, stereotypic movements of the head,

tachychardia, hypertonicity of the tail, and transient convulsions. All surviving animals appeared normal by 48 hours. No tabular clinical signs data were provided.

C. BODY WEIGHT: Body weight data were not provided.

D. NECROPSY: Necropsies were not performed.

E. REVIEWER'S CONCLUSIONS: Although the test article purity was not reported, treatment-related clinical signs and mortality were observed during the study. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

F. DEFICIENCIES: The following deficiencies were noted, but do not alter the conclusions of this DER:

- Test article purity and Batch/Lot # were not provided.
- Individual and/or summary tabular clinical signs data were not provided.
- Body weight data were not provided.
- Gross necropsies were not performed.
- Animal environmental conditions were not provided.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §81-1, Acute Oral Toxicity Study in Dogs

Work Assignment No. 4-02-189P (MRID 00098079)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.
Signature: David A. McEwen
Date: 7/3/02

Secondary Reviewer
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.
Signature: Steve Brecher
Date: 7/3/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** SWF
Registration Action Branch 2, Health Effects Division (7509C) **Date** 01/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Dog; OPPTS 870.1100 [§81-1]; OECD 401.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): RU22974 (Deltamethrin; purity not reported)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Glomont, R., B. Chevalier, E. Collas, et al. (1977) RU22974: Acute Toxicity by Oral Route in Male and Female Beagle Dogs. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Study No.: 77804/JL-5, March 17, 1977. MRID 00098079. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 00098079), groups of fasted Beagle dogs (2-3/sex) were given a single gavage dose (5 mL/kg) of RU22974 (Deltamethrin; purity not reported, Batch/Lot# 18) in polyethylene glycol 200 (PEG 200) at doses of 0 or 300 mg/kg and observed for 15 days. Additional groups of dogs (3/sex) received the test material in capsules at doses of 100 or 300 mg/kg.

Oral LD_{50} Males >300 mg/kg
Females >300 mg/kg

No mortality was observed during the study. RU22974 is considered to be of **Moderate Toxicity** and is classified as **EPA Toxicity Category II** based on the LD_{50} observed in males and females.

Clinical signs observed were similar in males and females, and included: stiffness of the hind legs, vomiting, akinesia, and slight diarrhea All animals appeared normal by 72 hours.

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.1100; OECD 401) for an acute oral toxicity study in the dog. Test article purity was not provided; however, treatment-related clinical signs were observed in most animals. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided; however, the study was conducted prior to the adoption of GLP Standards [40 CFR 160].

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** RU22974 (Deltamethrin)
   Description: Not reported
   Lot/Batch #: 18
   Purity: Not reported
   CAS # of TGAI: 52918-63-5

2. **Vehicle:** Polyethylene glycol 200

3. **Test animals**
   Species: Dog
   Strain: Beagle
   Age/weight at dosing: 6-16 months; 7.1-12.1 kg, males and 8.4-12.6 kg, females.
   Source: CERM breeding farm (Ricm), C.E.D.S. breeding farm (Toucy), or S.E.B.C. (Vert le Petit, France)
   Housing: Individually in heated kennels
   Diet: Standard Dog Diet (U.A.R. Company), *ad libitum*, except for 24 hours prior to dosing.
   Water: Tap water, *ad libitum*
   Environmental conditions
   Temperature: Not reported
   Humidity: Not reported
   Air changes: Not reported
   Photoperiod: Not reported
   Acclimation period: Not reported

B. STUDY DESIGN and METHODS

1. **In life dates:** Start: 10/27/76 End: 11/10/76

2. **Animal assignment and treatment:** Animals were assigned to the test groups noted in Table 1. (Following a 24 hour fast), the dogs were given a single gavage dose (5 mL/kg) of RU22974 in polyethylene glycol 200 (PEG 200) or in a capsule, and observed for 15 days. Details of sacrifice were not reported. Gross necropsies were not performed.

Table 1. Study design and mortality. [a]

Dose (mg/kg)	Mortality (number dead/number of animals)		
	Males	Females	Combined
PEG 200			
0	0/2	0/2	0/4
300	0/3	0/3	0/6
Capsule			
100	0/3	0/3	0/6
300	0/3	0/3	0/6

a Data obtained from Study Report, page 2.

3. **Statistics:** Statistical methods were not applied to the data.

II. RESULTS AND DISCUSSION

A. MORTALITY: No mortality was observed during the study (Table 1).

The oral LD_{50} for males is >300 mg/kg
females is >300 mg/kg

B. CLINICAL OBSERVATIONS: In the animals dose via capsules, clinical signs included: (i) at 100 mg/kg at 18 hours post-dosing, stiffness of the hind legs, vomiting, and slight diarrhea and (ii) at 300 mg/kg at 24-48 hours post-dosing, transient hyperexcitability, vomiting, and stiffness of the hind legs. All animals appeared normal by 72 hours post-dosing. In the animals dosed with RU22974 in PEG 200 at 300 mg/kg, clinical signs were limited to akinesia and vomiting shortly after dosing. All animals appeared normal at 24 hours post-dosing. No tabular clinical signs data were provided.

C. BODY WEIGHT: All animals were weighed on Days 0 (prior to dosing), 7, and 14. Body weights were similar to controls throughout the study.

D. NECROPSY: Necropsies were not performed.

E. REVIEWER'S CONCLUSIONS: Although the test article purity was not reported, clinical signs were observed in most treated animals. The reviewers feel that the animals were sufficiently dosed and that the observed LD_{50} is acceptable.

F. DEFICIENCIES: The following deficiencies were noted, but do not alter the conclusions of this DER:

- Test article purity was not provided.
- Individual and/or summary tabular clinical signs data were not provided.
- Gross necropsies were not performed.
- Animal environmental conditions were not provided.

DATA EVALUATION RECORD

DELTAMETHRIN/0050424
(RU 22974)

STUDY TYPE: SUBCHRONIC ORAL TOXICITY STUDY- RAT
[870.3100 (§82-1a)]
MRID 00098103

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 02-20

Primary Reviewer: Gary Sega, Ph.D.	Signature:	Gary Sega
	Date:	APR 17 2002
Secondary Reviewers: H. Tim Borges, Ph.D., D.A.B.T.	Signature:	HT Borges
	Date:	APR 17 2002
Robert H. Ross, M.S.,Group Leader	Signature:	Robert H. Ross
	Date:	APR 17 2002
Quality Assurance: Lee Ann Wilson, M.A.	Signature:	L. A. Wilson
	Date:	APR 17 2002

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

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EPA Reviewer: Stanley Gross, Ph.D.
Registration Action Branch 3,
Health Effects Division (7509C)

Signature:
Date 6/24/2002

EPA Secondary Reviewer: Stephen Dapson, PhD
Senior Scientist, Registration Action Branch 3,
Health Effects Division (7509C)

Signature
Date 06/27/2002

EPA Work Assignment Manager: Sanyvette Williams-Foy
Registration Action Branch 2,
Health Effects Division (7509C)

Signature:
Date 9/04/02

DATA EVALUATION RECORD
TXR#: 0050424

STUDY TYPE: 90-Day Oral Toxicity gavage - rat with 4 week Recovery Period. OPPTS 870.3100 [§82-1a] (rodent); OECD 408.

PC CODE:097805

DP BARCODE: D277538
SUBMISSION NO.: S541415

TEST MATERIAL (PURITY): RU22974 (Deltamethrin, Lot 17, purity not reported)

SYNONYMS: 3-(2,2-Dibromoethenyl)-2,2-dimethylcyclopropanecarboxylic acid cyano(3-phenoxyphenyl)methyl ester; Deltamethrin

CITATION: Hunter, B., Jordan, J., Heywood, R., et al. (1977) RU22974 - Assessment of toxicity to rats by oral administration for 13 weeks (followed by a 4-week withdrawal period). Huntingdon Research Centre (Cambridgeshire, England). Laboratory report number RSL254/76938/A3, March 21, 1977. MRID 00098103. Unpublished.

SPONSOR: Procida, 5-7 rue Beilini, 92Puteaux 92806, France.

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00098103) RU 22974 (purity not reported, Lot 17) was administered daily by gavage to 20 CD Sprague-Dawley rats/sex/dose at doses of 0, 0.1, 1.0, 2.5, or 10 mg/kg bw/day. The RU 22974 was suspended in polyethylene glycol and administered to the animals initially at the rate of 5 ml/kg, later reduced to 2.5 ml/kg because of gavage trauma to the animals. A recovery group of 5 animals/sex/group was followed during post-treatment weeks 14 to 17.

The animals were observed daily for toxicity. Body weights and food consumption were measured weekly. Eye examinations, hematology and clinical chemistry determinations were carried out initially and during treatment weeks 6 and 13; urinalyses carried out during weeks 6

and 12. Neurological examinations were carried out on control and high dose animals, prior to treatment and during weeks 6 and 13. Neurological examinations included a) "segmental" responses (flexor, extensor and patellar reflexes); b) Postural assessments including righting, placing and grip reflexes and extensor thrust; c) locomotion and muscle strength; and d) behavior changes and responses to noise. At termination of the treatment phase, the animals in the control and high dose groups were subjected to gross necropsy and histopathology. Recovery groups were observed daily for clinical signs and weighed weekly during weeks 14 to 17.

There were no animal deaths due to the treatment with RU 22974. Several animals died secondary to gavage trauma during the first few weeks of the study. These animals were replaced. Except for neurological effects, there were no treatment-related signs of systemic toxicity or effects on the eyes, hematology, or clinical chemistry. Toxic signs included slightly increased hypersensitivity to sound in 9 of 10 high dose males and 3 of 10 high dose females during week 6, but these signs cleared by week 13. Body weight gains in the 2.5 and 10.0 mg/kg/day group males were slightly lower throughout the treatment period, being 97 and 94%, respectively, of the controls during weeks 1 to 4; 90 and 88%, respectively, during weeks 5 to 8; and 81 and 87%, respectively, during weeks 9 to 12. For the entire treatment period, the overall weight gains of the 2.5 and 10.0 mg/kg/day group males were significantly reduced to 92 and 91%, respectively, of the controls. No significant changes in weight gain were found in treated female rats.

Post treatment animals regained body weights at rates greater than the treated animals to the extent and there were no significant differences among the treated groups and the control animals. There were no gross pathology findings and no treatment-related histological lesions found.

The LOAEL for deltamethrin (RU22794) in male rats is 2.5 mg/kg/day based on decreased body weight gains during the 90 day treatment period. The LOAEL for female rats is not established. The NOAEL is 1.0 mg/kg/day for male rats and 10.0 mg/kg/day for females.

This 90-day oral toxicity study in the rat is **Unacceptable/Nonguideline**. The study was conducted prior to establishment of EPA guidelines and GLP practicies, but does not meet the intent of these. The stability and purity of the test material were not provided. The dose levels selected did not produce sufficient toxicity, other than weight loss, to effectively assess the toxicity of RU 22974.

COMPLIANCE: There were no signed and dated GLP, Quality Assurance, and Data Confidentiality statements since this report was written in 1977, before current EPA requirements were established.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** RU 22974 (Deltamethrin)

Description:	white powder
Lot/Batch #:	Lot #17
Purity:	not given
Compound Stability:	not given
CAS #:	52918-63-5
Structure:	

2. **Vehicle and/or positive control:** The test material was dissolved in polyethylene glycol 200 prior to gavage. Control animals received only vehicle.

3. **Test animals:**

Species:	Rat
Strain:	Sprague-Dawley, CD
Age/weight at study initiation:	ages not provided; males 134 - 169 g; females 118 - 161 g.
Source:	Charles River Laboratories, Manston, England
Housing:	5/sex/suspended cage with wire-mesh floors.
Diet:	Spratt's Laboratory Diet 1, *ad libitum.*
Water:	Tap water, *ad libitum.*
Environmental conditions:	
Temperature:	21 ± 2 °C
Humidity:	50 ± 5 %
Air changes:	Not reported
Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	7 days

B. STUDY DESIGN:

1. **In life dates** - Start: July 15, 1976; End: ~Nov. 11, 1976

2. **Animal assignment**: Rats were weighed and allocated to one of several arbitrary weight groups with body weights differing by no more then ± 2.5 g. Equal numbers of animals within each weight range were allocated to one of five test groups noted in Table 1.

TABLE 1: Study design

Test group	Dose level (ppm)	Dose to animal (mg/kg/day)	# Male	# Female
1 (Control)	0	0	20*	20*
2	0.1	0.1	20	20
3	1.0	1.0	20	20
4	2.5	2.5	20	20
5	10.0	10.0	20*	20*

*** 5 animals in group were retained for recovery responses.**

Recovery Groups. Five animals per sex per group were retained for 4 weeks post-treatment (weeks 14 to 17) growth observations.

3. **Dose selection rationale:** No rationale was given for the dose selection.

4. **Diet preparation and analysis:** Solutions of RU 22974 were prepared twice weekly by mixing appropriate amounts of the test material with polyethylene glycol 200 and stored in amber bottles at room temperature. The concentrations were adjusted so that each group received a constant dose volume of 5 mL/kg. Because of occasional deaths, at the end of the fourth week the concentrations were adjusted to give a constant dose volume of 2.5 mL/kg. Stability of the test solutions was not reported.

5. **Statistics:** For comparisons of parameters such as group mean body weights, group mean water consumption, hematology, clinical chemistry and organ weights, Student's t-test was employed to assess differences. Levels of significance of 5, 1 and 0.1% were flagged.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations**: Since the animals were gavaged daily, it is assumed they were inspected daily for signs of toxicity and mortality, although this was not explicitly stated in the report.

   1b. **Clinical examinations:** Clinical examinations were conducted on the control group and the 10.0 mg/kg/day group at the time of neurological examinations at weeks 0, 6, and 13.

   1c. **Neurological evaluations:** The following evaluations were done on controls and high dose animals at weeks 0, 6 and 13:
   (a) segmental reflexes that included flexor, extensor, and patellar responses;
   (b) postural reactions that included righting reactions, placing reactions, extensor thrust and grip reflex;
   (c) locomotor system that included gait and muscles; and
   (d) general observation to look for any abnormality that might affect neurological behavior.

2. **Body weight:** Animals were weighed at the start of the study and weekly thereafter.

3. **Food consumption:** Food consumption per cage was determined weekly and weekly diet consumption was calculated as gm of food/rat/week.

4. **Ophthalmoscopic examination:** Before the study began and at weeks 6 and 13, the eyes of all male and female rats from the control group and the 10.0 mg/kg/day group were examined with a Keeler indirect ophthalmoscope.

5. **Hematology and clinical chemistry:** After overnight fasting, blood was collected from the orbital sinuses of 10 males and 10 females from the control group and the 10.0 mg/kg/day group during weeks 0, 6 and 12 for hematology and clinical chemistry analyses. The CHECKED (X) parameters were examined.

a. Hematology

	Hematocrit (HCT)*	X	Leukocyte differential count*
X	*Hemoglobin (HGB)**		Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
X	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

	ELECTROLYTES		OTHER
	Calcium	X	Albumin*
	Chloride		*Creatinine**
	Magnesium	X	Urea nitrogen*
	Phosphorus		Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES		Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)		*Triglycerides*
	Creatine phosphokinase	X	Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

c. **Urinalysis:** During weeks 6 and 12, individual overnight urine samples were collected from 5 males and 5 females in the control and 10.0 mg/kg/day groups. Food and water were removed from the animals during urine collection. The CHECKED (X) parameters were examined.

	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity/osmolality*	X	Bilirubin
X	pH*	X	Blood/blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Recommended for 90-day oral rodent studies

6. **Sacrifice and pathology:** All animals that died and those sacrificed on schedule by carbon dioxide asphyxiation were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. All organs and tissues other than the aorta, colon, jejunum, mammary glands, prostate, salivary glands, seminal vesicles, skeletal muscle, skin, tongue and trachea were collected and examined microscopically for animals in the control and 10.0 mg/kg/day groups. Tissues from rats in the remaining groups were not examined. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+		Parathyroid*
	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder (not rat)*		Epididymides*+		Bone (sternum and/or femur)
	Bile duct (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin*
	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*	X	Mammary gland*		
	Nose*				
	Pharynx*				
	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
\+ Organ weights required for rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Excepts for neurological effects, no signs of clinical toxicity were reported for any of the treated animals at any dose level.

2. **Mortality:** There was no dose-related increase in deaths of either male or female rats, although several rats died during the first three weeks. Their deaths were attributed to

injection of the test material and vehicle into the lungs. Rats that died during the first two weeks were replaced.

3. **Neurological evaluations:** A summary of the neurological evaluation is presented in Table 2. At week 6 it was noted that some rats of both sexes in the 10.0 mg/kg/day group were slightly hypersensitive compared with the controls. By week 13, the hypersensitivity had disappeared.

TABLE 2. Summary of selected neurological observations

Group/sex	Week	No. of rats examined	No. abnormal	Abnormalities			
				Flexor reflex	Grip reflex	Righting reflex	Hyper-sensitive
Control males	0	10	0	0	0	0	0
10 mg/kg/day males		10	0	0	0	0	0
Control females		10	0	0	0	0	0
10 mg/kg/day females		10	0	0	0	0	0
Control males	6	10	5	0	4	1	0
10 mg/kg/day males		10	9	0	3	0	9
Control females		10	3	1	2	0	1
10 mg/kg/day females		10	3	0	1	0	3
Control males	13	10	1	1	0	0	0
10 mg/kg/day males		10	1	1	0	0	0
Control females		10	2	1	1	0	0
10 mg/kg/day females		10	1	1	0	0	0

[a] Data obtained from Table 1, p 19 of MRID 00089103.

B. **BODY WEIGHT AND WEIGHT GAIN:** Group mean body weights for selected weeks and total body weight gains over the 13 weeks of treatment are shown in Table 3. In week 13, there was a statistically significant reduction in the mean weight of 10 mg/kg/day males compared to the controls. Males in the 2.5 and 10.0 mg/kg/day groups had overall weight gains that were statistically lower than controls. No treated female groups showed a significant weight reduction or decreased weight gain compared to the controls.

Recovery Period Changes. *All treatment group animals recovered weight losses during* the recovery weeks and exceeded the weight gains seen in the control animals.

TABLE 3. Selected group mean body weights and total weight gains during 90 day of treatment with RU 22974 [a]

Dose mg/kg/day	Body weight (g) ± SD[b]				Total weight Gain	
	Initial	Week 1	Week 7	Week 13	g	% of control
Male						
0	152 ± 8.7	213 ± 10	441 ± 33	540 ± 46	388	100
0.1	152 ± 7.8	214 ± 11	440 ± 35	538 ± 54	386	99.5
1	153 ± 6.9	214 ± 9	434 ± 22	517 ± 32	364	93.8
2.5	152 ± 7.7	215 ± 13	428 ± 26	509 ± 53	357*	92
10	152 ± 10	206 ± 13	421 ± 34	504 ± 46*[c]	352*	90.7
Female						
0	132 ± 8.7	168 ± 11	269 ± 24	303 ± 24	171	100
0.1	132 ± 7.6	167 ± 11	265 ± 23	299 ± 31	167	97.7
1	132 ± 11	170 ± 15	269 ± 29	302 ± 42	170	99.4
2.5	132 ± 7.9	172 ± 10	274 ± 27	310 ± 38	178	104.1
10	132 ± 9.6	172 ± 13	269 ± 25	302 ± 27	170	99.4

[a] Data obtained from Table 3a, p 21 and Appendix 4, pp 54 - 73, in the study report.
[b] SDs calculated by the contract reviewer
* Statistically different (p <0.05) from the control.
[c] p-value calculated by the reviewer

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** The authors reported the weekly group mean food consumption in a summary table but much of the data was illegible. The contract reviewer recalculated the food consumption from individual cage data in Appendix 3 of the study report. During the 90 day treatment period, food consumption was lower for all groups of treated males compared to controls. There was no evidence of a significant change in food intake among treated female groups. During the withdrawal period all treated male groups consumed more food than the controls, as did females in the 1.0, 2.5 and 10.0 mg/kg/day groups.

2. **Compound consumption:** Test material was administered by gavage.

3. **Food efficiency:** Food conversion ratios are presented in Table 4. No significant treatment-related effects on food conversion were noted during weeks 1-13.

TABLE 4. Group mean food conversion ratios at selected time intervals.					
Dose mg/kg/day	Food conversion ratios				
	Weeks 1 to 4	Weeks 5 to 8	Weeks 9 to 12	Weeks 1-13	Weeks 14 to 17[a]
Male					
0	3.5	6.6	10.8	6	11.8
0.1	3.3	7	9.8	6	11.1
1	3.4	7.1	11.6	6.2	11.1
2.5	3.4	7.1	12.1	6.2	12.3
10	3.5	7.5	11.8	6.4	11.1
Female					
0	4.9	11.3	18	9.4	21.2
0.1	5.1	11.6	16.6	9.6	23.3
1	4.9	11.4	18	9.6	14.4
2.5	4.8	10.6	20.1	9.3	24.8
10	4.9	11.5	19.7	9.6	18.2

[a] *Five rats per group. Animals were untreated during this time period.*
[b] Food Conversion Ratio=Mean g food consumed ÷ mean g body weight gained.
[c] Data obtained from Table 4, p. 23, MRID 00098103.

D. OPHTHALMOSCOPIC EXAMINATION: No significant findings were reported at weeks 6 or13 from rats receiving 10.0 mg/kg/day of the test material.

E. BLOOD ANALYSES:

1. **Hematology:** Hematological parameters for rats receiving 10.0 mg/kg/day after 6 and 12 weeks of treatment revealed no evidence of treatment-related effects. Although statistically significant effects were found, all were within the accepted historical range.

2. **Clinical chemistry:** Although sporadic statistically significant results were found, none were considered to be of toxicological significance since all were well within the accepted historical range.

F. Urinalysis: No treatment-related effects were found in 10.0 mg/kg/day male and female rats at 6 and 12 weeks.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Although there were sporadic statistically significant differences in absolute and/or relative organ weights, none were dose-related or of toxicological significance.

2. **Gross pathology:** There was no evidence of any treatment-related macroscopic changes seen in rats killed after 13 weeks of treatment or in rats killed at the end of the 4-week withdrawal period.

3. **Microscopic pathology:** Peribronchiolar lymphoid hyperplasia was seen in the lungs of all animals, both treated and controls, and was not considered treatment related. Vacuolated hepatocytes were seen in the centrilobular areas of most males examined and minimal chronic inflammatory cell infiltration was seen in small foci in the parenchyma and portal tracts in a proportion of males and females from both treated and control groups. Minimal fat deposits were seen in the periportal hepatocytes of a portion of males from both the treated and control groups and reduced glycogen was noted in many animals of both sexes from both the treated and control groups. Occasional small foci of chronic inflammatory cell infiltration were seen in the cortex of the kidneys in a portion of animals from both treated and control groups. None of these changes were considered toxicologically significant.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that the only overt reaction to treatment with RU 22974 was a slight hypersensitivity (reactivity to noise) by week 6 among some rats receiving 10.0 mg/kg/day which disappeared by week 13. Also, the body weights of males receiving 2.5 and 10.0 mg/kg/day of the test material were decreased. During the withdrawal period the rate of body weight gain among these rats was marginally higher than that of the controls.

B. **REVIEWER COMMENTS:** There were no treatment-related signs of systemic toxicity, effects on the eyes, or hematology or clinical chemistry parameters. No treatment-related histological lesions were found. Increased hypersensitivity was observed from 9 of 10 high-dose males and 3 of 10 high dose females, compared with 0/10 and 1/10 controls, respectively during week 6. Hypersensitivity disappeared in all animals by week 13, probably due to development of tolerance to the test substance. Body weight gains for the 2.5 and 10.0 mg/kg/day group males were slightly lower throughout the treatment period, being 97 and 94%, respectively, of the controls during weeks 1 to 4; 90 and 88%, respectively, during weeks 5 to 8; and 81 and 87%, respectively, during weeks 9 to 12. For the entire treatment period, the overall weight gains of the 2.5 and 10.0 mg/kg/day group males were significantly reduced to 92 and 91%. In treated female rats, there were no significant changes from the controls in weight gains.

The LOAEL for Deltamethrin in male rats was 2.5 mg/kg/day based on decreased body weight gain during the 90 day treatment period. The LOAEL for female rats was not established. The NOAEL is 1.0 mg/kg/day for male rats and 10.0 mg/kg/day for females.

This 90-day oral toxicity study in the rat is **Unacceptable/Nonguideline**. It was conducted prior to the establishment of EPA guidelines, but does not meet the intent.

C. **STUDY DEFICIENCIES:** Major deficiencies: there was no dose selection rationale provided. The dose levels selected did not produce sufficient toxicity, other than weight loss, to effectively assess the toxicity of RU 22974. There was no information given on the stability or purity of the test material.

Minor deficiencies: There were no signed and dated GLP, Quality Assurance, and Data Confidentiality statements provided because the report was written in 1977, before current EPA requirements were established. The ages of the animals at the start of the study and the air change frequency in the animal room were not provided.

DATA EVALUATION RECORD

DELTAMETHRIN/097805
(RU 22974)

STUDY TYPE: SUBCHRONIC ORAL TOXICITY STUDY- BEAGLE DOG
[870.3150 (§82-1)]
MRID 00098104

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 02-20

Primary Reviewer: Thomas C. Marshall, Ph.D., D.A.B.T.	Signature:	Robert H. Ross for TC Marshall
	Date:	APR 17 2002
Secondary Reviewer: H. Tim Borges, Ph.D., D.A.B.T.	Signature:	HT Borges
	Date:	APR 17 2002
Robert H. Ross, M.S.,Group Leader	Signature:	Robert H. Ross
	Date:	APR 17 2002
Quality Assurance: Lee Ann Wilson, M.A.	Signature:	L. A. Wilson
	Date:	APR 17 2002

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

Oak Ridge National Laboratory, managed and operated by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

EPA Reviewer: Stanley Gross, Ph.D.
Registration Action Branch 3,
Health Effects Division (7509C)

Signature: Stanley B Gross
Date 6/20/2002

EPA Secondary Reviewer: Stephen Dapson, PhD
Senior Scientist, Registration Action Branch 3,
Health Effects Division (7509C)

Signature Stephen C. Dapson
Date 06/24/2002

EPA Work Assignment Manager: Sanyvette Williams-Foy
Registration Action Branch 2,
Health Effects Division (7509C)

Signature:
Date 9/24/02

DATA EVALUATION RECORD
TXR # 0050424

STUDY TYPE: 90 Day Subchronic Oral Toxicity Study (Capsule) with 20 week Recovery Period. [OPPTS 870.3150 (§82-1b)] (Dog); OECD 409.

PC CODE: 097805

DP BARCODE: D277538
SUBMISSION NO.: S541415

TEST MATERIAL (PURITY): RU 22974 (Purity not reported)

SYNONYMS: Deltamethrin; Decamethrin

CITATION: Chesterman, H., Heywood, R., Perkin, C.J., et. al. (1977) Oral toxicity study in Beagle dogs. Huntingdon Research Centre. (Report Number RSL 253/77251), June 9, 1977. MRID 00098104. Unpublished.

SPONSOR: Procida, 5-7 rue Beilini, 92Puteaux 92806, France.

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID00098104), deltamethrin (purity not reported, Lot #17) was dissolved in polyethylene glycol 200 and administered by capsules daily to beagle dogs (3/sex/group) at 0, 0.1, 1.0, 2.5, and 10 mg/kg body wt/day. Additional dogs (2/sex/group) were included in the 1.0, 2.5. and 10 mg/kg main treatment groups which were observed for an additional 20 weeks after the 90 day treatment period as a recovery study group

All animals were observed daily for toxicity throughout the treatment and recovery periods. Body weights, food consumption and water consumption were measured weekly. Neurological examinations were performed prior to treatment, during weeks 6 and 12 (main treatment groups) and during weeks 5, 8, 15 and 18 of the recovery period. The neurological examinations consisted of the assessments of pupillary reflex, blink reflex, corneal reflex, gag reflex, flexor

reflex, crossed extensor reflex, extensor reflex, patellar reflex, tonic neck reflex, extensor postural thrust, righting reactions, placing reactions, and hopping reactions. EEGs were performed on each animal initially and during treatment week 12 and during post treatment weeks 5 and 17. Ophthalmological examinations were done initially, during weeks 5 and 12 (main treatment groups) and during 5 and 18 weeks (recovery groups). Hematology, clinical chemistry and urinalyses were carried out at the start of treatment, during treatment weeks 5 and 12 and post treatment weeks 5 and 16. Gross pathology, organ weights and histopathology were performed on the main treatment groups during week 13. Necropsy of the recovery animals after 20 weeks post-treatment was limited to observations on the nervous and muscular systems.

There were no mortality or treatment-related effects on clinical chemistry, hematology, urinalysis or ophthalmology. Mild to moderate CNS toxicity was observed 1 to 7 hours after dosing in both male and female dogs of the two highest dose groups. These effects declined in severity over the 13-week study period. Clinical signs of toxicity seen only in the high dose group (10 mg/kg) were excessive salivation, unsteadiness, tremors, and jerking movements. Pupil dilation was observed sporadically in the 2.5 mg/kg/day group, but more routinely at 10 mg/kg/day groups. Male and female dogs receiving 2.5 mg/kg/day and 10 mg/kg/day test material had significantly increased incidences of vomiting and diarrhea which decreased after first two weeks of treatment. Significant decreases in body weight relative to controls were observed in the female dogs at the three highest doses. Food consumption was significantly decreased in the high dose males and females during the first two weeks on treatment but not thereafter. Food consumption was normal during the first two weeks of dosing bu decreased for males and females in the 1 mg/kg/day during the 3-13 week periods.

Results of the neurology tests were mixed relative to dose-response characteristics. After 5 weeks of treatment, abnormalities in patellar reflex (either exaggeration or depression) were observed from 6/10 dogs in the 10 mg/kg, 5/10 from the 2.5 mg/kg/day group, 1/10 from the 1 mg/kg/day group, and from 1/6 control dogs after 5 weeks of treatment. After 12 weeks of treatment, abnormalities were also noted for 2/10 dogs in 10 mg/kg/day group, 7/10 dogs from the 2.5 mg/kg/day group, 3/10 dogs from the 1 mg/kg/day group, and 1/6 control dogs. By the end of the 20-week recovery period, 2/4 dogs from the 1 mg/kg/day group and 1/4 dogs from the 2.5 mg/kg/day were still showing abnormalities in this reflex, while none of the dogs at 10 mg/kg/day showed abnormalities after 8 weeks of recovery. One of the four high dose dogs (10 mg/kg/day) observed for 20 weeks after the treatment period showed evidence of sustained neurological effects. No control dogs were available for comparisons during the recovery period. No other abnormal findings in the neurology testing were remarkable due to their occurrence in controls animals, their sporadic nature or the lack of dose-response presentation.

EEG recordings made after 12 weeks of dosing were normal for control dogs, but showed abnormalities in the occipital region of one female dog in the 2.5 mg/kg/day dose group, and in one female and two males at the 10 mg/kg/day dose level. No histopathologic correlates for abnormal EEG recordings were found. After 5 weeks of recovery 1/4 dogs (a female) in the 10 mg/kg/day dose group was still exhibiting EEG abnormalities which persisted into the last EEG testing conducted during Week 17 of the 20-week recovery period. All other dogs held for the recovery period showed normal EEGs at both post-treatment recording intervals.

No treatment-related effects were found for the main treatment groups or for the recovery groups at necropsy or during histopathological assessment.

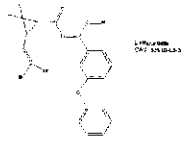
The LOAEL for RU 22974 is 2.5 mg/kg/day based on CNS effects, vomiting, diarrhea, and decreased body weight gains of treated male and female dogs. The NOAEL is 1.0 mg/kg/-day.

This 90-day oral toxicity study in the dog is **Unacceptable/Nonguideline** and does not satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs. The study was conducted prior to establishment of guideline requirements and GLP procedures, but meets the intent. The purity of the test agent was not provided. The numbers of animals used were too few and the number of the required observations for subchronic testing were lacking.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided.

I. MATERIALS AND METHODS:

A. MATERIALS:



1. Test material: RU 22974

Description:	White powder
Lot/Batch #:	Lot 17
Purity:	Not reported
Compound Stability:	Not reported
CAS # if TGAI:	52918-63-5

2. Vehicle and/or positive control: Polyethylene glycol 200

3. Test animals:

Species:	Dog
Strain:	Beagle
Age/weight at study initiation:	~21 weeks of age (range = 17-37); males: 7.5 – 10.3 kg; females: 6.1 – 9.5 kg
Source:	E. G. Crowley, Colwall, UK; Olac (Western) Ltd., Dyfed, Wales
Housing:	Kennels
Diet:	Spretts Dog Diet, 400 g/day *ad libitum*; 200 mL milk/day on weekdays
Water:	*ad libitum*
Environmental Conditions	
Temperature:	Not reported
Humidity:	Not reported
Air changes:	Not reported
Photoperiod:	Not reported
Acclimation period:	Nine weeks

B. STUDY DESIGN:

n9

1. **In life dates** - Start: 07/15/76 End: 10/13/76 (Recovery period ended 03/02/77)

2. **Animal assignment**: No approach was stated on how animals were assigned to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Dose to animal (mg/kg/day)	# Male	# Female
Control	0	3	3
Low	0.1	3	3
Mid low	1	5*	5*
Mid high	2.5	5*	5*
High	10	5*	5*

*Two dogs observed for 20 weeks after completing the 13-week dosing regimen.

3. **Dose selection rationale:** The dose selection rationale was not given.

4. **Dose preparation and analysis:** The appropriate amount of the test material for each dog was determined by body weight each week. Dosing solutions were prepared twice weekly. The appropriate amount of test material was dissolved in PEG 200 in a volume equal to 0.2 mL/kg body weight and transferred to one or more gelatin capsules daily for administration. Control animals received capsules containing 0.2 mL PEG/kg body weight. No stability analysis of the test material was reported.

Results:

Homogeneity analysis: Not applicable
Stability analysis: Not reported
Concentration analysis: Not reported

5. **Statistics:** Body weight, body weight change, food consumption, and organ weights were evaluated using analysis of variance (ANOVA) followed by Student's T Test. Differences among groups were identified using the Least Significant Difference test.

C. **METHODS:**

1. **Observations:**

1a. **Cageside observations**: Animals were inspected daily for signs of toxicity and mortality.

1b. **Clinical examinations:** Clinical examinations were conducted prior to initiation of treatment and daily thereafter. Extensive neurological examinations consisting of pupillary reflex, blink reflex, corneal reflex, gag reflex, flexor reflex, crossed extensor reflex, extensor reflex, patellar reflex, tonic neck reflex, extensor postural thrust, righting reactions, placing reactions, and hopping reaction were conducted prior to dosing, after 6 and 12 weeks of dosing, and after 5, 8, 12, 15, and 18 weeks of recovery. Electroencephalograms (EEG) were recorded on all animals prior to dosing, after 12 weeks of dosing, and at 5 and 17 weeks during the recovery period.

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2. **Body weight:** Animals were weighed weekly.

3. **Food and water consumption and compound intake:** Weekly food consumption was recorded for each animal as the quantity of food remaining of the 2800g offered. Gelatin capsules were prepared with the appropriate amount of test substance for each animal. Food efficiency was not estimated.

   Individual water consumption was measured daily and averaged over the week by group.

4. **Ophthalmoscopic examination:** Ophthalmoscopic examinations were performed on all dogs before treatment, after 5 and 12 weeks of dosing, and after 5 and 18 weeks of recovery.

5. **Hematology and clinical chemistry:** Blood was collected prior to study initiation, after 5 and 12 weeks of dosing, and after 5 and 16 weeks of recovery for hematology and clinical chemistry from all surviving animals. Animals were deprived of food and water overnight prior to sample collection. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*	X	Erythrocyte sedimentation rate (ESR)
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350

b. Clinical chemistry

	ELECTROLYTES		OTHER
	Calcium*		Albumin*
	Chloride*		Creatinine*
	Magnesium	X	Urea nitrogen*
	Phosphorus*		Total Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase	X	Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (also SGPT)*		
X	Aspartate aminotransferase (also SGOT)*		
	Sorbitol dehydrogenase*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

6. **Urinalysis**: Urine was collected overnight from fasted animals prior to study initiation, after 5 and 12 weeks of dosing, and after 5 and 16 weeks of recovery.

X	Appearance*	X	Glucose*
	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen
X	Reducing substances	X	Hemoglobin

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

7. **Sacrifice and pathology**: All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed. All collected tissues were examined microscopically. The surviving animals were euthanized by IV sodium pentobarbital anesthesia followed by exsanquination through the carotid artery.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	XX	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+		Parathyroid*+
	Rectum*	X	Urinary bladder*	XX	Thyroid*+
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder*+		Epididymides*+		Bone (sternum and/or femur)
XX	Pancreas*	XX	Prostate*	X	Skeletal muscle
	RESPIRATORY	XX	Ovaries*+	X	Skin*
X	Trachea*	XX	Uterus*+		All gross lesions and masses*
XX	Lung*	X	Mammary gland*		
	Nose*				
	Pharynx*				
	Larynx*				

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350
+ Organ weight required for non-rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. Mortality: All animals survived to termination.

2.. Clinical signs of toxicity:

Mild to moderate CNS toxicity was observed 1 to 7 hours after dosing in both male and female dogs of the two highest dose groups. These effects declined in severity over the 13-week study period. Clinical signs of toxicity seen only in the high dose group (10 mg/kg) were excessive salivation, unsteadiness, tremors, and jerking movements. Pupil dilation was observed sporadically in the 2.5 mg/kg/day group, but more routinely at 10 mg/kg/day.

Vomiting and diarrhea were common and their incidence was dose-related in all treatment groups (Table 2). The incidence of diarrhea decreased after two weeks of treatment except for the top two doses which persisted. to occasional incidence without relation to previous dosage levels. There were no clinical signs of toxicity in the lower dose groups.

TABLE 2. Incidence of vomiting and diarrhea of male and female dogs given RU22974 for 13 weeks

Findings	Dose (mg/kg/day)				
	0 (6 dogs)	0.1 (6 dogs)	1.0 (10 dogs)	2.5 (10 dogs)	10.0 (10 dogs)
Vomiting	2	3	8	11	47
Diarrhea	35	42	82	197	292

Data from Table 4, pp 393-394 and Table 6a pages 399-400 of MRID 00098104

3. Neurological Assessment.

Results of the neurology tests were mixed relative to dose-response characteristics. Abnormalities in patellar reflex (either exaggeration or depression) were observed from 6/10 dogs in the 10 mg/kg, 5/10 from the 2.5 mg/kg/day group, 1/10 from the 1 mg/kg/day group, and from 1/6 control dogs after 5 weeks of treatment. After 12 weeks of treatment, however, abnormalities were noted from 2/10 dogs in 10 mg/kg/day group, 7/10 dogs from the 2.5 mg/kg/day group, 3/10 dogs from the 1 mg/kg/day group, and 1/6 control dogs. By the end of the 20-week recovery period, 2/4 dogs from the 1 mg/kg/day group and 1/4 dogs from the 2.5 mg/kg/day were still showing abnormalities in this reflex, while none of the dogs at 10 mg/kg/day showed abnormalities after 8 weeks of recovery. No control dogs were available for comparisons during the recovery period. No other abnormal findings in the neurology testing were remarkable due to their occurrence in controls or their sporadic nature and lack of dose-response presentation.

EEG recordings made after 12 weeks of dosing were normal for control dogs, but showed abnormalities in the occipital region of one female dog in the 2.5 mg/kg/day dose group, and in one female and two males at the 10 mg/kg/day dose level. No histopathologic correlates were found. After 5 weeks of recovery 1/4 dogs (a female) in the 10 mg/kg/day dose group was still exhibiting EEG abnormalities which persisted into the last EEG testing conducted during Week

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17 of the 20-week recovery period. All other dogs held for the recovery period showed normal EEGs at both post-treatment recording intervals.

B. BODY WEIGHT AND WEIGHT GAIN: Selected body weight and body weight gain data are given in Table 3. Females at the three highest dose levels had significantly decreased body weight gains ($p<0.01$) relative to controls. Body weight gains were decreased in male dogs as well, but not to the extent of female dogs.

TABLE 3. Average body weights and body weight gains of dogs during 90 days of treatment with RU 22974[a]					
Dose rate (mg/kg/day)	Body weights (g±SD)**			Total weight gain (Weeks 1-13)	
	Initial	Week 2	Week 13	g	% of control
Male					
0	8700 (1400)	9500 (1500)	12300 (1200)	3567	100
0.1	9000 (1000)	9400 (900)	10500 (1500)	1533*	43
1	8900 (1000)	9500 (1100)	10900 (1800)	2040	57
2.5	8700 (800)	9200 (1100)	10900 (1800)	2180	61
10	8700 (500)	8700 (700)	11100 (1600)	2400	67
Female					
0	7100 (2000)	7900 (1900)	10800 (1800)	3667	100
0.1	7300 (800)	7900 (900)	9400 (1200)	2133	58
1	7400 (900)	7500 (1100)	8000 (1100)	580**	16
2.5	7200 (700)	7700 (600)	8800 (1100)	1520**	41
10	7600 (800)	7700 (1200)	9000 (1800)	1380**	38

[a] Data obtained from pages 404 - 405 of MRID 00098104
* Statistically different (p <0.05) from the control; ** Statistically different (p <0.01) from the control.
** Recalculated by contract reviewer.

C. FOOD CONSUMPTION AND COMPOUND INTAKE :

1. **Food consumption:** Food consumption was recorded weekly as the quantity of food remaining of the 2800 g/week offered. Results are presented in Table 4. Decreases in food consumption relative to controls were noted in the combined data for high-dose male and female dogs after the first 2 weeks of treatment (p<0.01). Overall (weeks 1 - 13), mean food consumption of all treated groups was lower than the controls, but none were statistically different. However, it is noteworthy that the greatest reductions in food consumption were from female dogs at the three highest dose levels, all of which showed statistically lower body weight gains when compared to controls (Tables 3 and 4).

2. **Compound consumption:** Not applicable

3. **Food efficiency:** Not applicable

TABLE 4. Food consumption (total g remaining of 2800g offered/dog/week) of dogs treated with RU22974 for 13 weeks										
Weeks	Exposure concentration (mg/kg/day)									
	Males					Females				
	0	0.1	1	2.5	10	0	0.1	1	2.5	10
1-2	217	1300	716	604	2040**	920	734	1926	516	1920**
3-13	107	5213	3686*	2404	3378	2413	5173	7814*	6830	6774
1-13	333	6513	4402	3008	5418	3333	5917	9740	8346	8694

Data obtained from pages 408 and Appendix 1, pp. 454 - 456 of MRID 00098104.
* Combined male and female data statistically different (p <0.05) from control.
** Combined male and female data statistically different (p <0.01) from control.

D. **OPHTHALMOSCOPIC EXAMINATION:** Ophthalmological examination data were not provided but the study authors reported no treatment-related changes were found.

E. **BLOOD ANALYSES:**

1. **Hematology:** No consistent, notable, or dose-related variations in hematologic parameters between the control and treated groups were found.

2. **Clinical chemistry:** There were no consistent, notable, or dose-related variations in the measured clinical chemistry values between the control and treated groups.

F. **URINALYSIS:** No dose- or treatment-related effects were found.

G. **SACRIFICE AND PATHOLOGY:**

1. **Organ weight:** Organ weights for control and treatment groups were within normal limits.

2. **Gross pathology:** No gross findings were attributed to treatment.

3. **Microscopic pathology:** No treatment-related microscopic findings were found. In additional studies, nerve tissue was specifically examined but no treatment-related damage was found.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The authors concluded that RU 22974 induced moderate CNS effects at 10 mg/kg/day and mild effects at 2.5 mg/kg/day. These decreased as the study progressed and ceased after completion of the treatment regimen. The three highest doses caused a significant decrease in body weight gain for female dogs compared to controls. Neurology tests and EEGs showed some abnormalities at the two highest dose levels, but these reversed during the 20-week recovery period with the exception of one female dog from the 10 mg/kg/day dose group. Neither a LOAEL nor a NOAEL were specified by the study authors.

B. **REVIEWER COMMENTS:** Moderate signs of central nervous system (CNS) toxicity (unsteady gait, body tremors, jerking movements, excessive salivation, and pupillary dilation) were observed from all high dose dogs. Clinical signs of toxicity in dogs of the 2.5 mg/kg/day group were limited to pupillary dilation. These effects decreased in severity over the course of the study in both treatment groups. There was no mortality or treatment-related effects on clinical chemistry, hematology of ophthalmology. No treatment-related effects were noted at necropsy or microscopically. Significant decreases in body weight relative to controls were observed from female dogs at the three highest dose levels. Both depression and exaggeration of the patellar reflex and some abnormalities in EEGs (occipital area) were found in dogs administered 2.5 mg/kg/day and 10 mg/kg/day test material. In addition, male and female dogs receiving 2.5 mg/kg/day and 10 mg/kg/day had significantly increased incidences of vomiting and diarrhea.

For the most part this reviewer agrees with the study report authors. Data obtained during the recovery period are of limited usefulness given the lack of control dogs for comparisons.

The LOAEL for RU 22974 is 2.5 mg/kg/day based on CNS effects, vomiting, diarrhea, and decreased body weight gains of treated male and female dogs. The NOAEL is 1.0 mg/kg/day.

This 90-day oral toxicity study in the dog is Unacceptable/Nonguideline. It was conducted prior to the establishment of EPA guidelines and does not satisfy OPPTS 870.3150; OECD 409, but does meet the intent..

C. **STUDY DEFICIENCIES:** Analyses of test article purity and stability were not given for this nonguideline study. The number of dogs per test group was below the minimum specified for a guideline study. Not all the guideline required hematology and clinical chemistry testing were done nor were all the guideline required tissues sampled and subjected to histology examination. No GLP statement or indication of quality control procedures were provided. Generally the study was poorly reported with information hard to find either because the print was light, changes in procedures were made ophthalmology examinations replace by light responses) and lack of detailed data reporting.

EPA Reviewer: Nancy McCarroll
Toxicology Branch, Health Effects Division (7509C)

EPA Secondary Reviewer: Alberto Protzel, PhD
Toxicology Branch Health Effects Division (7509C)

Signature: Nancy McCarroll
Date 10/02/02

Signature: Alberto Protzel
Date 10/02/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 010544 for previous review.

STUDY TYPE: 21-Day Dermal Toxicity Study - Rats; OPPTS 870.3200 [§82-2]; OECD 410.

PC CODE: 097805

DP BARCODE: D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.6% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Siglin, J.C. (1993) 21-Day Dermal Toxicity Study in Rats with Deltamethrin Technical - Springborn Laboratories, Spencerville, Ohio; Study No.: 3207.28; April 9, 1993. MRID 42773901. Unpublished.

SPONSOR: Hoechst-Russell Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 42773901), groups of five male and five female Sprague Dawley Crl:CD BR VAF/Plus rats received dermal applications of deltamethrin (99.6% a.i., Batch/Lot# 2NO398B2) in polyethlene glycol 400 at 0, 100, 300 or 1000 mg/kg/day (limit dose). On the day prior to application, a section of the dorsal-lumbar region was clipped and the test material was applied at a rate of 6 mL/kg. Applied doses were kept in contact with the skin for ≈6 hours using occlusive dressings secured with tape. At the end of the contact period, the dressings were removed and the area wiped with gauze and water. Animals were observed twice daily for death or clinical signs; body weight and food consumption were recorded weekly. At termination, rats were sacrificed and samples were taken for hematology and clinical chemistry; necropsies were performed; selected organ weights were determined and selected tissue were examined histologically.

There were no treatment- related deaths, clinical signs of toxicity, gross pathology or changes in hematology, clinical chemistry or organ weights. Body weight gain differences, seen only in the males, were considered minimal and of no toxicological concern. Dermal irritation was noted at all dose levels at the site of application and was characterized as eschar and eschar exfoliation at the low dose and as slight erythema, slight desquamation and thickening of the skin at higher doses. Microscopically, several conditions of the skin (abscesses, chronic dermatitis, exudate,

mononuclear cell foci in the dermis, epidermal necrosis, parakeratosis, ulcers and epidermal vesiculation) were noted in the treated animals that were not found in the controls. The lesions were localized primarily on the lateral side (away from the center of test material application and were possibly due to scratching) of the test site. None of these showed a dose response with respect to frequency or intensity, but their absence in the control group implied that they were related to treatment with deltamethrin.

At the Hazard Identification Assessment Review Committee (HIARC) meeting held on August 8, 2002, the study was revisited and it was determined that there were no treatment-related deaths, clinical signs of toxicity, gross pathology, or changes in hematology, clinical chemistry, or organ weights noted at any level. The NOAEL for males and females is >1000 mg/kg/day (limit dose). Signs of local dermal irritation at the site of application were noted for all deltamethrin dose levels. The localization of these lesions suggested that they were self-induced by the animals through scratching. This response is typical of the "pyrethroid reaction", also know as paresthesia which is induced by Type II pyrethroids and considered to be a localized rather than a systemic effect.

This study was classified as **acceptable/Guideline**. Several organs were, however, not assessed for weight as recommended in the series 82-2 guidelines. Histopathology was limited to liver, kidneys, and skin only. These deviations did not alter the outcome of the study. No other data were required.

DATA EVALUATION RECORD

DELTAMETHRIN/ 097805
(RU 22974)

STUDY TYPE: 14-DAY INHALATION TOXICITY STUDY IN RATS (NONGUIDELINE)
MRID 00098089

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 02-20

Primary Reviewer: Thomas C. Marshall, Ph.D., D.A.B.T.	Signature: Robert H. Ross for T.C. Marshall Date: APR 17 2002
Secondary Reviewers: H. Tim Borges, Ph.D., D.A.B.T.	Signature: HT Borges Date: APR 17 2002
Robert H. Ross, M.S.,Group Leader	Signature: Robert H. Ross Date: APR 17 2002
Quality Assurance: Lee Ann Wilson, M.A.	Signature: L. A. Wilson Date: APR 17 2002

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

Oak Ridge National Laboratory, managed and operated by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

EPA Reviewer: Stanley Gross, Ph.D.
Registration Action Branch 3,
Health Effects Division (7509C)

Signature: Stanley B Gross
Date 6/25/2002

EPA Secondary Reviewer: Stephen Dapson, PhD
Senior Scientist, Registration Action Branch 3,
Health Effects Division (7509C)

Signature Stephen C. Dapson
Date 06/27/2002

EPA Work Assignment Manager: Sanyvette Williams-Foy
Registration Action Branch 2,
Health Effects Division (7509C)

Signature:
Date 6/24/02

DATA EVALUATION RECORD
TXR#: 0050424

STUDY TYPE: 3 Week (14 exposure) inhalation toxicity study in rats (nonguideline)

PC CODE: 097805
TXR#: 0050424

DP BARCODE: D277538
SUBMISSION NO.: S541415

TEST MATERIAL (PURITY): RU 22974 (purity not reported)

SYNONYMS: *Deltamethrin; Decis; Decamethrin*

CITATION: Coombs, D.W., Clark, G.C., Street, A.E., et. al. (1978) Inhalation toxicity study in rats, 14 x 6 hour exposures, 5 days per week over 3 weeks. Huntingdon Research Centre, Huntingdon, England. (Report Number RSL 318/78638), October 19, 1978. MRID 00098089. Unpublished

SPONSOR: Centre de Recherches Roussel Uclaf, Dept. Toxicology, 102, Route de Naisy, BP No. 9, 93230, Romainville, France.

EXECUTIVE SUMMARY: In a 21 day inhalation toxicity study (MRID 00098089), rats of the CD strain (8/sex/group) were exposed in whole body exposure chambers to deltamethrin [RU 22974 (purity not reported)] at concentrations of 0, 3.0, 9.6, and 56.3 mg/m^3. The exposures were for six hours per day for five days a week for a total of 14 exposures. Clinical observations, body weights, food and water consumption were made daily. Selected hematology, clinical chemistry and urinalyses were carried out on exposure day 19. Complete gross necropsy and organ weights were carried out on day 22. Histopathology was limited to trachea, lungs, liver and nasal turbinates and other organs with gross pathology in the control and high dose groups.

No rats died as a result of the exposures. Toxic signs were limited to skin irritation (washing and scratching of the face) and nervous system stimulation were noted in the high-dose groups were seen in all treated animals. Nervous system effects included hunched posture, peripheral

vasodilation, minimal aggressive behavior, hypersensitivity to noise. Individual observational data were not provided.

Total weight gain of male rats in the mid- and high-dose groups was decreased 14-24% for male rats and 12-14% for female rats. The serum sodium of both male and female rats was increased in a dose-related manner, however the increase in males was not biologically significant while that of females borders on significance. The toxicological significance of the increased sodium is unclear as no changes were found with potassium or calcium and serum chloride and CO_2 analyses were not done. No histological correlates were found in the kidney. Gross findings were limited to scarring of the ears (presumed related to irritative properties of the test material). Other than scarred ears for high-dose male and female rats, no macro- or microscopic lesions were found in any of the examined organs and tissues.

The LOAEL for RU 22974 is 9.6 mg/m^3 based on clinical signs of irritative effects during exposure and on the >10% decreased weight gain of male and female rats during the study. The NOAEL is 3.0 mg/m^3.

This 21-day inhalation toxicity study in the rat is **Unacceptable/Nonguideline** not usable for inhalation risk. Deltamethrin was identified as a significant irritant yet there were no toxic effects seen in the pulmonary system. The lack of pulmonary adverse effects may be due to inadequate distribution of the deltamethrin aerosol within the chamber and to the fact that the particle sizes were too large to be inhaled by the test animals. Although the LOAEL of 9.6 mg/m^3 reflects severe toxicity, deltamethrin may be even more highly toxic if the testing was carried out using more current testing requirements.

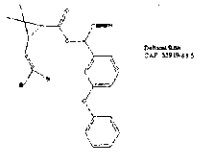
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: RU 22974
Supplied by Registrant

Description:	White powder, Labeled Caution Irritant
Lot/Batch #:	6E 0861 Lot 22
Purity:	Not reported
Compound Stability:	Not reported
CAS # if TGAI:	52918-63-5



2. Vehicle and/or positive control: None

3. **Test animals:**

Species:	Rat
Strain:	CD
Age/weight at study initiation:	7 Weeks/ males: approx. 212g; females: approx. 160g
Source:	Charles River UK, Kent, England
Housing:	Galvanized wire mesh
Diet:	Spratts Lab Diet 1, Barking, Essex, *ad libitum* (except during exposure)
Water:	Tap water, *ad libitum*
Environmental Conditions:	
Temperature:	21-29°C during exposure; 22-24°C in holding room
Humidity:	15-99% during exposure; 36-70% in holding room
Air changes:	11.5 volume changes/hr
Photoperiod:	Not reported
Acclimation period:	5 days

B. STUDY DESIGN:

1. **In life dates:** - Start: February 20, 1978 End: March 10, 1978

2. **Animal assignment:** Animals were assigned randomly by weight to the test groups noted in Table 1.

TABLE 1: Study design[a]

Test group	Nominal conc. (mg/m³)	Analytical conc. (mg/m³)	Particle size[b] µm	Rats/sex
Control (AIR??)	0	0	0	8
Low (LCT)	9.8	3.0 ± 1.6	87.1% <5.5	8
Mid (MCT)	18.0	9.6 ± 4.6	86.4% <5.5	8
High (HCT)	117.0	56.3 ± 16.1	87.2% <5.5	8

[a] Exposures 5 days/week for 14 exposures
[b] ***MMAD and GSD were not reported***

3. **Dose selection rationale:** The exposure concentrations were based on the results of an acute inhalation toxicity study (HRC Report RSL 310/78453) that established an LC_{50} of 600 mg/m³. The lowest concentration (49 mg/m³) resulted in signs of irritation, such as ptyalism, but no mortalities during the 6-hour exposure. The exposure concentrations were selected for the 14-day repeated exposure using 50 mg/m³ as the high dose and the concentration intervals of 10 mg/m³ and 1 mg/m³ determined by the limitations of the Wright dust generator.

4. **Generation of the test atmosphere/chamber description:** The exposure atmospheres of RU 22974 were generated by a Wright Dust generator. The generator consisted of a canister into which powder was packed and a scraper head that removed the powder at a preset rate. Whole body exposure chambers (130 L volume) constructed of perspex and fitted with a pyramidal-shaped top were used to expose rats (20 rats capacity per chamber). This chamber was an unconventionally shaped chamber in which the aerosol generated in the Wright dust feeder entered the center bottom of the chamber and somehow exited through

openings at the bottom perimeter (Fig. 1, page 51 of the study report). No analyses to demonstrate an adequate distribution throughout the chamber were provided in the report. The temperature and humidity measurements were taking at the apex of the chamber high above the animal area.

Test atmosphere concentration: The atmospheric concentrations of RU 22974 were determined twice per daily 6-hour exposure period by sampling the air and collecting the dust on filter paper. The filter paper was soaked in methanol and the concentration of RU 22974 was determined spectrophotometrically. Results are in Table 1 above. Time to equilibrium was not reported.

The site of the sampling port for aerosol samples was above the center of the chamber just above the intake flow of the aerosol from the Wright dust feeder rather than inside of the animals breathing zone.

Particle size determination: The particle sizes were determined using an Anderson Impactor with a series of 4 metal impaction stages and a back-up glass fiber filter. Results are in Table 1 above.

The site of the sampling port for aerosol samples was in the center just above the intake flow of the aerosol from the Wright dust feeder rather than inside of the animals breathing zone.

5. **Statistics:** Body weight, food and water consumption, hematology data, clinical chemistry data, and organ weights were evaluated statistically using analysis of variance (ANOVA) followed by Student's T Test. Williams test was done on selected data showing separation from control values.

C. METHODS:

1. Observations:

Cageside observations: Animals were inspected daily for signs of toxicity and mortality prior to exposure, every 30 minutes during exposure, and immediately following completion of each exposure period.

2. **Body weight:** Animals were weighed daily.

3. **Food and water consumption:** Food and water consumption for each cage of animals was determined daily and the mean daily diet consumption was calculated as g food/group/day.

4. **Ophthalmoscopic examination:** No ophthalmology examinations were reported.

5. **Hematology & Clinical Chemistry:** Blood was collected after overnight fasting from 5 animals/sex/group on Day 19 of exposure by puncture of the orbital sinus with a glass

pipette while the rats were under ether anesthesia. The CHECKED (X) parameters were examined.

a. **Hematology**

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements		Erythrocyte sedimentation rate (ESR)
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

b. **Clinical chemistry**

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
	Chloride	X	Creatinine
	Magnesium	X	Urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium		Globulins
X	Sodium	X	Glucose
	ENZYMES (more than 2 hepatic enzymes eg.,)		Total bilirubin
X	Alkaline phosphatase	X	Total serum protein (TP)
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)		
	Aspartate aminotransferase (AST/also SGOT)		
	Sorbitol dehydrogenase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

6. **Urinalysis:** Urine was collected after overnight fasting from 5 animals/sex/group on Day 19 of exposure. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity / osmolality	X	Bile pigments
X	pH	X	Blood / blood cells
X	Sediment (microscopic)	X	Total reducing substances
X	Protein	X	Urobilinogen

7. **Sacrifice and pathology:** All animals that died and those sacrificed on schedule were subjected to a gross pathology examination and the CHECKED (X) tissues were collected for possible histological examination. Microscopic examinations were conducted on all

collected tissues only in the control and high-dose groups. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain
X	Salivary glands*	XX	Heart	X	Peripheral nerve
	Esophagus		Bone marrow	X	Spinal cord
	Stomach	X	Lymph nodes	XX	Pituitary
X	Duodenum	XX	Spleen	X	Eyes (optic nerve)
	Jejunum	X	Thymus*		GLANDULAR
X	Ileum			XX	Adrenal gland
X	Cecum		UROGENITAL		Lacrimal gland
	Colon	XX	Kidneys	XX	Parathyroid
	Rectum	X	Urinary bladder	XX	Thyroid
XX	Liver	XX	Testes		OTHER
	Gall bladder (not rat)	XX	Epididymides		Bone (sternum and/or femur)
	Bile duct (rat)	XX	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin*
	RESPIRATORY	XX	Ovaries*	X	All gross lesions and masses
X	Trachea	XX	Uterus*		
X	Lung		Mammary gland		
	Nose				
	Pharynx				
	Larynx				

* Preserved but not processed further.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Signs of nervous system stimulation and/or sensory irritation (washing and scratching of the face above the incidence in control rats) were noted in all dosed groups during exposure, however a reporting of the incidence of these effects was not found in the study report. The study authors reported one rat in the low dose group displayed ptyalism, the incidence of which increased with the increasing RU 22974 atmospheric concentration. The rats exposed to the highest level reacted by walking with an arched back. Other signs noted in the high dose group and occasionally in the mid dose group included hunched posture, peripheral vasodilation, minimal aggressive behavior, hypersensitivity to noise, and scarring of the ears (presumably related to excessive scratching). Rats in all dose groups were normal between exposure periods.

2. **Mortality:** No rats died as a result of the exposure.

B. BODY WEIGHT AND WEIGHT GAIN:

A statistically significant dose-related reduction of body weight and weight gain was observed for all male treated groups (Table 2). The female rats also showed evidence of reduced body weight and weight gain, although the decreases were not statistically significant.

TABLE 2. Average body weights and body weight gains during 14 days of treatment over a period of 3 weeks.				
Analytical concentration (mg/m^3)	Body weights (g) ± SD[a]		Total weight gain	
	Day 0	Day 22	g	% of control
Male				
0.0	215 ± 11.7	363 ± 16.2	148	100
3.0	210 ± 8.0	344 ± 20.6	134	91*
9.6	212 ± 6.1	340 ± 17.2	128	86**
56.3	215 ± 6.7	328 ± 22.3[b]	113	76**
Female				
0.0	161 ± 8.6	237 ± 23.6	76	100
3.0	159 ± 5.7	233 ± 8.0	74	97
9.6	158 ± 5.1	225 ± 9.9	67	88
56.3	160 ± 6.8	225 ± 19.9	65	86

Data obtained from Table 3, page 29 and pages 39-45 of MRID 00098089.
[a]Calculated by reviewer
[b] $p \leq 0.05$ calculated by reviewer
* $p < 0.05$ for days 5-22
** $p < 0.01$ for days 5-22

C. FOOD CONSUMPTION:

1. **Food consumption:** The study authors reported that rats dosed with RU 22974 consumed less food than controls, but the decrease was not statistically significant. Review of the data suggests there were essentially no differences in food consumption between treated and control rats.

2. **Water Consumption.** Water consumption was variable in all treatment groups without an apparent dose relationship.

D. OPHTHALMOSCOPIC EXAMINATION: Not done.

E. BLOOD ANALYSES

1. **Hematology:** No biologically relevant effects were found.

2. **Clinical chemistry:** Serum sodium levels were statistically increased over control rats in the mid and high dose groups of both sexes (Table 3). No statistically or biologically significant differences from control were found for potassium or calcium and chloride and CO_2 analyses were not done. While the increase in sodium borders on biological significance, particularly for high dose female rats, no correlating pathology in the kidney was found. Therefore the toxicological significance of the increased sodium is unknown. While there were other random statistically significant differences found, none were of biological significance.

TABLE 3. Serum sodium concentrations in male and female rats treated for 6-hours 5 days/week for 14 exposures with RU 22974.

Exposure Conc. mg/m³	*Sodium (mEq/L) ± SD*	
	Males	Females
0.0	142 ± 2.1	141 ± 0.8
3.0	143 ± 2.6	142 ± 2.3
9.6	146 ± 1.6**	147 ± 4.3**
56.3	147 ± 1.2***	150 ± 1.9***

Data from Table 8, page 36 of MRID 00098089
** $p \leq 0.01$
***$p \leq 0.001$

F. **URINALYSIS:** Statistically significant decreases in volume and pH, and increases in specific gravity were noted from high dose females, but the differences were not biologically relevant. No dose- or treatment-related changes were found in any other urinalysis value.

G. **SACRIFICE AND PATHOLOGY:**

1. **Organ weight:** No biologically significant differences in absolute or relative organ weight among the treated groups were found.

2. **Gross pathology:** The only compound-related, grossly observable lesions were scarred ears in some rats of the two highest exposure groups, presumably from scratching caused by irritation of RU 22974 particles during exposure. Other grossly observable lesions were considered to be within normal limits for the species.

3. **Microscopic pathology:** Histopathology was reported for control and high dose treatment groups. Other than ear scarring, no increased incidence of microscopic lesions in other tissues.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study authors concluded that there was an irritant effect of RU 22974 in all three exposure groups as indicated by agitated grooming and ptyalism. More severe toxic effects were noted at the highest exposure level of 56.3 mg/m³ typified by ataxia and walking with arched backs. Scarring of the ears was noted both macroscopically and microscopically in the high-dose group of both sexes. The study authors speculated that renal effects may be implicated by the elevated serum sodium in both sexes and the effects noted on the urine volume, pH, and specific gravity of high-dose females. No LOAEL or NOAEL were suggested by the study authors.

B. **REVIEWER COMMENTS:**

1. **Exposure Effects.** Signs of skin irritation or nervous system stimulation (washing and scratching of the face, above the incidence of control rats) were noted in all dosed groups and

according to the study authors, the incidence was related to the dose. Rats exposed to the highest level reacted by walking with an arched back. (A reporting of the incidence of these effects was not included in the study report.) Other signs noted in the high-dose group and occasionally in the mid-dose group included hunched posture, peripheral vasodilation, minimal aggressive behavior, hypersensitivity to noise, and scarring of the ears (presumed related to irritative properties of the test material). However, the incidence of these effects was not provided in the study report. No rats died as a result of the exposure. Total weight gain by male rats in the mid- and high-dose groups was decreased 14-24% for male rats and 12-14% for female rats. The serum sodium of both male and female rats was increased in a dose-related manner, however the increase in males was not biologically significant while that of females borders on significance. The toxicological significance of the increased sodium is unclear as no changes were found with potassium or calcium and serum chloride and CO_2 analyses were not done. In addition, no histological correlates were found in the kidney. Other than scarred ears for high-dose male and female rats, no macro- or microscopic lesions were found in any of the examined organs and tissues.

2. Exposure Conditions. Deltamethrin used in this study was described as an **irritant** from the suppler which produced localized skin (ear and face) irritation clinically and histopathologically. Because of the chamber design and the large particle sizes there are questions concerning the adequacy of the experimental exposures of the animals.

a) Chamber Design. Although analytical aerosol concentrations were reported it is probable that a fraction of the aerosol may have reached the animals. The aerosol generated by the Wright dust feeder was fed into the bottom center of the chamber without a physical design that would lead to a uniform distribution of the deltamethrin in the breathing zone of the animals. The investigators did not provide data from the study to indicate the uniform distribution of the aerosol within the chamber. Further, sampling sites for concentrations and particle sizes were not from the breathing zone of the animals.

b) Particle Sizes. It is apparent that enough of the deltamethrin was deposited on the skin of the test animals to cause irritation of the ears of the animal. The investigators reported the partical sizes as percents in the particle range of less than 5.5 micrometers (approximately 87%). The mass median diameters of the particles were not determined.; however Table 2 (page 60 of the report indicates 11 to 21 % of the particles were less than 0.3 micrometers and 50% to 36% were in the range of 2.0 to 0.3 micrometers. These particle sizes in the lower ranges when inhaled by the animals should have produced some nasal and pulmonary irritation if the chamber design assured adequate distribution of the deltamethrin within the chamber. was but the majority of the particles either did not reach the breathing zone of the animals and/or the particles that could be inhaled were too large to reach the trachea and deep lung of the animals.

3. Conclusions. From the study:

The LOAEL for RU 22974 is 9.6 mg/m^3 based on clinical signs of irritative effects during exposure and on the >10% decreased weight gain of male and female rats. The NOAEL is 3.0 mg/m^3.

However, this 21-day inhalation toxicity study in the rat is an **Unacceptable/Nonguideline**. The study was conducted prior to establishment of GLP procedures but does not meet the intent.

a) **Study Deficiencies:** The animals were not adequately exposed to appropriate aerosol concentrations of deltamethrin. Analyses for test article purity and stability were not given for this non-guideline study. The incidence of irritative effects during exposure for treated animals was not provided. No GLP statement or indication of quality control procedures were provided.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §83-1b, Chronic (52-Week) Oral Toxicity Study in Dogs

Work Assignment No. 2-01-43C (formerly 1-01-43C) MRID 44372601

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer Kimberly Woodard, B.S.	Signature: Mary Menetrez for Kimberly Woodard Date: 12/8/99
Secondary Reviewer Kelley Van Vreede, M.S.	Signature: Kelley Van Vreede Date: 12/8/99
Program Manager Mary L. Menetrez, Ph.D.	Signature: Mary L Menetrez Date: 12/8/99
Quality Assurance Steve Brecher, Ph.D.	Signature: Steven Brecher Date: 12/8/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Primary Reviewer: Waheeda Tehseen, Ph.D.
Registration Action Branch 3/HED (7509C)
EPA Secondary Reviewer: Meta Bonner, Ph.D.
Registration Action Branch 3/HED (7509C)

TXR# 0050424

DATA EVALUATION RECORD

STUDY TYPE: Chronic Oral Toxicity - dog
OPPTS Number: 870.4100 OPP Guideline Number: §83-1b

DP BARCODE: D245495 SUBMISSION CODE: S541415
P.C. CODE: 097805 TOX. CHEM. NO.: 463B

TEST MATERIAL (PURITY): Deltamethrin, technical (98.9% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Ryle, Buist, Crook, Rao, and Gopinath. (1993), Deltamethrin: Toxicity to Dogs by Repeated Oral Administration for 52 Weeks. Huntington Research Centre, Ltd. Huntington, Cambridgeshire, England. Laboratory Project ID RSL 816/920929. October 21, 1993. MRID 44372601. Unpublished.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE

EXECUTIVE SUMMARY: In this chronic toxicity study (MRID 44372601), deltamethrin (98.9% a.i.) was administered via gelatin capsule to purebred 4 beagle dogs/sex/group at doses of 0, 1, 10, or 50 mg/kg/day for 52 weeks. Dose level selection was based on the results of a previous 13-week study in which the test substance was administered to dogs at doses of 0, 2, 10, or 50 mg/kg/day.

No treatment-related findings were observed in the 1 mg/kg/day groups. Mortality, food consumption, organ weights, ophthalmoscopic observations, hematology parameters, clinical chemistry findings, urinalysis parameters, and gross and histopatholgical findings were unaffected by the test substance.

Dose-related decreases in male body weight gains were seen at 1, 10 and 50 mg/kg/day, respectively. For weeks 0-52, significant decreases were seen (↓37, 37 and 49%) at 1, 10 and 50 mg/kg/day, respectively. There were also nonsignificant decreases in body weight gain (↓33, 35 and 42%) during weeks 0-26 at 1, 10 and 50mg/kg/day, respectively. However, the growth of

dogs, particularly in the 1 mg/kg/day group were within expected limits and, therefore, not related to treatment.

Early clinical signs were seen at 10 mg/kg/day and included chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30).

At 50 mg/kg/day, chewing of extremities was observed in 4 males (69 incidences) and 4 females (102 incidences); liquid feces was reported during weeks 1-13, weeks 14 to 23 and sporadically, thereafter. Abnormal gait was noted in all animals (8/8 treated) during clinical examinations. During neurological examinations at week 26, the following signs were observed: (i) slight trembling in males (1/4 treated); (ii) generalized trembling with splayed digits (fore and hindlimb) in females (1/4 treated); and (iii) alterations in gait (slight high-stepping) in females (1/4 treated). At week 52, neurological observations included the following: (i) slight trembling during the physical examination (males- 1/4 treated, females 2/4 treated); (ii) general slight unsteadiness of gait in males (1/4 treated); (iii) high-stepping in males (2/4 treated); (iv) splayed digits and slight high-stepping in females (1/4 treated); (v) trembling during wheelbarrowing, thoracic hopping, and pelvic hopping in males (1/4, each); and (vi) splayed digits and slight high-stepping of limbs during wheelbarrowing and hopping in females (1/4, each).

The chewing of extremities was observed in 4 males (30 incidences) and 3 females (4 incidences) in the mid-dose group, in the high-dose group in 4 males (69 incidences) and 4 females (102 incidences), and observed in none or 1/sex in control and low-dose groups.

The LOAEL for this study is 10 mg/kg/day, based on the ≥35% reduction in body weight gain over weeks 0 to 26, which was significant over weeks 0 to 52, in conjunction with the reported clinical signs (i.e., chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30) during the early segment of the study. The NOAEL for this study is 1 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.4100/OPP 83-1[b])** and does satisfy the guideline requirements for a chronic toxicity study dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

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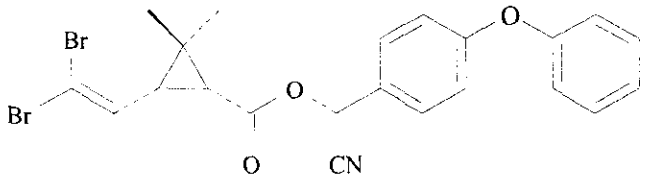
I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Deltamethrin (technical)
   Description: Beige powder
   Lot/Batch #: 9N1239 B2
   Purity: 98.9% a.i.
   Stability of compound: It was stated that the test material was stable for two years and the expiration date of the test material batch 9N1239 B2 was December 1992 (after study termination).
   CAS #: 52918-63-5
   Structure:



2. Vehicle: Gelatin capsule

3. Test animals: Species: Dog
   Strain: Purebred Beagle
   Age and weight at the start of dosing: 22-26 days old; 8.3-12.0 kg (males), 8.0-12.3 kg (females)
   Source: Interfauna UK Limited, Abbots Ripton Road, Wyton, Huntingdon
   Housing: Kennels with a floor area of 4.5 m^2, housed 2/kennel
   Diet: Diet A standard dry diet (Special Diets Services, Ltd), 400 g/day, except prior to blood and urine sample collection
   Water: Tap water, ad libitum, except for 5 hours prior to urine sample collection
   Environmental conditions:
   Temperature: 15-24° C
   Humidity: Not reported.
   Air changes: 12/hour
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: At least 4 weeks

B. STUDY DESIGN

1. In life dates - start: 2/28/91 end: 3/2/92

2. Animal assignment - The dogs were pseudo-randomly assigned (stratified by body weight) to the test groups shown in Table 1.

Table 1. Study design.[a]

Test Group	Dose (mg/kg/day)	Animals Assigned	
		Male	Female
Control	0	4	4
Low	1	4	4
Mid	10	4	4
High	50	4	4

a *Data were obtained from study report, page 14.*

3. Dose rationale - Dose level selection was based on the results of a previous 13-week study in which the test substance was administered to dogs at doses of 0, 2, 10, or 50 mg/kg/day. Decreased weight gains and adverse effects in locomotor activity were observed at the high-dose.

4. Treatment preparation and dosing - Once a week, the required amount of neat test substance was inserted into gelatin capsules (5 mL capacity). Doses were based on the weekly body weights of the dogs and were administered once daily in capsules for 52 weeks. One high-dose male was not dosed for two days during week 50 due to persistent clinical signs. Control animals received the same number of empty capsules as the treated animals.

5. Statistics - The following sequence of statistical tests was used for body weight, food consumption, water consumption, heart rate, organ weight, and clinical pathology data: Bartlett's test was applied to test for homogeneity of variance; if the variance was homogeneous, then analysis of variance (ANOVA) or covariance was applied followed by Williams' test as necessary; if the variance was heterogeneous and could not be removed by logarithmic transformation, then Kruskal-Wallis analysis of ranks was performed followed by Shirley's test (non-parametric equivalent of Williams' test) as necessary.

C. METHODS.

1. Observations

A. Clinical signs - All animals were observed daily for indications of ill health and for clinical signs of toxicity.

B. Neurological examination - All animals were subjected to a neurological examination before the initiation of dosing; only control and high-dose dogs were examined at

weeks 26 and 52. The full neurological assessment included the following parameters:

General physical examination	Spinal reflexes	Postural and attitudinal reactions
Behavior and gait	Flexor reflex	Wheelbarrowing
Cranial nerve function	Extensor reflex	Extensor postural thrust
Pupillary light reflex	Triceps reflex	Righting reactions
Blink reflex	Patellar reflex	Hopping reactions
Corneal reflex	Crossed extensor reflex	Placing reactions-visual and tactile
Gag reflex	Perineal reflex	Tonic neck reactions

2. Body weight - All animals were weighed weekly (prior to feeding).

3. Food consumption - Food consumption for each animal was measured daily throughout the treatment period and was reported as g/animal/day.

4. Ophthalmoscopic examination - Ophthalmoscopic examinations were conducted on all animals once prior to treatment and during weeks 13, 26 and 52.

5. Blood - Blood was collected from the jugular or cephalic vein of all animals once prior to treatment and at weeks 13, 26, and 52. The animals were fasted overnight prior to blood sample collection. The checked (X) hematology and clinical blood chemistry parameters were examined.

a. Hematology

X	Hematocrit (PCV)	X	Leukocyte differential count
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count	X	Reticulocyte count
X	Blood clotting measurements	X	Cell morphology
	Thromboplastin time		
	Clotting time		
X	Prothrombin time (PT)		
X	Activated partial thromboplastin time (APTT)		

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Total cholesterol
X	Potassium	X	Globulin (calculated)
X	Sodium	X	Glucose
		X	Total bilirubin
		X	Total serum protein (TP)
	ENZYMES		Triglycerides
			A/G Ratio
X	Alkaline phosphatase (AP)		
	Cholinesterase		
X	Creatine phosphokinase		
X	Lactate dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT, SGPT)		
X	Serum aspartate aminotransferase (AST, SGOT)		
X	Gamma glutamyltransferase (GGT)		
	Glutamate dehydrogenase		
X	Ornithine carbamoyl transferase		

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6. Urinalysis - Urine was collected from all animals over a period of 16 hours from fasted, water-deprived animals once prior to treatment and during weeks 13, 26, and 52. The checked (X) parameters were measured in all samples.

	Appearance (color, turbidity)	X	Glucose
X	Volume	X	Ketones
X	Specific Gravity	X	Bile pigments
X	pH	X	Heme pigments
X	Sediment (microscopic)		Nitrite
	Protein	X	Urobilinogen
X			Sodium
			Potassium
			Chloride
		X	Total reducing substances (TRS)

7. Bone marrow examination - Bone marrow was collected from each animal by sternal puncture prior to necropsy and a smear was prepared for microscopic examination.

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8. Sacrifice and pathology - After 52 weeks of treatment, all animals were fasted overnight, and then sacrificed by exsanguination under pentobarbitone anaesthesia. The following checked (X) tissues were collected and examined for gross and histopathological abnormalities. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta	XX	Brain, 3 levels
X	Salivary glands	XX	Heart	X	Periph.nerve
X	Esophagus	X	Bone marrow	X	Spinal cord
X	Stomach	X	Lymph nodes	XX	Pituitary
X	Duodenum		(cervical and mesenteric)	X	Eyes
X	Jejunum	XX	Spleen		
X	Ileum	X	Thymus		
X	Cecum				GLANDULAR
X	Colon				
X	Rectum		UROGENITAL	XX	Adrenal gland
XX	Liver			X	Lacrimal gland
	Gall bladder	XX	Kidneys	X	Mammary gland
X	Pancreas	X	Urinary bladder	X	Parathyroids
		XX	Testes with epididymides	XX	Thyroids
	RESPIRATORY	X	Prostate		OTHER
			Urethra		
X	Trachea	X	Seminal vesicle	X	Bone (sternum, femur and joint)
X	Lung	XX	Ovaries		
	Pharynx	XX	Uterus/oviducts	X	Skeletal muscle
	Larynx	X	Vagina	X	Skin
					All gross lesions and masses

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II. RESULTS

A. Observations

1. Mortality - No unscheduled deaths occurred during the study.

2. Clinical signs - Selected clinical signs observed in dogs dosed with deltamethrin are presented in Table 2. Abnormal gait was noted in all high-dose animals (8/8 treated) in 379-632/1456 incidences. Other observed clinical signs observed at the high-dose, such as chewing of extremities and liquid feces, occurred during weeks 1-13, weeks 14 to 23 and sporadically, thereafter. Note, however, that chewing of extremities was observed in 7/8 of the mid-dose animals and in 8/8 of the high-dose animals.

   Early clinical signs were seen at 10 mg/kg/day and included chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30).

Table 2. Selected clinical signs in dogs following dosing with deltamethrin.[a]

Clinical Observations	Males				Females			
	Dose (mg/kg)							
	0	1	10	50	0	1	10	50
abnormal gait (stiff/unsteady)	0(0)	0(0)	1(3)	4(632)	0(0)	0(0)	3(4)	4(379)
unwilling to stand/walk	0(0)	0(0)	0(0)	4(54)	0(0)	0(0)	0(0)	1(4)
trembling	0(0)	0(0)	1(1)	4(88)	0(0)	0(0)	1(1)	3(24)
chewing of extremities	0(0)	1(1)	4(30)	4(69)	1(1)	1(4)	3(4)	4(102)

a Data obtained from the study report Table 1, page 49. Data presented as [# affected animals (#incidences)]. Total number of incidences are out of a maximum of 1456; n=4.

B. Neurological examination - Observed neurological signs of toxicity in dogs dosed with deltamethrin are presented in Table 3. During neurological examinations at week 26, the following signs were observed at the high-dose: (i) slight trembling in males (1/4 treated); (ii) generalized trembling with splayed digits (fore and hindlimb) in females (1/4 treated); and (iii) alterations in gait (slight high-stepping) in females (1/4 treated). At week 52, observations at the high-dose included the following: (i) slight trembling during the physical examination (males- 1/4 treated, females 2/4 treated); (ii) general slight unsteadiness of gait in males (1/4 treated); (iii) high-stepping in males (2/4 treated); (iv) splayed digits and slight

high-stepping in females (1/4 treated); (v) trembling during wheelbarrowing, thoracic hopping, and pelvic hopping in males (1/4, each); and (vi) splayed digits and slight high-stepping of limbs during wheelbarrowing and hopping in females (1/4, each). None of these findings were observed in concurrent controls.

Table 3. Observed neurological signs of toxicity (# affected animals) in dogs following dosing with deltamethrin for up to 52 weeks.[a]

Neurological Signs of Toxicity	Males		Females	
	Dose (mg/kg)			
	0	50	0	50
Week 26				
slight trembling during physical exam	0	1	0	0
generalized trembling with splayed digits during physical exam	0	0	0	1
slight high-stepping	0	0	0	1
Week 52				
slight trembling during physical exam	0	1	0	2
general slight unsteadiness of gait	0	1	0	0
high-stepping	0	2	0	0
splayed digits and slight high-stepping	0	0	0	1
trembling during wheelbarrowing	0	1	0	0
splayed digits and slight high-stepping of limbs during wheelbarrowing	0	0	0	1
trembling during thoracic hopping	0	1	0	0
trembling during pelvic hopping	0	1	0	0
splayed digits and slight high-stepping of limbs during hopping	0	0	0	1

a Data obtained from the study report Table 4, pages 55 and 56; however, individual data (Appendix 5, page 150) indicated that wheelbarrowing was normal in all animals; n=4.

C. Body weight and weight gain - Body weight gains (weeks 0-26) were decreased in the low-, mid-, and high-dose males (↓33%, 35, and 42%, respectively) in Table 4. Overall (weeks 0-52) body weight gains were also decreased ($p<0.01$) in these animals (↓37%, 37, and 49%, respectively). However, the growth of dogs, particularly in the 1 mg/kg/day group were within expected limits and, therefore, not related to treatment. Historical control data were provided for body weight gains in males (week 0-26), and suggested that the body weight gains observed in control males in this study were unusually high. Body weight gains were decreased in mid- and high-dose females at the week 0-26 interval (↓18 and 27%, respectively) and at the week 0-52 interval (↓12 and 21%, respectively); however these data were not statistically significant.

Table 4. Mean body weights (g) and weight gain for selected weeks up to 52 weeks.[a]

Week	Dose (mg/kg/day)							
	Control		1		10		50	
	male	female	male	female	male	female	male	female
pre-dose -1	9.9	9.2	9.7	9.7	9.5	9.3	9.7	9.5
dosing 0	10.5	9.6	10.0	10.1	9.8	9.7	10.0	9.9
1	10.8	9.8	10.2	10.4	10.0	9.9	9.6	10.0
13	14.1	12.0	12.9	12.9	12.6	11.8	12.2	11.9
26	15.3	12.9	13.2	14.1	12.9	12.4	12.8	12.3
52	15.5	13.0	13.2	14.4	13.0	12.7	12.7	12.6
change 0 to 26	4.8	3.3	3.2 (↓33%)	4.3 (↑30%)	3.1 (↓35%)	2.7 (↓18%)	2.8 (↓42%)	2.4 (↓27%)
change 0 to 52	5.1	3.4	3.2** (↓37%)	4.3 (↑26%)	3.2** (↓37%)	3.0 (↓12%)	2.6** (↓49%)	2.7 (↓21%)

a Data obtained from the study report pages 50-51; n=4. ** $p<0.01$

D. Food consumption - Decreased overall (weeks 1-52) food consumption in high-dose males (↓2%, $p<0.01$) was observed; however, this decrease was minor and considered not to be treatment-related. In all other treated groups, food consumption was comparable to concurrent controls.

E. Ophthalmoscopic examination - No treatment-related ophthalmoscopic abnormalities were observed in any of the treated groups.

F. Blood work

1. Hematology - When compared to concurrent controls (Table 5), decreases ($p<0.05$) were observed at week 52 in hematocrit and hemoglobin in the high-dose (↓14%, each) and mid-dose (↓12%, each) males. These values were within historical control ranges. Platelets were increased ($p<0.05$) in low-, mid-, and high-dose males at weeks 26 (↑32, 38, and 18%, respectively) and 52 (↑40, 42, and 26%, respectively); however these

measurements were not dose-dependent and therefore considered not to be treatment-related.

Table 5. Hematology changes in dogs following deltamethrin treatment for up to 52 weeks.[a]

Parameter	Sex	Dose (mg/kg/day)			
		Control	1	10	50
26 weeks					
platelets ($10^3/mm^3$)	male	260±38.5	343±59.4 (↑32%)	358±34.4 (↑38%)	308±14.2 (↑18%)
	female	361±105.2	377±60.4	289±64.4	326±28.5
52 weeks					
platelets ($10^3/mm^3$)	male	248±19.0	348±31.4 (↑40%)	352±64.4 (↑42%)	313±42.5 (↑26%)
	female	330±114.9	376±26.6	308±85.6	359±52.8
hemoglobin (g/dl)	male	16.2±0.53	15.1±0.86	14.3±0.97 (↓12%)	13.9±1.81 (↓14%)
	female	16.2±0.52	15.8±1.06	15.6±0.97	16.1±0.70

a Data obtained from the study report pages 160-163; n=4.

2. Clinical chemistry - In high-dose males (Table 6), decreased ($p<0.05$ or 0.01) urea (↓27%) was observed at week 52 and decreased creatine was observed at weeks 26 (↓10%) and 52 (↓22%). The toxicological significance of these decreases is equivocal, and therefore, considered not to be treatment-related. In high-dose females, decreased phosphorus (↓26%, $p<0.05$) was observed at week 52. This isolated occurrence appears incidental, but may be due to poor nutritional status of the animals; however, no other changes in electrolyte levels were observed at the high-dose. Other differences from controls in clinical chemistry parameters were either minor (1-10%), not sustained over time, or lacked dose-dependence.

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Table 6. Biochemistry (Clinical Chemistry) changes in dogs following deltamethrin treatment for up to 52 weeks.[a]

Parameter	Sex	Dose (mg/kg/day)			
		Control	1	10	50
26 weeks					
creatinine (mg/dl)	male	1.0±0.08	0.9±0.10	0.8±0.05	0.9±0.00 (↓10%)
	female	0.9±0.08	0.8±0.14	0.8±0.06	0.8±0.10
52 weeks					
creatinine (mg/dl)	male	0.9±0.05	0.8±0.05	0.8±0.05	0.7±0.14 (↓22%)
	female	0.9±0.06	0.8±0.08	0.8±0.08	0.8±0.12
urea (mg/dl)	male	33±4.9	33±5.3	32±3.4	24±3.9 (↓27%)
	female	31±4.1	27±3.0	33±5.9	33±4.6
phosphorus (mEq/l)	male	2.5±0.10	2.9±0.56	2.6±0.24	2.3±0.33
	female	3.1±0.37	2.8±0.35	2.7±0.50	2.3±0.43 (↓26%)

a Data obtained from the study report pages 172-179; n=4.

G. Urinalysis - When compared to concurrent controls (Table 7), variations ($p<0.05$ or 0.01) in urinalysis parameters in the high-dose animals at week 52 included the following: (i) increased protein levels in females (↑31%); (ii) decreased volume in females (↓40%); and (iii) increased pH values in males and females (6.8 & 6.5 vs 6.2 & 6.1 in controls). In addition, the mid-dose females displayed increased protein levels (↑25%, $p<0.05$) at week 52. In the absence of any corroborating blood chemistry or histopathological data that would indicate renal dysfunction, these changes in urinalysis parameters are considered not to be of toxicological significance.

Table 7. Urinalysis observations in dogs at 52 weeks following deltamethrin treatment. [a]

Parameter	Sex	Dose (mg/kg/day)			
		Control	1	10	50
volume (ml)	male	84±17.2	102±46.5	118±49.4	65±21.4
	female	164±54.4	151±45.1	110±19.1	101±30.5 (↓40%)
pH	male	6.2±0.06	6.4±0.24	6.1±0.29	6.8±0.10 (↑10%)
	female	6.1±0.17	6.2±0.08	6.3±0.33	6.5±0.05 (↑7%)
protein (mg/dl)	male	58±13.4	44±13.4	39±8.5	67±14.0
	female	32±2.9	38±4.2	40±2.2	42±5.9 (↑31%)

a Data obtained from the study report pages 186-187; n=4.

H. Sacrifice and pathology

1. Organ weight - Absolute heart weights were decreased (↓21%, $p<0.01$) in high-dose males when compared to concurrent controls in Table 8. Brain weights, covariately adjusted to body weight, were increased (↑26%, $p<0.05$) in the high-dose males. In addition, increased ($p<0.05$) adjusted kidney weights were observed in the low-, mid-, and high-dose males (↑14, 16, and 14%, respectively). These changes in absolute and adjusted organ weights were not corroborated by histopathological findings, and are therefore not of toxicological concern. All other relative (to body) organ weights were comparable between treated animals and concurrent controls.

Table 8. Organ weights in dogs at 52 weeks following deltamethrin treatment. [a]

Parameter	Sex	Dose (mg/kg/day)			
		Control	1	10	50
absolute heart weights (g)	male	128.3	120.4	120.4	106.2 (↓21%)
	female	104.7	132.2	109.9	104.6
relative brain weights	male	0.54	0.61	0.61	0.68 (↑26%)
	female	0.60	0.55	0.69	0.63
relative kidney weights	male	0.44	0.50 (↑14%)	0.51 (↑16%)	0.50 (↑14%)
	female	0.48	0.47	0.50	0.51

a Data obtained from the study report pages 188-189; n=4. Standard deviations were not provided.

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2. Bone marrow smears - It was stated that no abnormalities were observed in bone marrow smears and that all smears were found to be normal in cellularity, distribution, and morphology; however, no data were provided.

3. Gross pathology - No treatment-related differences in gross postmortem findings were observed in any the treated group.

4. Microscopic pathology - No treatment-related microscopic findings were observed in any of the treated animals.

III. DISCUSSION

A. Investigator's conclusions - Deltamethrin administered to beagle dogs yielded neurological effects at 50 mg/kg/day and dose-related decreases in body weight gains (in males). The NOAEL for this study was 1 mg/kg/day.

B. Reviewer's discussion - In this chronic study, deltamethrin (98.9% a.i.) was administered via gelatin capsule to 4 Beagle dogs/sex/group at concentrations of 0, 1, 10, or 50 mg/kg/day for 52 weeks. No treatment-related findings were observed in the 1 mg/kg/day groups. Mortality,food consumption, organ weights, ophthalmoscopic observations, hematology parameters, clinical chemistry findings, urinalysis parameters, and gross and histopatholgical findings were unaffected by the test substance. Minor effects were noted at 10 mg/kg/day. Chewing of extremities was observed in 7/8 of the mid-dose animals (incidence # of 30 for males and 4 for females), while much higher number of incidences were noted for 8/8 of the high-dose animals (incidence # of 69 for males and 102 for females). Chewing of extremities occurred in none to one per sex for control and low-dose groups.

Dose-related decreases in male body weight gains were seen at 1, 10 and 50 mg/kg/day, respectively. For weeks 0-52, significant decreases were seen (↓37, 37 and 49%) at 1, 10 and 50 mg/kg/day, respectively. There were also nonsignificant decreases in body weight gain (↓33, 35 and 42%) during weeks 0-26 at 1, 10 and 50mg/kg/day, respectively. However, the growth of dogs, particularly in the 1 mg/kg/day group were within expected limits and, therefore, not related to treatment.

During clinical examinations, liquid feces was reported at 50 mg/kg/day during weeks 1-13, weeks 14 to 23 and sporadically, thereafter. Abnormal gait was also noted in all high-dose animals (8/8 treated). During neurological examinations at week 26, the following signs were observed at the high-dose: (i) slight trembling in males (1/4 treated); (ii) generalized trembling with splayed digits (fore and hindlimb) in females (1/4 treated); and (iii) alterations in gait (slight high-stepping) in females (1/4 treated). At week 52, neurological observations at the high-dose included the following: (i) slight trembling during the physical examination (males- 1/4 treated, females 2/4 treated); (ii) general slight unsteadiness of gait in males (1/4 treated); (iii) high-stepping in males (2/4 treated); (iv) splayed digits and slight high-stepping in females (1/4 treated); (v) trembling during wheelbarrowing, thoracic hopping, and pelvic

hopping in males (1/4, each); and (vi) splayed digits and slight high-stepping of limbs during wheelbarrowing and hopping in females (1/4, each).

Early clinical signs were seen at 10 mg/kg/day and included chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30).

The LOAEL for this study is 10 mg/kg/day, based on ≥35% reduction in male body weight gain over weeks 0 to 26, which was significant over weeks 0 to 52, in conjunction with the reported clinical signs (i.e., chewing, scratching of extremities (seen in week 2, reported sporadically thereafter, and seen in 2 dogs at week 37) and liquid feces (during week 1, reported sporadically thereafter, and noted in 2 dogs at week 30) during the early segment of the study. The NOAEL for this study is 1 mg/kg/day.

This study is classified **acceptable (§83-1[b])** and does satisfy the guideline requirements for a chronic toxicity study dogs.

C. Study Deficiencies - None found.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §83-2 (b); Oncogenicity Study in CD-1 Mice

Work Assignment No. 2-01-43D (MRID 44372602)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer: Kelley Van Vreede, M.S.	Signature: Kelley Van Vreede Date: 11/9/99
Secondary Reviewer: Guy Beretich, Ph.D.	Signature: Guy Beretich Date: 11/9/99
Project Manager: Mary L. Menetrez, Ph.D.	Signature: Mary L. Menetrez Date: 11/11/99
Quality Assurance: Steven Brecher, Ph.D.	Signature: Steven Brecher Date: 11/9/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Waheeda Mani Tehseen, Ph.D. **Signature:** Stephen C. Dapson for
OPP-HED Registration Action Branch III (7509C) **Date** 09/25/2002
EPA Secondary Reviewer: Steve Dapson, Ph. D. **Signature:** Stephen C. Dapson
Registration Action Branch 3 (7509C) **Date** 09/25/2002
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** Ghazi A. Dannan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 09/25/2002

DATA EVALUATION RECORD
TXR# 0050424

STUDY TYPE: Oncogenicity Study in Mice
OPPTS Number: 870.4200 OPP Guideline Number: §83-2 (b)

DP BARCODE: D245495 SUBMISSION CODE: S541415
P.C. CODE: 097805 TOX. CHEM. NO.: 463B

TEST MATERIAL (PURITY): Deltamethrin (98.0% a.i.)

SYNONYMS: (S)-*a*-cyano-3-phenoxybenzyl (1R,3R)-3-(2,3-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Richard, J. (1995) Deltamethrin: 97-Week Carcinogenicity Study by Oral Route (Dietary Admixture) in Mice. Centre International de Toxicologie (C.I.T.) Miserey, Evreux, France. Project No. 7347TCS. December 26, 1995. MRID 44372602. Unpublished.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, Delaware

EXECUTIVE SUMMARY: In this oncogenicity study (MRID 44372602), deltamethrin (98% a.i.) was administered for 97 weeks to 50 Crl:CD-1(ICR)BR mice/sex/dose at dietary concentrations of 0, 10, 100, 1000, or 2000 ppm (equivalent to [M/F] 0, 1.5/2.0, 15.7/19.6, 155.4/189.3 or 314.8/395.1 mg/kg/day). The animals were examined daily throughout the dosing period and palpated for tumors every two weeks after 6 months of treatment. Body weights and food consumption were determined weekly. Routine hematological analyses were determined at weeks 52, 78 and 97. Organ weights, gross pathology and histopathology were assessed at necropsy after the 97 week treatment period.

No clinical toxicity or palpable masses were found during the study. Survival at 52 weeks ranged from 94% to 100% for males and females. Male survival exceeded female survival ranging from 54% to 64% for males and 44% to 56% for females. There were no dose related survival changes due to the treatments with deltamethrin. Body weight gains were not dose

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related however high dose males had significant (p>0.05) decreases of 5%-7% over control males and females had significant decreases (3%-6%) over control females. Food consumption differences were not significant or related to treatment levels.

There were no significant dose related effects on hematological findings. Necropsy at the termination of the study was negative for organ weight differences, gross organ findings and for histopathological effect related to treatment with deltamethrin. An increased incidence of bronchoalveolar carcinoma was found in high-dose females (10% treated vs. 2% controls); however, it was stated that this finding is within the normal range (0-24%) for mice of this strain and age. Under the conditions of this study, there was no evidence of carcinogenic potential of deltamethrin.

The dose levels employed in this study were assumed to be adequate to characterize the carcinogenic potential of deltamethrin in both sexes of Crl:CD-1(ICR)BR mice based on a previous 12-week toxicity study in mice (CIT/Study No. 5566TSS) in which deltamethrin was administered at 0, 30, 300, 3000, or 6000 ppm. At 6000 ppm, 14/15 males and 13/15 females died by day 8; clinical signs were convulsions. At 3000 ppm, 3/10 males and 1/10 females died during the study, and body weights differed from controls by ↓13%.

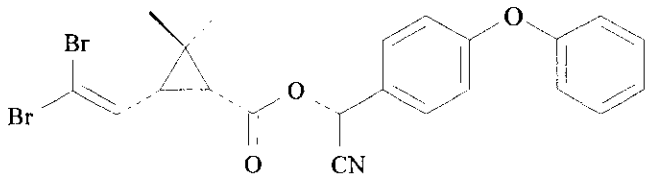
The NOAEL for this study is ≥2000 ppm (equivalent to 314.8 mg/kg/day in males and 395.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable (§83-2(b))** and satisfies the guideline requirements for an oncogenicity study in mice.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Deltamethrin (technical)
   Description: Beige powder
   Lot/Batch #: 1N0187B2 (used weeks 1-83); 693; 2N0398B2 (used week 84-termination)
   Purity (m/m): 98.0% a.i.
   Stability of compound: Stable at room temperature for up to 35 days in closed bags and up to 14 days in open containers.
   CAS #: 52918-63-5
   Structure:



2. Vehicle: Diet

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3. Test animals: Species: Mouse
   Strain: Crl: CD-1 (ICR) BR
   Age and weight at study initiation: Approximately 6 weeks old; 29g (males), 23g (females)
   Source: Charles River France, Saint-Aubin-lès-Elbeuf, France
   Housing: Individually in polycarbonate cages.
   Diet: A04 C (U.A.R., Villemoisson sure Orge, France), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
      Temperature: Approximately 21±2° C
      Relative humidity: 50±20%
      Air changes: Approximately 13/hour
      Photoperiod: 12 h dark/12 h light
   Acclimation period: 14 days

B. STUDY DESIGN:

1. In life dates - start: 4/23/91 end: 3/12/93

2. Animal assignment: Animals were randomly assigned (stratified by body weight) to treatment groups as indicated in Table 1.

Table 1. Study design

Test Group	Concentration in Diet (ppm)	Dosages Achieved M/F (mg/kg/day)[a]	Number of Mice	
			Males	Females
Control	0	0	50	50
Low	10	1.5/2.0	50	50
Mid	100	15.7/19.6	50	50
Mid-high	1000	155.4/189.3	50	50
High	2000	314.8/395.1	50	50

a Achieved dosages were provided in the study report Table 9, page 64.

3. Dose rationale: Dose selection was based on a previous 12-week toxicity study in mice (CIT/Study No. 5566TSS) in which deltamethrin was administered at 0, 30, 300, 3000, or 6000 ppm. At 6000 ppm, 14/15 males and 13/15 females died by day 8; clinical signs were convulsions. At 3000 ppm, 3/10 males and 1/10 females died during the study, and body weights differed from controls by ↓13%. The NOAEL was 300 ppm.

4. Diet preparation and analysis: The test diets were prepared approximately every 4 weeks and stored at room temperature until use. Prior to the study, dose formulations of 10 and 2000 ppm were evaluated for homogeneity (top, middle, bottom) and stability when stored at room temperature for up to 35 days in closed bags, or up to 14 days in open containers. Concentration analyses were performed during week 1 and then every 8 weeks throughout the study (during weeks 61-80, concentration analyses were performed every 4 weeks).

   Results: Homogeneity analyses (range as % of nominal): 96-103% with coefficients of variation of 2.1-4.1%.

   Stability Analyses: Samples stored for up to 35 days in closed bags were 92-104% of nominal. Samples stored for up to 14 days in open containers were 91-104% of nominal.

   Concentration analyses (range as % of nominal): 10 ppm formulation, 94-146%; 100 ppm formulation, 86-110%; 1000 ppm formulation, 86-121%; 2000 ppm formulation, 89-126%. Although the range for the 10 ppm formulation was occasionally high, the magnitude of the excess with respect to the concentration at higher doses (equivalent to 4.6 ppm) was low. Therefore the reviewers found the concentration of the 10 ppm sample to be acceptable.

   The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

5. Statistics: Body weight, food consumption, hematological parameters, and organ weight data were subjected to decision-tree analysis, which included the following tests: Kolmogorov-Smirnov's test, Bartlett's or Fisher's tests, Dunnett's test, Dunn's and/or Mann Whitney's tests. Logarithmic transformation was performed if values were not normally distributed. Neoplastic lesion data were evaluated with Peto's test (statistically significant if $p \leq 0.05$ for common tumors or $p \leq 0.01$ for rare tumors).

C. METHODS:

1. Observations: All animals were checked at least twice daily for viability, except for weekends and holidays when they were checked once daily. Clinical examinations were made at least once daily throughout the study. All mice were palpated every two weeks after the first 6 months of the study.

2. Body weight: All animals were weighed once a week during the first 13 weeks of the study, and then every 4 weeks for the duration of the study.

3. Food consumption: Food consumption was determined weekly during the first 13 weeks of the study, and then every 4 weeks for the duration of the study.

4. Ophthalmoscopic examination: Ophthalmoscopic examinations were not performed in this study. These data are not required for carcinogenicity studies based on Subdivision F Guidelines.

5. Blood analyses: Blood samples were obtained by incision of the caudal vein from all surviving, unfasted animals at weeks 52, 78, and 97. Differential white cell count was evaluated in control and high-dose groups only, unless abnormalities in other groups warranted their evaluation.

	Hematocrit (HCT) Hemoglobin (HGB) Leukocyte count (WBC) Erythrocyte count (RBC) Platelet count Blood clotting measurements (Thromboplastin time) (Prothrombin time)	X	Leukocyte differential count Mean corpuscular HGB (MCH) Mean corpusc. HGB conc.(MCHC) Mean corpusc. volume (MCV) Reticulocyte count Cell morphology

6. Urinalysis: Data on urinalyses were not submitted. These data are not required for carcinogenicity studies based on Subdivision F Guidelines.

7. Sacrifice and pathology: All surviving animals were sacrificed by CO_2 asphyxiation and exsanguination at the end of the treatment period (following approximately 18 hours of fasting). All mice, including those that died prematurely, received a complete gross pathological examination. The following CHECKED (X) tissues were collected. Additionally, the (XX) organs were weighed for the first 10 surviving animals of each sex and group.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT		NEUROLOGIC
X	Tongue	X	Aorta	XX	Brain, 3 levels
X	Salivary glands	X	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (cerv., thor., lumb.)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum		UROGENITAL	XX	Adrenal glands
X	Cecum	XX	Kidneys	X	Harderian gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	X	Thyroid with parathyroid
XX	Liver	X	Epididymides		
X	Gall bladder	X	Prostate		OTHER
X	Pancreas	X	Seminal vesicles	X	Bone with joint

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	RESPIRATORY	XX	Ovaries	X	Skeletal muscle
X	Trachea	X	Cervix	X	Skin
XX	Lungs	X	Uterus		Lacrimal gland
	Nasopharynx	X	Vagina	X	All gross lesions and masses
	Pharynx		Ureter		
	Larynx		Urethra		

All masses, macroscopic lesions, and preserved tissues were examined microscopically from control and high-dose animals, and all animals that died prematurely during the course of the study. Masses, macroscopic lesions, lungs, livers, and kidneys of animals in the low and intermediate dose groups were also examined.

II. RESULTS

A. Observations

1. Clinical signs - No treatment-related palpable masses were observed in any treated group. Increased dyspnea was observed (30% treated vs. 18% control) in high-dose females; however, 14 of the15 animals displaying dyspnea died prior to study termination, and their mortality was not considered to be treatment-related.

2. Mortality - Survival rates among treated males at week 52 at 0, 10, 100, 1000, and 2000 ppm were 98%, 94%, 98%, 100%, and 94%, respectively. Survival rates among treated males at week 97 were 60%, 64%, 54%, 58%, and 64%, respectively. Survival rates among treated females at week 52 at 0, 10, 100, 1000, and 2000 ppm were 94%, 96%, 96%, 96%, and 92%, respectively. Survival rates among treated females at week 97 were 56%, 54%, 44%, 48%, and 44%, respectively. The survival rates exceeded the guideline requirement (not less than 25%) for these intervals.

B. Body weight and body weight gain: For weeks 26 to 46, the mean body weights of the high-dose males were slightly lower (↓5-7%, $p \leq 0.05$) than concurrent controls at every interval. In the high-dose females, body weights were decreased (↓3-6%, $p \leq 0.05$ or 0.01) during 13/27 intervals between treatment weeks 1 and 66. Minor, sporadic decreases were observed in the other treatment groups. Overall (weeks -2-98) body weight gains (as calculated by the reviewers) were slightly reduced in the 2000 ppm males (↓5%) and females (↓5%). All of the observed decreases in body weights and body weight gains were minor and considered not to be of toxicological concern.

C. Food consumption and compound intake:

1. Food consumption - The observed differences in food consumption were minor and sproradic, and therefore considered not to be treatment-related.

2. Compound intake - The achieved mean dosages based on nominal dietary concentrations, actual body weights, and actual food consumption are shown in Table 1.

D. Blood analyses:

1. Hematology and Differential Blood Count: At week 78, neutrophils were increased in high-dose males (↑14%, $p \leq 0.05$) and decreased in high-dose females (↓12%, $p \leq 0.05$); leukocytes were decreased in high-dose males (↓10%, $p \leq 0.05$) and increased in high-dose females (↑10%, $p \leq 0.05$). At week 97 in high-dose males, neutrophils were increased (↑12%, $p \leq 0.05$) while eosinophils were decreased (↓50%, $p \leq 0.05$). These hematology results are equivocal, and therefore considered not to be treatment-related. No other differences in hematological parameters were observed in any other treated group.

2. Clinical Chemistry - Clinical chemistry data were not submitted. These data are not required for carcinogenicity studies based on Subdivision F Guidelines.

E. Sacrifice and Pathology:

1. Organ weights - No treatment-related differences were observed in organ weights when compared to concurrent controls

2. Gross pathology - No treatment-related gross pathological differences from controls were observed in any treated group.

3. Microscopic pathology

a) Non-neoplastic- No treatment-related non-neoplastic lesions were observed in any treatment group when compared to concurrent controls.

b) Neoplastic - No treatment-related neoplasms were observed in any treated group relative to concurrent controls. An increased incidence of bronchoalveolar carcinoma was found in high-dose females (10% treated vs. 2% controls); however, it was stated that this finding is within the normal range (0-24%) for mice of this strain and age (Lang, 1976; Faccini, et al, 1990). In addition, no positive trend in tumor incidence in any tissue was observed when data were subjected to a statistical trend test (Peto et al. 1980).

III. DISCUSSION

A. Investigators conclusions - Oral administration of deltamethrin to CD-1 mice for 97 weeks produced slightly higher incidences of poor clinical condition, lower body weight (in males), and increased cutaneous lesions in 2000 ppm animals. There was no evidence of carcinogenic potential of the test substance. The LOAEL for this study was 2000 ppm.

B. Reviewer's discussion - In this oncogenicity study, deltamethrin was administered for 97 weeks to 50 Crl:CD-1(ICR)BR mice/sex/dose at dietary concentrations of 0, 10, 100, 1000 or 2000 ppm (equivalent to [M/F] 0, 1.5/2.0, 15.7/19.6, 155.4/189.3 or 314.8/395.1 mg/kg/day). The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

No treatment-related findings were observed in any treated group. Clinical observations, mortality, body weight, body weight gain, food consumption, hematological parameters, organ weights, and gross and microscopic pathological findings were all unaffected by the test substance.

According to the sponsor's dose rationale, the dose levels employed in this study were adequate to characterize the carcinogenic potential of deltamethrin in both sexes of Crl:CD-1(ICR)BR mice.

Under the conditions of this study, there was no evidence of carcinogenic potential.

The NOAEL for this study is ≥2000 ppm (equivalent to 314.8 mg/kg/day in males and 395.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable (§83-2(b))** and satisfies the guideline requirements for an oncogenicity study in mice.

C. Study deficiencies - None observed.

Summ Rev. June 12, 2002 SBGross

REVISED EXECUTIVE SUMMARY

DECAMETHRIN (DELTAMETHRIN)

Study Type: §83-5a; Combined Chronic Toxicity/Carcinogenicity Study in Rats

Work Assignment No. 4-02-189 M (MRID 00098105)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer Ronnie J. Bever Jr., Ph.D.	Signature: Ronnie J. Bever Jr. Date: 7/8/02
Secondary Reviewer Mary L. Menetrez, Ph.D.	Signature: Mary L. Menetrez Date: 7/8/02
Program Manager Mary L. Menetrez, Ph.D.	Signature: Mary L. Menetrez Date: 7/8/02
Quality Assurance Steve Brecher, Ph.D.	Signature: Steven Brecher Date: 7/8/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

EPA Work Assignment Manager: Sanyvette Williams-Foy, D.V.M. **Signature:** SWF
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See 21110 HIARC Briefing Package for Deltamethrin for previous review.

STUDY TYPE: Combined chronic toxicity/carcinogenicity [feeding]- rat; OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Decamethrin (Deltamethrin; purity not reported)

SYNONYMS: [(S)-α-cyano-3-phenoxybenzyl (1R,3S)-3-(2 dibromovinyl)-2,2-dimethylcyclopropanecarboxylate]

CITATION: Goldenthal, E.I, A.C. Kahn III, R.J. Arceo, et al. (1980) Two-year oral toxicity and carcinogenicity study in rats. International Research and Development Corporation. Laboratory Report No.: IRDC 406-002/A4, May 6, 1980. MRID 00098105. Unpublished.

SPONSOR: American Hoeschst Corporation, Somerville, NJ

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 00098105), decamethrin (deltamethrin; purity not reported; Lot 22) was administered daily in the diet to 90 CD rats/sex/dose at dose levels of 0, 2, 20, or 50 ppm (approximately equivalent to 0, 0.1, 1.0, or 2.5 mg/kg/day, calculated by Agency reviewers) for 24 months. An additional 60 rats/sex were included as a second control group. Ten rats/sex/dose were sacrificed at Months 6, 12, and 18, and the remaining rats were sacrificed during Month 24.

There were no treatment-related adverse effects on mortality, clinical signs, ophthalmology, body weights, body weight gains, food consumption, hematology, clinical chemistry, urinalysis, or gross and histological (including tumors) pathology.

The LOAEL was not determined. The NOAEL for this study is >50 ppm (approximately equivalent to >2.5 mg/kg/day, calculated by the Agency reviewers).

Under the conditions of this study, the carcinogenic potential of decamethrin is considered negative. Dosing was considered inadequate. An adverse effect was not observed, and the limit dose was not tested.

At the August 2002 meeting of the Hazard Identification Assessment Review Committee (HIARC), it was determined that there were no adverse effects on body weight or body weight gain. Data showed significant ($p<0.01$ or <0.05) body weight reductions for males but these decreases ranged from -3 to -7% of control for both sexes. Additionally, body weight gain differences ranged from a 5 to an 8% decrease for males and a 4 to 8% decrease for the females. Since neither parameter exceeded a $\geq 10\%$ difference from the vehicle control group, the Committee concluded that differences were not biologically relevant. Accordingly, the NOAEL has been revised from 1.0 mg/kg/day to >2.5 mg/kg/day and the LOAEL from 2.5 mg/kg/day to "not determined".

This study is **unacceptable (not upgradable)/guideline** and does not satisfy the guideline requirement for a chronic/ carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §83-5(a); Combined Chronic/Oncogenicity Study - Rats

Work Assignment No. 2-01-43F (formerly 1-01-43F) MRID 44398102

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kelley Van Vreede, M.S.
Signature: Kelley Van Vreede
Date: 11/24/99

Secondary Reviewer:
Guy R. Beretich, Jr., Ph.D.
Signature: Guy Beretich
Date: 11/24/99

Program Manager:
Mary L. Menetrez, Ph.D.
Signature: Mary L. Menetrez
Date: 11/24/99

Quality Assurance:
Steve Brecher, Ph.D.
Signature: Steve Brecher
Date: 11/24/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Waheeda Mani Tehseen, Ph.D.
OPP-HED Registration Action Branch III (7509C)

EPA Secondary Reviewer: Steve Dapson, Ph. D.
Registration Action Branch 3 (7509C)

06/18/2002

DATA EVALUATION RECORD
TXR# 0050424

STUDY TYPE: Combined Chronic/Oncogenicity -Rats
OPPTS Number: 870.4300 OPP Guideline Number: §83-5a

DP BARCODE: D245495 SUBMISSION CODE: S541415
P.C. CODE: 097805 TOX. CHEM. NO.: 463B

TEST MATERIAL (PURITY): Deltamethrin (98.9%, a.i.)

SYNONYMS: (S)-α-cyano-3-phenoxybenzyl (1R, 3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Ryle, P.R. (1995). Deltamethrin: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats. Huntington Research Centre, Ltd. Huntington, Cambridgeshire, England. Laboratory Project ID RSL814, December 11, 1995. MRID 44398102. Unpublished.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE

EXECUTIVE SUMMARY: In this combined chronic/oncogenicity study (MRID 44398102), deltamethrin (purity 98.9% a.i.) was administered continuously in the diet to 50 Crl:CD(SD)BR rats/sex/group for approximately 104 weeks (main treatment group) at nominal dose levels of 0, 25, 125, 500, or 800 ppm (equivalent to [M/F] 0, 1.1/1.5, 5.4/7.3, 22.2/29.5, or 35.9/47.1 mg/kg/day). An additional 20 rats/sex/dose (satellite group) were designated for toxicological evaluation, including blood sampling. At week 52, 10 rats/sex/dose in the satellite group were terminated for interim sacrifice.

Each animal was examined daily for signs of toxicity throughout the treatment period. Each animal was also palpated daily for tumor masses for the first four weeks of the study and every other day there after. Body weights and food consumption were determined weekly. Weekly food conversion (food consumed/body weight gain) was calculated during weeks 1-26 from the body weight and food consumption data. Water consumption as measured for 7 consecutive days for all satellite group animals during treatment weeks 12, 25, 51, 77, and 105.

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Ophthalmoscopic examinations were performed on all animals assigned to the satellite group prior to dose initiation, at week 52, and prior to termination. Routine hematological and clinical chemistry analyses were carried out using blood collected from the orbital sinuses of 10 fasted animals/sex/dose from the satellite group during weeks 13, 26, 52, 78, and at study termination. Urinalyses were performed on urine during weeks 13, 26, 52, 78 and 104 collected overnight from the same 10 animals/sex/dose of the satellite group as the blood samples. Routine pathological assessments were carried out on 10 rats/sex/dose in the satellite group at 52 weeks and the remaining animals terminated at 104 weeks.

No treatment-related deaths occurred during the study. Survival at weeks 104 ranged from 40% to 70% for males and 42% to 52% for females. A negative survival trend was observed in males; however, no intergroup differences in survival were found. Survival for upper dose males were 67% for the 500 ppm treatment group and 70% for the 800 ppm treatment group which exceeded the control group (53%), the LD 25 ppm group (53%) and 40% for the 125 ppm group.

There were no treatment-related differences in body weights. However, body weight gains were significantly lower during the first week of treatment in the 500 and 800 ppm males (28 and 61 %, respectively) and in the 800 ppm females (20%). These decreases were not considered treatment-related because they corresponded to reduced food consumption and were not sustained throughout the study. The 800 ppm males continued to display minor changes (↑5-↓7%) in body weight gains throughout the first half of the study (weeks 0-52) relative to concurrent controls; and were not considered toxicologically significant.

There were no treatment-related differences in overall mean food consumption in the treated groups compared to controls. A significant decrease in food consumption was only observed during the first week in the 500 and 800 ppm males (18-32%) and females (6-12%); however food consumption returned to control levels by week 2.

There were no differences in water consumption attributable to treatment with deltamethrin. There were no treatment-related Ophthalmological findings detected in rats dosed with deltamethrin for 104 weeks.

Sporadic variations in Hb and lymphocytes were observed in males and/or females. These were not considered to be of any toxicological significance, since they were only observed in weeks 13, 26 and 78 weeks and not at later stages of the study. At the week 13 evaluation, platelets were decreased in the high-dose females (↓16%, $p \leq 0.05$), and total white blood cell count and lymphocytes were decreased ($p \leq 0.05$ or 0.01) in the high-dose males (↓20-22%) and in the 125 ppm, 500 ppm and 800 ppm females (↓16-35%). At the week 78 evaluation, hemoglobin was increased (↑10-11%, $p \leq 0.05$) in 500 and 800 ppm females. These hematological findings were sporadic and therefore considered not to be treatment-related.

Differences ($p \leq 0.05$ or 0.01) occurred in clinical chemistry parameters in either sex at various times throughout the study, but these were either minor, not dose-dependent, or not sustained

over time; and therefore, not considered to be treatment-related. For example, decreased total protein (↓4-8%); decreased albumin (↓8-11%); decreased globulins (↓9%); increased creatine (↑17%); increased aspartate aminotransferase (↑40%); decreased total lactate dehydrogenase (↓27-38%); decreased gamma glutamyltransferase (<1 mU/mL treated vs. 2 mU/mL controls); decreased ornithine carbamoyl transferase (↓28-42%); increased ornithine carbamoyl transferase (↑186%); increased creatine phosphokinase (↑34%); decreased bilirubin (↓50%); increased sodium (↑0.7-1.4%); decreased potassium (↓11%); decreased calcium (↓9%); decreased phosphorus (↓6-19%); increased chloride (↑1-5%); and decreased cholesterol (↓22-25%) were observed.

No treatment related differences in any urinalysis occurred in any treatment groups.

No treatment-related differences in organ weights were observed in rats treated with deltamethrin. Decreased pituitary gland weights were observed in all treated females during the interim sacrifice at week 53 (↓17-27%, $p \leq 0.05$), as well as at the terminal sacrifice at week 105 (↓14-19%, p=not statistically significant); however, this decrease did not show a typical dose-response, nor did the magnitude of the change increase over time. At the interim sacrifice, the 500 and 800 ppm females displayed decreased liver weights (adjusted for body weight, ↓6-14%, $p \leq 0.05$), but this difference was not dose-dependent and was not observed at the terminal sacrifice. At the terminal sacrifice, the 500 and 800 ppm males showed decreased testes/epididymides weights (↓10-15%, $p \leq 0.05$); however these findings were not dose-dependent. No differences in organ weights were observed in any other treated group during the interim or terminal sacrifices.

No treatment-related gross pathological findings were reported at the interim or terminal sacrifices. A dose-dependent increase in marked eosinophilic hepatocytes was observed in treated males (↑7-17%) which was within historical ranges. In addition, experimental animals did not show dose-dependent differences in total eosinophilic hepatocytes, and there was no corroborating evidence of liver changes in any treated group. Therefore, the increase in marked eosinophilic hepatocytes was considered not to be treatment-related. An increased incidence of ballooned cells (↑30-107%) relative to concurrent controls was observed in all treated groups; however these differences were not dose-dependent and considered not to be treatment-related.

Neoplastic organ changes included exocrine adenoma, islet cell carcinoma, follicular carcinoma, and parafollicular cell adenoma. These occurrences were within the normal range for this strain and species of rat were considered not to be treatment-related.

Under the conditions of this study, there were no treatment-related effects on the incidence of tumors in animals. Dose selection was based on subacute toxicity studies (RSL/813/827/901757) in which deltamethrin was administered orally at dietary levels of 0, 1000, 3000, or 6000 ppm for 13 weeks to Crl: CD(SD)BR rats. In that study, treatment-related effects included marked neurological disturbances, decreased food intake, and reduced body weight gains which resulted in the early sacrifice of the 3000 and 6000 ppm animals. Three

treatment-related deaths occurred at the 1000 ppm dose.

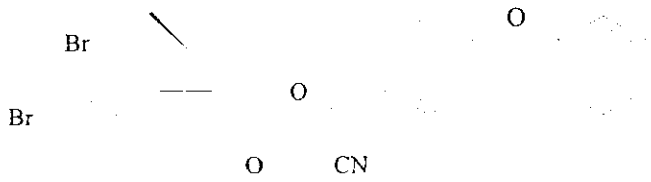
The NOAEL for chronic toxicity is 800 ppm (equivalent to 35.9 mg/kg/day in males and 47.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable (§83-5[a])** and does satisfy the guideline requirements for a combined chronic toxicity/oncogenicity study in rats.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Deltamethrin, technical
   Description: Beige powder
   Lot/Batch #: 9N 1239 B2
   Purity: 98.9%, a.i.
   Stability of compound: The test compound is stable in the diet for up to 18 days at room temperature.
   CAS #: 52918-63-5
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain: Crl:CD(SD)BR (Sprague-Dawley)
   Age and weight at study initiation: Approximately 6 weeks old; 145-193 g (males) and 118-162 g (females)
   Source: Charles River Breeding Laboratories, Portage, Michigan
   Housing: Suspended with wire mesh; 5 rats/cage
   Diet: SDS Rat and Mouse No. 1 modified maintenance diet, ad libitum except prior to blood and urine sampling.
   Water: Tap water, ad libitum except prior to blood and urine sampling.
   Environmental conditions:
   Temperature: 21±2° C
   Humidity: 55±10%

Air changes: Not reported
Photoperiod: 12 h dark/12 h light
Acclimation period: 12-13 days

B. STUDY DESIGN:

1. In life dates - start: 4/30/91 end: 5/19/93

2. Animal assignment: Animals were randomly assigned (stratified by weight) to treatment groups as indicated in Table 1.

Table 1. Study design

Test Group	Dose (ppm)	Achieved Dosage [a] M/F (mg/kg/day)	Number of Animals			
			Main group		Satellite group [bc]	
			Males	Females	Males	Females
Control	0	0	50	50	20	20
Low	25	1.1/1.5	50	50	20	20
Mid	125	5.4/7.3	50	50	20	20
Mid-high	500	22.2/29.5	50	50	20	20
High	800	35.9/47.1	50	50	20	20

a Achieved dosages obtained from the study report, Table 5 page 76.
b Animals in the satellite group were used for toxicological evaluation (including blood sampling).
c 10 rats/sex/dose in the satellite group were scheduled for interim sacrifice after 52 weeks.

3. Dose rationale: Dose selection was based on subacute toxicity studies (RSL/813/827/901757) in which deltamethrin was administered orally at dietary levels of 0, 1000, 3000, or 6000 ppm for 13 weeks to Crl: CD(SD)BR rats. Treatment-related effects included marked neurological disturbances, decreased food intake, and reduced body weight gains which resulted in the early sacrifice of the 3000 and 6000 ppm animals. Three treatment-related deaths occurred at the 1000 ppm dose. Based on these results, the doses presented in Table 1 were selected for the current study.

4. Test article preparation and analysis: Dose formulations were prepared weekly by mixing appropriate amounts of the test substance with the feed, and stored at room temperature (assumed). Homogeneity (samples from top, middle, and bottom) and stability were

confirmed prior to study initiation by analyzing the 25 ppm and 800 ppm dose formulations. Stability analyses were conducted on samples stored for up to 18 days at room temperature. Concentration analyses were performed on all dose formulations at week 1 and every 4 weeks until study termination.

Results - Results for the analysis of test samples were corrected for the appropriate mean procedural recovery (%): 99.7-102.5.

Homogeneity analysis (range as mean % of nominal): 97.3-99.2 with coefficients of variation (%) of 2.0-2.1.

Concentration analysis (range as mean % of nominal): 92.2-109.6

Stability analysis (range as mean % of day 0): 99.1-99.6 following storage for 8 days; 98.6-98.8 following storage for 18 days.

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosages to the study animals was acceptable.

5. Dose administration - The test substance was administered continuously in the diet for the duration of the study. Control animals received the untreated diet only.

6. Statistics - The following sequence of statistical tests was used for food consumption, body weight, organ weight, and clinical pathology data: Bartlett's test for homogeneity of variances, followed by analysis of variance (or covariance where appropriate) or the non-parametric Kruskal-Wallis test. These were followed by Student's t-test and Williams' test or their non-parametric equivalents. Logrank methods and/or trend tests were used to analyze mortality data.

C. METHODS:

1. Observations - All animals were checked for mortality twice daily. The animals' overall state of health was observed once daily. Detailed palpations were performed on all animals every day for the first 4 weeks of the study, and once weekly for the remainder of the study.

2. Body weight - All animals were weighed prior to randomization, on the first day of treatment, weekly throughout the study, and on the day of death or sacrifice.

3. Food consumption and efficiency - Food consumption for each cage of rats was determined weekly. Food conversion ratios (food consumed/body weight gain) were calculated during weeks 1-26 from the body weight and food consumption data.

4. Water consumption - Water consumption as measured for all satellite group animals for 7 consecutive days during treatment weeks 12, 25, 51, 77, and 105.

5. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all animals assigned to the satellite group prior to dose initiation, at week 52, and prior to termination.

6. Blood analyses - Blood was collected under light ether anaesthesia from the orbital sinuses of 10 fasted animals/sex/dose from the satellite group during weeks 13, 26, 52, 78, and at study termination. The CHECKED (X) parameters below were examined in each blood sample.

a.. Hematology:

X	Hematocrit (HCT)	X	Leukocyte differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes)
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
	Corrected leukocyte count (Cor WBC)	X	Mean corpusc. volume (MCV)
X	Erythrocyte count (RBC)	X	Reticulocyte count
X	Platelet count	X	Cell morphology
	Blood clotting measurements (Thrombotest) (Prothrombin time)		

b. Clinical chemistry:

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium	X	Globulins (calculated)
X	Sodium	X	Glucose
	Carbon dioxide	X	Total bilirubin
			Total serum protein
	ENZYMES		Triglycerides
X	Alkaline phosphatase (AP)		Albumin/globulin ratio
	Plasma cholinesterase (PL-ChE)	X	Total protein
	Erythrocyte cholinesterase (RBC-CHE)		
	Brain cholinesterase (BR-CHE)		
X	Creatine phosphokinase (CPK)		
X	Lactate dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
X	Gamma glutamyltransferase (GGT)		
	Glutamate dehydrogenase (GLDH)		
X	Ornithine carbamoyl transferase		

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7. Urinalysis - Urine was collected overnight from the same 10 animals/sex/dose of the satellite group as the blood samples during weeks 13, 26, 52, and 78. The following CHECKED (X) parameters were examined.

X	Appearance		Bilirubin
X	Volume		Blood
X	Specific gravity	X	Color
X	pH	X	Urobilinogen
X	Sediment (microscopic)		Nitrate
X	Protein	X	Total reducing substances
X	Glucose	X	Bile pigments
X	Ketones	X	Haem pigments

8. Sacrifice and pathology - Ten rats/sex/dose in the satellite group were killed by CO_2 asphyxiation and necropsied at 52 weeks. The remaining animals in the satellite group were maintained until study termination (104 weeks). Upon study termination, all surviving rats in the main group and satellite group were sacrificed by CO_2 asphyxiation and necropsied. The following CHECKED (X) tissues were collected. Additionally, the (XX) organs were weighed. The (*) tissues were subjected to microscopic examination for all control and high-dose animals, and all animals that died during the study. The livers, lungs, and kidneys from all animals were examined microscopically.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT		NEUROLOGIC
X	Tongue *	X	Aorta *	XX	Brain (3 levels) *
X	Salivary glands *	XX	Heart *	X	Peripheral nerve *
X	Esophagus *	X	Bone marrow *	X	Spinal cord (3 levels) *
X	Stomach *	X	Lymph nodes *	XX	Pituitary *
X	Duodenum *	XX	Spleen *	X	Eyes *
X	Jejunum *	X	Thymus *		GLANDULAR
X	Ileum *		UROGENITAL	XX	Adrenal glands *
X	Cecum *	XX	Kidneys *	X	Harderian gland
X	Colon *	X	Urinary bladder *	X	Mammary gland *
X	Rectum *	XX	Testes *	X	Parathyroids
XX	Liver *	XX	Epididymides *	XX	Thyroid *
	Gall bladder	X	Prostate *		OTHER
X	Pancreas *	X	Seminal vesicles *	X	Bone * with joint
	RESPIRATORY	XX	Ovaries *	X	Skeletal muscle *
X	Trachea *		Oviducts	X	Paranasal sinuses
X	Lungs *	X	Uterus *	X	Skin *
X	Nasal cavity	X	Vagina *	X	Lacrimal gland
X	Pharynx		Ureter	X	All gross lesions and masses *

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X	Larynx		Urethra	X	Middle ear
				X	Teeth
				X	Zymbal's gland

* Tissues required for histopathology study.

II. RESULTS

A. Observations:

1. Mortality - No treatment-related deaths occurred in this study. A negative survival trend was observed in males; however, no intergroup differences in survival were found. The overall incidence of deaths was as follows (data from p 32 vol. 1):

	Males					Females				
Total deaths	Control	25	125	500	800	Control	25	125	500	800
(wk 1- 4)	28	28	36	20	18	30	29	35	31	29
% Survival*	53	53	40	67	70	50	52	42	48	52

* = Excluding animals sacrificed at the week 53 interim kill

2. Clinical signs - No treatment-related clinical signs were observed in rats dosed with deltamethrin. During the first week of the study, majority of males at the highest dose showed uncoordinated movement of limbs and unsteady gate. However, these clinical signs and incidences declined slowly and disappeared after 8 weeks.

B. Body weight and body weight gain - There were no treatment-related differences in body weights. Body weight gains were significantly lower during the first week of treatment in the 500 and 800 ppm males (28 and 61 %, respectively) and in the 800 ppm females (20%); however, these decreases were not considered treatment-related because they corresponded to reduced food consumption and were not sustained throughout the study. The 800 ppm males continued to display minor changes (↑5-↓7%) in body weight gains throughout the first half of the study (weeks 0-52) relative to concurrent controls; and were not considered toxicologically significant.

Table 2. Mean body weight gains (g) in rats treated with deltamethrin for 104 weeks.[a]

Dose (ppm)	0-1 wks	1-4 wks	0-52 wks	0-90 wks	0-104 wks
Males					
0	55.7	131.4	586.6	658.8	627.3
25	55.3	128.1	569.3	649.5	613.5
125	55.6	125.8	572.0	636.9	644.9
500	40.0*(↓28)	135.6	558.6	644.5	640.0
800	21.9**(↓61)	138.1*(↑5)	545.3*(↓7)	632.3	642.6

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Females					
0	22.1	46.5	275.8	380.9	375.3
25	22.3	46.6	271.4	391.1	387.4
125	22.7	48.1	282.3	384.7	402.9
500	21.7	46.0	267.4	390.5	399.9
800	17.6**(↓20)	48.3	268.3	386.9	376.2

a Data obtained from the study report pages 33. Percent difference from controls is listed parenthetically.
* or ** Statistically different from controls at p≤0.05 or 0.01

C. Food consumption and efficiency - There were no treatment-related differences in overall mean food consumption in the treated groups compared to controls. A significant decrease in food consumption was only observed during the first week in the 500 and 800 ppm males (18-32%) and females (6-12%); however food consumption returned to control levels by week 2. This pattern suggests that the diet formulation may have been slightly unpalatable. Food efficiency was comparable among all groups during weeks 1-26 (period of fastest growth).

D. Water consumption - During week 12, females showed significant decrease in water consumption (17%). This finding was considered to be incidental and not treatment-related, as no differences were observed during any other interval. No differences in water consumption were observed in any other treated group.

E. Ophthalmoscopic examination - There were no treatment-related ophthalmological findings detected in rats dosed with deltamethrin for 104 weeks.

F. Blood analyses -

1. Hematology - Sporadic variations in Hb and lymphocytes were observed in males and/or females. These were not considered to be of any toxicological significance, since they were only observed in weeks 13, 26 and 78 weeks and not at later stages of the study. At the week 13 evaluation, platelets were decreased in the high-dose females (↓16%, p≤0.05), and total white blood cell count and lymphocytes were decreased (p≤0.05 or 0.01) in the high-dose males (↓20-22%) and in the 125 ppm, 500 ppm and 800 ppm females (↓16-35%). At the week 78 evaluation, hemoglobin was increased (↑10-11%, p≤0.05) in 500 and 800 ppm females. These hematological findings were sporadic and therefore considered not to be treatment-related. Minor differences (p≤0.05 or 0.01) were observed in hematocrit (↓4%), mean corpuscular hemoglobin concentration (↑2-4%), mean corpuscular volume (↓1-3%), hemoglobin (↓4%), and Thrombotest (↓5%) in either sex at various times throughout the study.

2. Clinical chemistry - Differences ($p \leq 0.05$ or 0.01) occurred in clinical chemistry parameters in either sex at various times throughout the study, but these were either minor, not dose-dependent, or not sustained over time; and therefore, not considered to be treatment-related. For example, decreased total protein (↓4-8%); decreased albumin (↓8-11%); decreased globulins (↓9%); increased creatine (↑17%); increased aspartate aminotransferase (↑40%); decreased total lactate dehydrogenase (↓27-38%); decreased gamma glutamyltransferase (<1 mU/mL treated vs. 2 mU/mL controls); decreased ornithine carbamoyl transferase (↓28-42%); increased ornithine carbamoyl transferase (↑186%); increased creatine phosphokinase (↑34%); decreased bilirubin (↓50%); increased sodium (↑0.7-1.4%); decreased potassium (↓11%); decreased calcium (↓9%); decreased phosphorus (↓6-19%); increased chloride (↑1-5%); and decreased cholesterol (↓22-25%) were observed.

G. Urinalysis - At week 78, males in all treatment groups displayed lower ($p \leq 0.05$ or 0.01) urine pH values (6.6-6.9) than concurrent controls (7.3). High-dose females displayed higher urine pH values (6.6, $p \leq 0.05$) than controls (6.3) at week 78. These variations in pH were incidental and considered to be unrelated to treatment. No other differences in any urinalysis parameter occurred in any other treated group during the study.

H. Sacrifice and pathology:

1. Organ weights - No treatment-related differences in organ weights were observed in rats treated with deltamethrin. Decreased pituitary gland weights were observed in all treated females during the interim sacrifice at week 53 (↓17-27%, $p \leq 0.05$), as well as at the terminal sacrifice at week 105 (↓14-19%, p=not statistically significant); however, this decrease did not show a typical dose-response, nor did the magnitude of the change increase over time. At the interim sacrifice, the 500 and 800 ppm females displayed decreased liver weights (adjusted for body weight, ↓6-14%, $p \leq 0.05$), but this difference was not dose-dependent and was not observed at the terminal sacrifice. At the terminal sacrifice, the 500 and 800 ppm males showed decreased testes/epididymides weights (↓10-15%, $p \leq 0.05$); however these findings were not dose-dependent. No differences in organ weights were observed in any other treated group during the interim or terminal sacrifices.

2. Gross pathology - No treatment-related gross pathological findings were reported at the interim or terminal sacrifices.

3. Microscopic pathology at necropsy:

a) Non-neoplastic - A dose-dependent increase in marked eosinophilic hepatocytes was observed in treated males (↑7-17%). According to control data from the animal supplier, values for acidophilic altered hepatocytes may range from 2-27.1% (Charles River Laboratories, 1992). In addition, experimental animals did not show dose-dependent differences in total eosinophilic hepatocytes, and there was no

corroborating evidence of liver changes in any treated group. Therefore, the increase in marked eosinophilic hepatocytes was considered not to be treatment-related. An increased incidence of ballooned cells (130-107%) relative to concurrent controls was observed in all treated groups; however these differences were not dose-dependent and considered not to be treatment-related.

b) Neoplastic - Several incidences of neoplastic tissue (table 3) were observed in all treated groups, such as exocrine adenoma, islet cell carcinoma, follicular carcinoma, and parafollicular cell adenoma. These occurrences were within the normal range for this strain and species of rat (Charles River Laboratories, 1992), and were considered not to be treatment-related.

Table 3. Intergroup comparison of tumor incidence with deltamethrin for 104 weeks.[a]

	0 ppm		25 ppm		125 ppm		500 ppm		800 ppm	
Males (70/dose group)										
Tumors	Deceased	Terminal	Deceased	Terminal	Deceased	Terminal	Deceased	Terminal	Deceased	Terminal
Animals Completed	28	32	30	30	37	23	21	39	19	41
# of tumor bearing animals	24	28	25	24	28	19	15	29	13	36
Animals with malignant tumors	13	10	10	6	14	5	7	5	7	15
Benign tumors	16	27	22	21	25	19	13	29	9	30
Multiple tumors	8	20	18	11	21	11	12	16	6	17
Single tumors	16	8	7	13	7	8	3	13	7	19
Multiple malignant tumors	0	1	1	1	2	1	1	0	0	1
Multiple benign tumors	5	16	13	10	12	8	9	15	5	13
Metastatic tumors	3	0	1	1	2	0	0	1	0	1
Females (70/dose group)										
Animals Completed	30	30	29	31	35	25	31	29	29	31
# of tumor bearing animals	29	24	28	28	34	20	31	25	29	27
Animals with malignant tumors	13	9	10	12	12	7	13	6	9	8
Benign tumors	24	23	23	27	30	20	27	25	28	24

Multiple tumors	17	16	14	22	17	16	12	19	13	16
Single tumors	12	8	14	6	17	4	19	6	16	11
Multiple malignant tumors	3	1	0	1	0	2	0	0	2	2
Multiple benign tumors	10	12	12	17	11	12	9	17	9	13
Metastatic tumors	1	0	2	0	1	1	0	0	1	0

a Data obtained from the table 13, pages 151-152.

III. DISCUSSION

A. Investigators conclusions - Oral administration of deltamethrin to Sprague-Dawley rats for approximately 104 weeks produced a higher incidence of eosinophilic hepatocytes in 500 and 800 ppm males and ballooned cells in the livers of 125 and 800 ppm males. There was no evidence of carcinogenic potential of the test substance. The chronic NOAEL for this study is 25 ppm (equivalent to 1.1 mg/kg/day in males and 1.5 mg/kg/day in females).

B. Reviewer's discussion/conclusions - In this combined chronic/oncogenicity study, deltamethrin (98.9%, a.i.) was administered continuously in the diet to 50 Sprague-Dawley rats/sex/group (main group) at nominal dose levels of 0, 25, 125, 500, or 800 ppm (equivalent to [M/F] 0, 1.1/1.5, 5.4/7.3, 22.2/29.5, or 35.9/47.1 mg/kg/day) for approximately 104 weeks. An additional 20 rats/sex/dose (satellite group) were designated for toxicological evaluation, including blood sampling. At week 52, 10 rats/sex/dose in the satellite group were terminated for interim study. Analysis of the test substance indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

No treatment-related findings were observed in any treated group. Mortality, clinical observations, body weight, body weight gain, food consumption and efficiency, water consumption, ophthalmoscopic observations, hematological parameters, clinical chemistry findings, urinalysis parameters, organ weights, and gross and microscopic pathological findings were all unaffected by the test substance. In addition, no treatment-related neoplastic tissue was observed in any treated group.

According to the sponsor's dose rationale, the dose levels employed in this study were adequate to characterize the carcinogenic potential of deltamethrin in both sexes of Crl:CD(SD)BR rats.

Under the conditions of this study, there was no treatment-related effect on the incidence of tumors in animals.

The NOAEL for chronic toxicity is 800 ppm (equivalent to 35.9 mg/kg/day in males and

47.1 mg/kg/day in females). The LOAEL was not observed.

The submitted study is classified as **acceptable (§83-5[a])** and does satisfy the guideline requirements for a combined chronic toxicity/oncogenicity study in rats.

C. Study deficiencies - None observed

\44398102\revised– Ex. Sum. Revised June 12, 2002 SBGross

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §83-3a, Prenatal Developmental Toxicity Study in Rats

Work Assignment No. 4-02-189G MRID 41651025

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer
John W. Allran, M.S.
Signature: John W. Allran
Date: 7-08-02

Secondary Reviewer
Kelley Van Vreede, M.S.
Signature: Kelley Van Vreede
Date: 7/8/02

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L. Menetrez
Date: 7/8/02

Quality Assurance
Steve Brecher, Ph.D.
Signature: Dilh S. Waly for Steve Brecher
Date: 7/8/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

EPA Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT
see TXR #009425 for previous review

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (>99% a.i.)

SYNONYMS: Butoflin, Butox, (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2-dimethylcyclopropanecarboxylate

CITATION: Schardein, J.L. (1990) Developmental toxicity study of deltamethrin in rats. International Research and Development Corporation, Mattawan, MI. Laboratory Study No.: 327-120, July 6, 1990. MRID 41651025. Unpublished.

SPONSOR: Hoechst-Roussel Agi-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41651025), deltamethrin (>99% a.i., Lot/Batch# 8B 0153 B3 and 8N 0701 B2) in corn oil was administered to pregnant Crl:CD VAF/Plus rats (25/dose) via gavage in a dosing volume of 1 mL/kg at concentrations of 0, 1.0, 3.3, 7.0, or 11.0 mg/kg/day on gestation days (GDs) 6 through 15. All dams were sacrificed on GD 21 and their uterine contents examined.

When compared to concurrent controls, there were no effects of treatment on maternal gross pathology, gravid uterine weights, numbers of live fetuses, dead fetuses, early or late resorptions, post-implantation loss, sex ratio, or fetal weight.

At 7 mg/kg, one dam was sacrificed following convulsions after dose administration. Additionally, increased salivation and body surface staining were noted. Maternal body weights were decreased ($p<0.05$) on GD 0, 9, 12, and 16; and body weight gains were decreased during the dosing period (decr. 16%; $p<0.01$).

At 11 mg/kg, 14/25 (56%) dams were either sacrificed *in extremis* or found dead. Convulsions, anogenital staining, sensitivity to external stimuli, and body surface staining were observed in the maternal animals. Body weight gains were decreased during the dosing period (decr. 16%; $p<0.05$); and body weight gains, corrected for gravid uterine weight, were decreased (decr. 22%; not significant) for the entire (days 0-20) gestation period.

The maternal LOAEL is 7 mg/kg/day based on decreased body weights and body weight gains and on clinical signs of toxicity. The maternal NOAEL is 3.3 mg/kg/day.

There were no effects of treatment on fetal malformations or variations.

The developmental LOAEL was not observed. The developmental NOAEL is >11 mg/kg/day.

This developmental toxicity study is classified **acceptable/guideline (OPPTS 870.3700; §83-3[a])** and satisfies the requirement for a developmental toxicity study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §83-3b, Prenatal Developmental Toxicity Study in Rabbits

Work Assignment No. 4-02-189H MRID 41651026

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer
John W. Allran, M.S.

Signature: John W. Allran
Date: 7-08-02

Secondary Reviewer
Kelley Van Vreede, M.S.

Signature: Kelley Van Vreede
Date: 7/8/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 7/8/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Deborah S Wesly for Steve Brecher
Date: 7/8/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy S. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

EPA Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT
see TXR #009425 previous review

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.4% a.i.)

SYNONYMS: *Butoflin*, Butox, (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2-dimethylcyclopropanecarboxylate

CITATION: Schardein, J.L. (1990) Developmental toxicity study of deltamethrin in New Zealand white rabbits. International Research and Development Corporation, Mattawan, MI. Laboratory Study No.: 327-112, May 7, 1990. MRID 41651026. Unpublished.

SPONSOR: Hoechst-Roussel Agi-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a prenatal developmental toxicity study (MRID 41651026), deltamethrin (99.4% a.i., Lot/Batch# 8N 0701 B2) in 0.5% carboxymethylcellulose (CMC) was administered to pregnant New Zealand White rabbits (16/dose) via gavage in a dosing volume of 3 mL/kg at concentrations of 0, 10, 25, or 100 mg/kg/day on gestation days (GDs) 7 through 19. All does were sacrificed on GD 29 and their uterine contents examined.

When compared to concurrent controls, there were no effects of treatment on maternal body weight gains, gross pathology, gravid uterine weight, numbers of resorptions (early and late), numbers of fetuses (live and dead), post-implantation loss, sex ratio, or fetal weight.

At 10, 25, and 100 mg/kg, an increased incidence of clinical signs of toxicity (anogenital staining, no stool, decreased defecation, and excessive lacrimation) was observed. The number (%) of animals exhibiting one or more of these signs was 8 (50%), 12 (75%), 13 (81%), and 14 (88%) in the control, 10, 25, and 100 mg/kg groups, respectively. However, in the absence of corroborating evidence of an effect of treatment, the toxicological relevance of these findings is

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uncertain. Additionally at 100 mg/kg, one pregnant doe died on GD 27; necropsy revealed congestion of the lungs. It was uncertain whether this death was due to the test substance or gavage error.

The maternal LOAEL was not established. The maternal NOAEL is 100 mg/kg/day.

At 100 mg/kg, dose-related increases in fetal and/or litter incidences of selected variations (>12 full pairs of ribs and 27 pre-sacral vertebrae) were observed. Additionally at this dose, increased fetal and/or litter incidences of non-ossification of the hyoid body, sternebrae (#5 and/or #6), pubic bones, and tail bone were observed.

The developmental LOAEL is 100 mg/kg/day based on increases in the incidences of delayed ossification and skeletal variations (>12 pairs of full ribs and 27 pre-sacral vertebrae. The developmental NOAEL is 25 mg/kg/day.

At the August 2002 meeting of the Hazard Identification Assessment Review Committee (HIARC), it was determined that the study was Unacceptable. The study can, however, be upgraded if the sponsor can justify the used of the aqueous vehicle (CMC) since there are results in the submitted data base and the published literature indicating that deltamethrin is less toxic when delivered orally in aqueous vehicles such as CMC.

Accordingly, this developmental toxicity study is classified **unacceptable (OPPTS 870.3700; §83-3[b])** and does not satisfy the requirement for a developmental toxicity study in the rabbit.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided.

EPA Reviewer: Nancy McCarroll
Toxicology Branch, Health Effects Division (7509C)
Signature: Nancy McCarroll
Date 10/10/02

EPA Secondary Reviewer: Alberto Protzel, Ph. D.
Toxicology Branch, Health Effects Division (7509C)
Signature: Alberto Protzel
Date 10/10/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT
see TXR #003066

STUDY TYPE: Prenatal Developmental Toxicity Study - (Multiple Species); OPPTS 870.3700 [§83-3]; OECD 414.

PC CODE: 097805

DP BARCODE: D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): RU 22974 (unspecified purity)

SYNONYMS: Deltamethrin, Butoflin, Butox, (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2-dimethylcyclopropanecarboxylate

CITATION: Glomot, R. and Vannier, B. (1977). RU 22974: Teratological Study in Mouse–Rat–Rabbit. Roussel Uclaf, France; Reference No. 76534–7636/Z/A. Unpublished study received March 25, 1982; MRID 00098092.; 00098091

SPONSOR: American Hoechst Corp., Somerville, NJ

EXECUTIVE SUMMARY: In three different developmental toxicity studies (MRID 0009802, 00098091) deltamethrin as RU 2974 (% a.i. not indicated) was administered to 24 CD-1 mice/dose, 24 Sprague-Dawley rats/dose, and 15 New Zealand White rabbits/dose. Doses to rats and rabbits were prepared in sesame oil. Neither the route of administration nor the vehicle used for mice were specified, and the route(s) of administration for the rats or the rabbits were not indicated.

Mice: Mice were dosed at 0, 0.1, 1.0, or 10 mg/kg/day on gestational days 6-17 and were sacrificed on day 18. There was no maternal toxicity noted at any dose level. Body weight gains and conception rates were comparable between the control and treated groups and there was no treatment-related effect on mortality. **There was no maternal LOAEL observed. The maternal NOAEL is ≥10 mg/kg/day.** Developmental toxicity was demonstrated as significantly ($p<0.05$ = *) reduced average fetal weights at 1.0 and 10 mg/kg/day (controls 1.35g; low-dose 1.28g; mid-dose 1.26g*; high-dose 1.24g*). In

addition, the incidences of delayed ossification of the sternebra and paws were statistically significantly higher in all dose groups. It is not indicated if the increases were seen in fetal and/or litter incidence for these variations. The study author stated that the frequency of these findings was within normal variation for this strain of mouse. **The developmental LOAEL is 1.0 mg/kg/day based on increase incidence (fetal and/or litter) of delayed ossification of the sternebrae and paws together with decreased fetal body weights. The developmental NOAEL is 0.1 mg/kg/day.**

Rats: Rats were dosed at 0, 0.1, 1.0, or 10 mg/kg/day on days 6-18 of gestation and were sacrificed on day 21. Maternal toxicity was demonstrated at 10 mg/kg/day as slightly reduced body weights (approximately 10%, individual body weights were not reported in the registrant's submission). There were no deaths or clinical signs of toxicity at any dose level and conception rates were comparable between the control and treated groups. **The maternal LOAEL is 10 mg/kg/day based on slightly reduced body weights. The maternal NOAEL is 1.0 mg/kg/day.** Developmental toxicity was suggested at 10 mg/kg/day as a statistically significant increase in delayed ossification of the sternebrae. It is not indicated if the increase was in the fetal and/or litter incidence for this skeletal variation. Fetal losses were also increased at the high dose, however, the difference from controls was not reported to be statistically significant (2.19, 2.60, 2.71, and 3.97% average fetal loss for the control, low-, mid-, and high-dose groups). No treatment-related effects were noted in other fetal malformations or variations, fetal weights, gestation period, total number of living pups at birth, day 4, and day 21, or in the viability and lactation indices. **The developmental LOAEL is equivocally set at 10 mg/kg/day, based only on a statistically significant increased incidence (fetal and/or litter) of delayed ossification of the sternebrae. The developmental NOAEL is 1.0 mg/kg/day.**

Rabbits: Rabbits were dosed at 0, 1, 4, or 16 mg/kg/day on days 6-19 of gestation and were sacrificed on day 28; two separate groups of rabbits received 16 mg/kg/day. There was no maternal toxicity noted at any dose level. There were no treatment-related changes in body weight gains or mortality. **The maternal NOAEL is ≥16 mg/kg/day. There was no maternal LOAEL observed.** Developmental toxicity was demonstrated at 16 mg/kg/day as an increase in fetal losses. The average fetal losses per group were 6.6, 18.5, 15.5, 10.2, and 27.4% for the control, low-dose, mid-dose, and two high-dose test groups, respectively. In addition, pup body weights were decreased by 8% and 4% for the low- and mid-dose groups relative to the control, and decreased by 14 and 13% for the two high-dose group. There was no evidence of teratogenic effects noted in the pups (details of the parameters examined were not given). **The developmental LOAEL is 16 mg/kg/day based on increased fetal losses and decreased fetal weights. The developmental NOAEL is 4 mg/kg/day.**

HIARC concluded that while these multiple species studies were unacceptable and did not provide a robust assessment of fetal sensitivity, the developmental effects

seen in mice (i.e., delayed ossification and decreased fetal body weights), rats (i.e., delayed ossification) and rabbits (i.e., increased fetal loss or decreased fetal body weight) appeared to occur either in the absence of maternal toxicity (mice or rabbits) or the presence of mild maternal toxicity (slightly reduced maternal body weight in rats).

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §83-4a; Two-Generation Reproduction Study of Deltamethrin Administered in the Diet to Sprague-Dawley Rats

Work Assignment No. 2-01-43E (Formerly 1-02-43E) MRID 44398101

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Guy R. Beretich, Ph.D.
Signature: Mary Menetrez for Guy Beretich
Date: 02/28/02

Secondary Reviewer:
Kelley Van Vreede, M.S.
Signature: Ronnie J. Berry Jr. for Kelley Van Vreede
Date: 2/28/02

Project Manager:
Mary L. Menetrez, Ph.D.
Signature: Mary Menetrez
Date: 2/28/02

Quality Assurance:
Steven Brecher, Ph.D.
Signature: Steven Brecher
Date: 2/28/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: William Greear, MPH, DABT — **Signature:** Stephen C. Dapson for
Registration Action Branch 3, Health Effects Division (7509C) — **Date** 11/20/2002
EPA Secondary Reviewer: Stephen C. Dapson, Ph.D. — **Signature:** Stephen C. Dapson
BSS, RAB3, Health Effects Division (7509C) — **Date** 11/20/2002
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. — **Signature:** Ghazi A. Dannan
Registration Action Branch 2, Health Effects Division (7509C) — **Date** 11/20/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study - Rat OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 097805

DP BARCODE: D245495
SUBMISSION NO.: S541415

TEST MATERIAL (PURITY): Deltamethrin (99.7% a.i.)

SYNONYM: (S)-α-cyano-3-phenoxybenzyl (1R, 3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Hoberman, A.M. (1992) Deltamethrin: Reproductive Effects of Deltamethrin Administered Orally in the Diet to Crl:CDBR VAF/Plus Rats for 2-Generations. Argus Research Laboratories, Inc., 905 Sheehy Drive, Horsham, PA 19044. Laboratory Project ID 818-001. AgrEvo Report Reference A70863, January 17, 1992 (Unpublished.). EPA MRID # 44398101.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE

EXECUTIVE SUMMARY: In a 2-generation reproduction toxicity study (MRID 44398101), deltamethrin (99.7% a.i.) was administered continuously in the diet to Sprague-Dawley rats (30/sex/dose) at dose levels of 0, 5, 20, 80, or 320 ppm (equivalent to 0, 0.3/0.4, 1.3/1.5, 5.4/6.1, or 21.2/23.5 mg/kg/day in the P animals [M/F] and 0, 0.4/0.4, 1.4/1.7, 5.8/6.7, or 24.9/27.2 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at approximately 6 weeks of age and lasted for at least 82 days prior to mating. F_1 pups selected (30/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents on postnatal day (PND) 21 and continuously throughout the rest of the study. F_1 animals were administered the test article for at least 86 days prior to mating to produce the F_2 litters. Mating to produce a second F_{2b} generation was not performed. Exposure of all animals to the test material was continuous throughout the study.

When compared to concurrent controls, there were no differences in food efficiency. There was no evidence of histopathological changes in the organs specified for examination. The brain was not examined. There were no differences of toxicological concern in organ weights.

In the high-dose, treatment-related mortality occurred in P females (1), F_1 males (17) and F_1 females (19). Clinical signs observed in these rats included: ataxia, impaired righting reflex, and stained abdomen, nose, mouth, neck, and chest, hyperactivity, splayed limbs, vocalization, and excess salivation. Necropsy findings included: black, red, and/or brown material in the gastrointestinal tract, stomach erosions, enlarged adrenals, cerebral congestion, and blood clots in the brain.

Treatment-related clinical signs observed in the P males were lesions on the head, neck, or forelimbs (11/30 treated vs. 1/30 controls) and alopecia (8/30 treated vs. 2/30 controls). In the P females, clinical signs observed were limited to ataxia (22/25 treated vs. 0/25 controls) and hypersensitivity (3/25 treated vs. 0/25 controls) during lactation. In the F_1 males and females, clinical signs observed were ataxia (27-28/28 treated vs. 0/30 controls), impaired righting reflex (23-25/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (6-10/28 treated vs. 1/30 controls), hyperactivity (8-9/28 treated vs. 0/30 controls), splayed limbs (3-8/28 treated vs. 0/30 controls), vocalization (7/28 treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red or brown or yellow, wet or dried substance on nose, mouth, neck, chest, fur, and/or abdomen (13-14/28 vs. 0/30 treated). During gestation and lactation, F_1 females demonstrated lesions (1/9 treated vs. 0/25 controls), foot splay (6/8 treated vs. 0/20 controls), and ataxia (2/8 treated vs. 1/20 controls).

Body weights were decreased compared to concurrent controls throughout the premating period in P (decr 7-16%) and F_1 (decr 15-49%) males and females. Body weights were decreased in P females during gestation days (GDs) 0-15 and lactation days (LDs) 1-14 (decr 7-16%). In F_1 females, body weights were decreased throughout gestation and during LDs 1-14 (decr 11-15%). Body weight gains were decreased during premating 3-5/12-14 weeks in P males (decr 16-89%) and F_1(decr 26-81%) males and females and highly variable in P females (decr 30-incr. 300%). Body weight gains for the overall premating periods (1-82 days for P; 1-99 days for F_1) were decreased in all high-dose groups (decr 20-24%). Absolute food consumption was decreased in high-dose groups throughout the premating period (decr 8-59%). The largest decrease in food consumption was observed during the first week of dosing in all groups (decr 34-59%), suggesting that the diet was unpalatable. During lactation, P dams and F_1 dams ate less (decr 16-26%) than controls at all intervals.

Treatment-related gross pathological findings were limited to the F_1 males and females that died during the study. These animals demonstrated cerebral congestion and/or blood clots (9-12/28 treated vs. 0/30 controls).

There were no treatment-related findings at any of the lower doses.

The LOAEL for parental systemic toxicity is 320 ppm in males and females (equivalent to 21.2/23.5 mg/kg/day [M/F]) based on increased mortality and clinical signs, decreased body weights, body weight gains, and absolute food consumption, and gross pathological findings in both sexes. The NOAEL is 80 ppm (equivalent to 5.4/6.1 mg/kg/day [M/F]).

There were no differences of toxicological concern in reproductive performance. Sexual

maturation and developmental parameters were not measured.

The LOAEL for reproductive toxicity is greater than 320 ppm (equivalent to >21.2/23.5 mg/kg/day [M/F]). The NOAEL is equal to or greater than 320 ppm (equivalent to ≥24.9/27.2 mg/kg/day [M/F]).

No treatment-related differences in clinical signs were observed at any time in the F_1 and F_2 litters. There were no treatment-related findings of toxicological concern at necropsy of the F_1 or F_2 litters.

In the high-dose, an increase in mortality relative to concurrent controls in the F_1 pups (13/200 treated vs. 0/184 controls) from PND 8 to 14 caused a decrease in the lactation index (decr 8%) for this group. Body weights were decreased relative to concurrent controls in F_1 pups (decr 14-25%) for PNDs $4_{(precull)}$-21, and in F_2 pups (decr 12-24%) for PNDs 7-21. Overall body weight gains were reduced (decr 27-28%) for PNDs 1-21 in F_1 and F_2 pups.

There were no treatment-related findings at any of the lower doses.

The LOAEL for offspring systemic/developmental toxicity is 320 ppm (equivalent to 24.9/27.2 mg/kg/day [M/F] based on increased pup mortality and decreased body weights and body weight gains). The NOAEL is 80 ppm (equivalent to 5.8/6.7 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS# 870-3800; OECD# 416) for a multigenerational reproductive toxicity study in the rat.

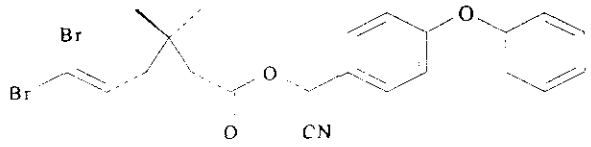
At the August 2002 meeting of the Hazard Identification Assessment Review Committe (HIARC), it was noted that there was qualitative evidence of increased susceptibility at 320 ppm as indicated by effects on the F_1 generation which were not seen in the P generation or when the F_1 generation were pups but only when they were adults. These effects included increased death (P ♀: 1, 3% vs. F_1 ♂: 17, 61% and F1 ♀: 19, 68%; F_1 pups: 13/200, 7%), clinical findings not seen in the P generation or the F_1 or F_2 litters (i.e. impaired righting reflexes, hyperactivity, splayed limbs, vocalization, and excessive salivation) and cerebral congestion and/or blood clots [9/28 (F_1 ♂) 12/28 (F_1♀) at the highest dose tested vs. 0/30 in male or female controls or in the high dose-group of both sexes in the P adults).

<u>COMPLIANCE</u>: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Deltamethrin, technical
Description: Slightly beige white powder
Lot/Batch #: 9N 1084 B2
Purity: 99.7% a.i.
Stability of compound: The compound was stable in the diet at room temperature for up to 21 days.
CAS #: 52918-63-5
Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
Strain: Sprague-Dawley (Crl:CD®BR VAF/Plus)
Age at start of dosing: P - approx. 6 weeks; F_1 - approx. 21 days
Weight at start of dosing:
(P) Males: 151-276 g; Females: 141-203 g
(F_1, group means): 52.5-53.6 g
Source: Charles River Laboratories, Inc. Raleigh, North Carolina
Housing: Stainless-steel wire-bottom cages during premating (1/cage), mating (1 male and 1 female/cage) and early gestation (1 female/cage). During late gestation and lactation, 1 dam and litter/cage were housed in nesting boxes
Diet: Certified Rodent Chow #5002M (Ralston Purina), ad libitum
Water: Reverse osmosis purified water, ad libitum
Environmental conditions:
Temperature: 74±4°F
Humidity: 40-70%
Air changes: ≥10/hour
Photoperiod: 12 h dark/12 h light
Acclimation period: 16 days

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: One female was caged with one male from the same test group for up to 14 days or until a vaginal plug was observed and/or sperm was observed in a vaginal smear. If mating did not occur within 14 days, an alternate male that had previously mated was assigned to the female, and cohabitation continued for up to an additional 7 days. The day sperm was observed in a vaginal smear was designated gestation day (GD) 0.

2. Study schedule: Starting at approximately 6 weeks of age, P animals (30 rats/sex/dose) were given test article diet formulations for 82 days prior to mating to produce the F_1 litters. On PND 21, F_1 animals (30 rats/sex/dose) were selected to become the F_1 parents of the F_2 generation and were given the same concentration test formulation as their dam. F_1 animals were given test formulations for at least 86 days prior to mating the first time to produce the F_2 litters. Mating to produce a second F_2 generation was not performed. P and F_1 adult males were sacrificed following production of their respective litters; P and F_1 dams were sacrificed at 21 or 22 days postpartum. Exposure of all animals to the test material was continuous throughout the study.

3. **Animal assignment:** P and F_1 animals were randomly assigned to test groups as shown in Table 1.

Table 1. Animal assignment

Test Group	Dose (ppm)[a]	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low	5	30	30	30	30
Mid	20	30	30	30	30
High-mid	80	30	30	30	30
High	320	30	30	30	30

a Diets were administered from the beginning of study until sacrifice.

4. **Dose selection rationale:** Dose levels were based on a range-finding 1-generation reproduction study in which rats (8/sex/group) were dosed at 0, 30, 300, 3000, and 6000 ppm. All male and female rats in the 3000 and 6000 ppm groups died or were sacrificed *in extremis*. No other deaths occurred. Treatment-related observations in these animals included clinical and gross necropsy signs, weight loss, and/or reduced food consumption. The 30 and 300 ppm males had decreases in body weights, body weight gains, and food consumption. The 300 ppm females had decreases in body weights and food consumption during the premating, gestation, and lactation periods. 30 ppm females were not affected. Clinical signs were observed in 300 ppm males and females, and included impaired righting reflex, ataxia, excessive salivation, perianal staining, and stained fur. The fertility indices were decreased in the 30 and 300 ppm males - 3/8 matings did not result in pregnancy. Pup viability was reduced for the 30 and 300 ppm groups, and pup body weights were decreased for the 300 ppm group. One 300 ppm litter did not nurse and was cold to the touch; another was ataxic.

Based on the results of this study, the dose levels shown in Table 1 were selected for the subsequent reproductive toxicity study in rats.

5. **Dosage preparation and analysis:** The test diets were prepared at weekly or biweekly intervals by mixing deltamethrin with the diet at concentrations of 5, 20, 80, or 320 ppm. Diet was stored at ambient temperature. For homogeneity analyses, 3 samples each from the top, middle, and bottom of the 5 and 320 ppm diet formulations were used. For stability analyses, samples from the 5 and 320 ppm diet formulations were stored for up to 21 days at ambient temperature and analyzed. For concentration analyses, 9 samples from the low and high-dose were analyzed from the first diet formulation, and 2 samples of each dose level were analyzed for the first 4 weeks of the study and monthly thereafter.

Results - Homogeneity analyses (range as % of nominal, range of RSD): 86-101%, 2-4%.

Stability analyses (range as % of day 0, range of RSD): 93-96%, 0-2%

Concentration analyses (range as % of nominal, range of RSD): 86-115%, 0-5%. On one occasion the diet concentration was 126-128% of nominal in the 20 ppm diet. This deviation was not considered to have affected the integrity of the study because there were no observations at that dose.

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

C. OBSERVATIONS

1. Parental animals: All parental animals were observed at least twice daily for morbidity and mortality and once daily for clinical signs. Males were weighed weekly during the study. Females were weighed weekly during premating and on GDs 0, 6, 10, 15, 20, and 25. During lactation, P dams were weighed on lactation days (LDs) 1 (birth), 4, 7, 14, and 21 and F_1 dams on LDs 1, 4, 7, 10, 14, 16, 18, and 21. Food consumption was measured weekly for both sexes during the premating period, on GDs 0, 6, 10, 15, 20, and 25 for the presumed pregnant females, and on LDs 1, 4, 7, 10, 14, 16, 18, and 21 for the dams. These data were then used to calculate the average test substance intake for individuals and treatment groups. Estrous cycles were monitored for one week prior to mating and until mating was confirmed as previously described.

2. Litter observations: Litters were examined at least twice daily for morbidity and mortality and once daily for clinical signs and external anomalies. Pups that died or were sacrificed prematurely were necropsied. Pups were weighed on PND 1 (birth), 4, 7, 14, and 21. The following litter observations (X) were made (Table 2):

Table 2. F_1 litter observations[a]

Observation	Time of observation (LD)				
	Day 1	Day 4	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X
Pup weight	X	X	X	X	X
External alterations	X	X	X	X	X
Number of dead pups	X	X	X	X	X
Sex of each pup	X	X	X	X	X

a Data extracted from the study report, page 47.

On PND 4, litters were standardized to a maximum of 8 pups/litter with 4/sex/litter, as nearly as possible.

3. **Postmortem observations:**

1) **Parental animals:** All surviving P and F_1 adult males were sacrificed approximately 3 weeks after mating. Females that littered were sacrificed on LD 21-22. Females that did not litter were sacrificed 25-48 days after cohabitation. All parental animals were subjected to a complete external and internal postmortem examination. At the scheduled necropsy, the animals were weighed and the following organs or tissues were weighed (XX) and/or preserved (X) in neutral buffered formalin for examination:

	Adrenals	XX	Brain
	Kidneys		Spleen
	Liver		Thymus
XX	Prostate	XX	Testes
XX	Seminal Vesicles	XX	Epididymides
XX	Coagulating glands		Oviducts
XX	Ovaries	XX	Uterus/Cervix
X	Vagina	XX	Pituitary gland
X	Mammary gland	X	Gross lesions

Slides prepared from these tissues were examined for all high-dose and control adults. Tissues demonstrating treatment-related histopathological lesions in the high-dose group were examined in all groups. All gross lesions were examined histologically. The uteri from nonpregnant rats were examined for implantation sites.

2) **Offspring:** Preweaning pups that were culled, died or were euthanized were necropsied. At weaning, pups not selected to become the F_1 parents and all F_2 pups were sacrificed and necropsied. Tissues with gross lesions were preserved in neutral buffered formalin for possible future examination.

D. DATA ANALYSIS

1. **Statistical analyses:** Incidence data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution. Body weights, body weight gains, food consumption, organ weights, pup body weights, percent male pups, percent mortality, and cumulative survival were analyzed for homogeneity of variance using Bartlett's Test. If the variances were homogeneous, the data were analyzed using an analysis of variance (ANOVA). If the ANOVA was significant, Dunnett's Test was used to determine the statistical significance of the individual groups. Data with nonhomogeneous variances were analyzed with the Kruskal-Wallis Test if 75% or fewer ties were present; or with Fisher's Exact Test when more than 75% ties were present. If the Kruskal-Wallis Test was significant, Dunn's Test was used to determine the statistical significance of the individual groups. All other natural delivery data were analyzed with the Kruskal-Wallis Test if 75% or fewer ties were present followed by Dunn's Test if significant.

2. Indices:

Reproductive indices: The following reproductive indices as presented in the study report were calculated for the P and F_1 adults:

male mating index = # of males that mated during days 1-14 of cohabitation/total # of males in cohabitation x 100%
male impregnation index = # of pregnant females/# of males paired x 100%
male fertility index= # of pregnant females/# of males that inseminated females x 100%
female pregnancy index = # of pregnant females/# of females paired x 100%
female fertility index = # of pregnant females/# of inseminated females x 100%
gestation index = # of females delivering live litters/# of pregnant females x 100%

Offspring viability indices: The following viability indices as presented in the study report were calculated for the F_1 and F_2 litters:

livebirth index - not defined in the study report. Surmised by the reviewers to be:
# of pups born live/total # of pups born

stillbirth index - not defined in the study report. Surmised by the reviewers to be:
# of pups born dead/total pups born
viability index = # of live pups at day 4 (preculling)/# of pups born alive x 100%
lactation index = # of live pups at day 21/# of live pups at day 4 (postculling) x 100%

3. Historical control data: Historical control data were provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: There were no treatment-related deaths in the P males. Two 5 ppm P males died, one on day 74, the other on day 112, but the deaths were not dose-dependent and therefore considered unrelated to treatment. One high-dose P female rat was found dead on day 56. The death was considered treatment-related because of the observed erosions in the stomach and because the animal progressively lost weight for two weeks prior to death. One 20 ppm P female died on day 5 of lactation, but the death was not dose-dependent and therefore considered unrelated to treatment. One high-dose female was found dead on day 3 of presumed gestation, but the only necropsy finding was a liver fibroma with associated hepatonecrosis and therefore this death was considered unrelated to treatment. Seventeen high-dose F_1 male pups died between days 2 and 44 postweaning. All deaths were considered treatment-related. Clinical signs observed included: ataxia, impaired righting reflex, and stained abdomen, nose, mouth, neck, and chest, hyperactivity, splayed limbs, vocalization, and excess salivation. Necropsy findings included: black, red, and/or brown material in the gastrointestinal tract, stomach erosions, enlarged adrenals, cerebral congestion, and blood clots in the brain. Nineteen high-dose F_1 female pups died between days 2 and 44 postweaning. Clinical signs and necropsy

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findings were similar to those observed in F_1 male pups. One 20 ppm F_1 female died, but the death was not dose-dependent and therefore considered unrelated to treatment. One control F_1 female died on day 20 postpartum.

Treatment-related clinical signs (Table 3a and b) observed ($p \leq 0.01$) in the high-dose P males were lesions on the head, neck, or forelimbs (11/30 treated vs. 1/30 controls) and alopecia (8/30 treated vs. 2/30 controls). In the high-dose P females, clinical signs observed ($p \leq 0.01$) were limited to ataxia (22/25 treated vs. 0/25 controls) and hypersensitivity (3/25 treated vs. 0/25 controls) during lactation. In the high-dose F_1 males, clinical signs observed were ataxia (28/28 treated vs. 0/30 controls), impaired righting reflex (23/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (10/28 treated vs. 1/30 controls), hyperactivity (9/28 treated vs. 0/30 controls), splayed limbs (8/28 treated vs. 0/30 controls), vocalization (7/28 treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red, dried, and/or yellow substance on nose, mouth, neck, chest, fur, and/or abdomen (13/28 vs. 0/30 treated). In the high-dose F_1 females, clinical signs observed during premating were ataxia (27/28 treated vs. 0/30 controls), impaired righting reflex (25/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (6/28 treated vs. 1/30 controls), hyperactivity (8/28 treated vs. 0/30 controls), splayed limbs (3/28 treated vs. 0/30 controls), vocalization (7/28 treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red or brown, wet, dried, and/or yellow substance on nose, mouth, neck, chest, fur, and/or abdomen (14/28 vs. 0/30 treated). During gestation and lactation, F_1 females demonstrated ($p \leq 0.01$) skin lesions (1/9 treated vs. 0/25 controls), foot splay (6/8 treated vs. 0/20 controls), and ataxia (2/8 treated vs. 1/20 controls).

Table 3a. Select clinical signs observed in P adult rats fed deltamethrin.[a]

Clinical Sign	Dietary Level (ppm)				
	0	5	20	80	320
P Males-Premating and Mating					
Total examined	30	30	30	30	30
Skin lesions	1	1	3	1	11**
Alopecia	2	1	3	3	8**
P Females-Lactation					
Total examined	25	21	25	22	25
Ataxia	0	0	0	0	22**
Hypersensitivity	0	0	0	0	3**

a Data extracted from the Study Report, Tables B2 and C2, pages 107 and 190, MRID 44398101.
** Significantly different from controls at $p \leq 0.01$.

Table 3b. Select clinical signs observed in F_1 adult rats fed deltamethrin.[a]

Clinical Sign	Dietary Level (ppm)				
	0	5	20	80	320
F_1 Males-Premating and Mating					
Total examined	30	30	30	30	28
Ataxia	0	0	0	0	28**
Impaired righting reflex	0	0	0	0	23**
Urine-stained abdominal fur	0	0	0	0	15**
Skin lesions	1	1	0	1	10**
Hyperactivity	0	0	0	0	9**
Splayed limbs	0	0	0	0	8**
Vocalization	0	0	0	0	7**
Excessive salivation	0	0	0	0	4**
External red, dried, and/or yellow substance	0	0	0	0	13**
F_1 Females-Premating					
Total examined	30	30	30	30	28
Ataxia	0	0	0	0	27**
Impaired righting reflex	0	0	0	0	25**
Urine-stained abdominal fur	0	0	1	0	15**
Hyperactivity	0	0	0	0	8**
Vocalization	0	0	0	0	7**
Skin lesions	1	0	1	0	6**
Excessive salivation	0	0	0	0	4**
Splayed limbs	0	0	0	0	3**
External red or brown, wet, dried, and/or yellow substance	0	0	0	0	14**
F_1 Females-Gestation					
Total examined	25	19	28	28	9
Lesion	0	0	0	0	1**
F_1 Females-Lactation					
Total examined	20	11	21	23	8
Foot splay	0	0	0	0	6**
Ataxia	1	0	0	0	2**

a Data extracted from the Study Report, Tables D2 and E2, pages 315, 316, 431 through 433, 436, and 437, MRID 44398101.

** Significantly different from controls at $p \leq 0.01$.

2. Body weight, body weight gains, and food consumption: Body weights (Tables 4a and b) were decreased ($p \leq 0.01$) relative to concurrent controls throughout the premating period in high-dose P males (↓13-16%), P females (↓7-11%), F_1 males (↓23-49%), and F_1 females (↓15-47%). Body weights were decreased ($p \leq 0.05$ or 0.01) in P females for GDs 0-15 (↓7-11%) and for LDs 1-14 (↓7-16%). In F_1 females, body weights were decreased ($p \leq 0.05$ or 0.01) throughout gestation (↓11-15%) and LDs 1-14 (↓11-15%). There were no differences in body weight in the other treatment groups.

Body weight gains (Tables 4c and d) were decreased ($p \leq 0.01$) during premating in high-dose P males (↓16-89 in 4/12 weeks), F_1 males (↓26-75% in 4/14 weeks), and F_1 females (↓30-81% in 3/14 weeks); and highly variable in P females (↓30-↑300% in 5/12 weeks). Body weight gains for the overall premating periods (1-82 days for P; 1-99 days for F_1) were decreased in all high-dose groups (P males - ↓24%; P females - ↓20%; F_1 males - ↓24%; F_1 females - ↓22%). There were sporadic differences in body weights gains in the 80 ppm F_1 females (↓45-↑8%, $p \leq 0.05$ or 0.01), but these were not considered of toxicological concern. Body weight gains were increased in P females during gestation days 6-10 (↑52%, $p<0.01$), but decreased during lactation (↓3625% - days 1-4; ↓221% - days 1-14; $p \leq 0.01$). The increases observed during gestation were not of toxicological concern. The decreases observed during lactation were highly variable and therefore should not be used to assess the toxicity of deltamethrin during this period. There were no differences in body weight gains in F_1 females during gestation or lactation.

Table 4a. Selected mean body weights (g); P and F_1 generation males and females during premating.[a]

Study Day	Dose Group (ppm)				
	0	5	20	80	320
P Generation Males					
Day 1	239.6±25.8	245.0±11.8	244.1±12.5	244.2±12.3	244.1±12.7
Day 8	296.7±14.8	295.5±19.1	294.3±18.0	290.6±29.7	250.2±22.0(↓16)**
Day 50	499.8±44.1	495.8±41.1	495.2±34.8	501.0±40.0	432.0±38.9(↓14)**
Day 82	582.1±58.6	573.6±52.8	574.7±44.5	584.1±50.8	503.9±48.7(↓13)**
P Generation Females					
Day 1	174.5±11.3	173.9±11.5	171.3±11.9	173.1±13.0	174.1±11.5
Day 8	198.5±13.7	198.6±15.4	197.2±13.9	198.9±16.1	179.4±20.6(↓10)**
Day 15	223.0±17.2	221.7±17.9	220.4±17.1	222.8±18.9	206.6±18.2(↓7)**
Day 43	288.3±24.2	292.8±25.2	287.7±29.6	285.6±27.2	256.5±20.9(↓11)**
Day 82	318.0±29.1	326.3±30.3	315.8±29.1	318.8±33.1	287.8±25.5(↓9)**
F_1 Generation Males					
Day 1	58.9±9.6	60.1±8.1	57.8±10.0	58.4±7.2	38.9±7.5(↓34)**
Day 8	106.0±14.6	110.3±12.1	104.7±13.4	107.9±9.6	56.1±12.4(↓47)**
Day 15	172.6±20.4	179.7±18.8	168.8±19.4	176.8±13.9	88.7±23.0(↓49)**
Day 43	416.6±34.3	437.0±40.7	414.7±29.9	429.5±29.4	276.2±62.4(↓34)**
Day 92	593.9±53.3	630.1±67.0*	604.8±53.9	622.7±48.2	456.6±64.9(↓23)**
Day 99	612.2±57.4	643.4±61.5	620.0±55.8	639.8±46.7	462.4±61.4(↓24)**
F_1 Generation Females					
Day 1	52.7±9.6	56.6±7.3	55.0±7.5	55.5±6.5	38.3±6.7(↓27)**
Day 8	95.9±13.6	102.0±8.7	97.2±10.5	97.6±9.2	50.8±11.9(↓47)**
Day 15	145.4±15.5	154.8±13.3*	146.8±13.1	151.1±11.7	86.0±19.0(↓41)**
Day 71	319.1±39.0	340.1±40.1	311.8±31.4	315.1±23.5	271.9±22.4(↓15)**
Day 99	361.4±44.8	374.2±51.8	338.0±38.9	338.5±31.9	285.2±21.9(↓21)**

a Data extracted from the Study Report, Tables B7, C7, D7, and E7; pages 112, 196, 325, 326, 444, and 445, MRID 44398101. Percent change from controls is presented parenthetically.

** Significantly different from controls at $p \leq 0.01$.

Table 4b. Mean body weights (g); P and F_1 females during gestation and lactation.[a]

Study Day	Dose Group (ppm)				
	0	5	20	80	320
P Generation Females-Gestation					
GD 0	316.6±25.9	326.0±28.0	311.1±32.0	315.7±29.2	281.7±28.8(↓11)**
GD 6	352.1±25.5	365.2±27.8	345.5±28.7	353.5±30.6	312.8±27.8(↓11)**
GD 10	363.8±28.4	375.4±29.5	358.8±30.6	366.0±33.3	330.6±26.6(↓9)**
GD 15	384.4±22.1	402.0±27.0	382.4±35.1	386.6±44.8	357.8±28.9(↓7)**
GD 20	451.0±36.6	468.8±39.2	456.0±35.9	453.0±45.6	426.3±30.2
P Generation Females-Lactation					
LD 1	350.6±30.2	370.8±35.1	353.7±35.9	355.0±33.6	325.4±28.6(↓7)*
LD 4	354.4±26.5	369.0±36.2	348.1±33.4	348.6±32.0	311.1±27.2(↓12)**
LD 7	364.0±29.3	372.2±33.4	354.3±30.5	352.0±33.3	308.5±29.3(↓15)**
LD 14	367.0±23.2	379.1±32.0	365.5±27.9	365.8±27.5	307.4±31.1(↓16)**
F_1 Generation Females-Gestation					
GD 0	338.7±51.4	367.2±48.3	339.1±40.5	338.9±35.5	288.2±19.2(↓15)**
GD 6	361.4±43.4	400.5±51.1*	372.3±39.3	369.0±35.3	316.8±22.4(↓12)*
GD 10	374.4±44.5	411.3±51.8*	383.2±38.3	378.7±34.6	330.4±25.8(↓12)*
GD 15	399.0±49.9	438.6±57.8	412.8±37.4	407.3±33.5	353.6±26.2(↓11)*
GD 20	469.6±61.7	498.8±62.5	483.5±40.3	474.6±42.1	411.9±48.6(↓12)*
F_1 Generation Females-Lactation					
LD 1	371.0±51.9	406.7±56.1	384.0±37.5	382.6±38.1	329.4±29.7(↓11)*
LD 4	378.5±45.5	412.1±55.7	386.0±38.1	382.3±36.9	326.8±33.1(↓14)**
LD 7	378.2±45.0	411.7±51.9	388.3±37.9	379.9±37.2	320.6±25.3(↓15)**
LD 14	373.7±49.5	404.4±45.1	388.4±39.2	375.3±40.0	315.9±30.7(↓15)**

a Data extracted from the Study Report, Tables C9, C11, E9, and E11; pages 198, 200, 448, and 450, MRID 44398101. Percent change from controls is presented parenthetically.

* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.

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Table 4c. Selected mean body weight gains (g); P and F_1 generation males and females during premating.[a]

Study Period	Dose Group (ppm)				
	0	5	20	80	320
P Generation Males					
Day 1-8	57.1±21.5	50.5±14.2	50.2±11.6	46.4±24.8	6.1±16.7(↓89)**
Day 8-15	46.2±9.3	46.1±9.4	47.6±8.3	51.7±14.7	42.8±7.8
Day 15-22	40.7±8.1	36.6±9.4	37.3±7.8	41.4±7.6	34.0±8.6(↓16)**
Day 22-29	40.2±8.2	42.3±11.5	39.3±7.0	41.0±8.6	30.9±7.5(↓23)**
Day 57-64	25.2±9.1	26.7±6.8	25.5±9.1	25.1±6.9	16.6±7.2(↓34)**
Day 1-82	342.5±52.4	328.9±50.1	330.6±39.9	339.9±47.4	259.8±43.7(↓24)**
P Generation Females					
Day 1-8	24.0±4.9	24.7±6.2	25.9±9.2	25.8±6.4	5.4±14.9(↓78)**
Day 8-15	24.5±6.8	23.1±10.5	23.1±9.5	24.0±6.7	27.1±10.8
Day 15-22	20.6±8.8	24.8±13.9	24.0±10.6	20.0±6.2	14.4±5.6(↓30)**
Day 29-36	16.9±7.2	17.0±7.2	16.8±8.8	14.2±7.6	10.3±6.3(↓39)**
Day 43-50	2.3±6.4	3.7±6.6	0.5±6.2	4.7±7.2	5.4±12.6(↑35)*
Day 78-82	1.6±5.4	2.4±5.0	2.9±3.6	4.2±5.2*	6.4±3.5(↑300)**
Day 1-82	143.5±20.7	152.4±23.5	144.5±24.7	145.7±26.0	114.6±17.1(↓20)**
F_1 Generation Males					
Day 1-8	47.1±7.9	50.2±6.6	46.9±5.0	49.6±4.4	12.0±10.1(↓75)**
Day 8-15	66.6±7.4	69.4±9.9	64.1±7.2	68.9±5.8	31.2±16.5(↓53)**
Day 15-22	70.1±6.2	71.6±8.9	69.7±7.5	70.4±15.3	39.4±17.6(↓44)**
Day 22-29	67.6±7.8	69.8±9.0	66.5±7.8	68.6±12.7	49.7±10.8(↓26)**
Day 1-99	548.9±52.8	583.8±61.6*	553.8±58.0	577.9±47.5	418.2±59.5(↓24)**
F_1 Generation Females					
Day 1-8	43.2±5.6	45.3±5.7	42.2±6.0	42.2±4.9	8.3±8.8(↓81)**
Day 8-15	49.5±5.1	52.8±7.1	49.6±5.1	53.4±5.3(↑8)*	34.5±10.3(↓30)**
Day 15-22	39.8±7.2	39.0±7.2	38.9±8.3	37.5±5.0	33.8±15.8
Day 22-29	29.2±8.2	33.1±7.9	27.0±7.1	28.7±6.9	32.4±8.6
Day 71-78	12.9±7.5	13.6±10.3	8.7±10.3	7.1±6.9(↓45)**	4.9±5.2(↓62)**
Day 1-99	309.6±43.2	317.2±48.2	283.0±36.4	282.9±31.0(↓9)*	242.3±17.2(↓22)**

a Data extracted from the Study Report, Tables B8, C8, D8, and E8; pages 113, 197, 327, 328, 446, and 447, MRID 44398101. Percent change from controls is presented parenthetically.

* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.

Table 4d. Mean body weight gains (g); P and F_1 females during gestation and lactation.[a]

Study Period	Dose Group (ppm)				
	0	5	20	80	320
P Generation Females-Gestation					
GD 0-6	35.5±8.9	39.2±12.8	34.4±10.8	37.8±6.7	31.1±7.3
GD 6-10	11.7±7.3	10.1±7.3	13.3±5.2	12.5±4.9	17.8±5.9(↑52)**
GD 10-15	20.6±14.3	26.7±8.4	23.6±13.8	20.6±22.6	27.2±7.0
GD 15-20	66.5±22.5	66.7±22.2	73.6±14.2	66.4±26.7	68.5±8.8
GD 0-20	134.4±34.5	142.7±33.7	144.9±23.2	137.3±23.4	144.6±14.1
P Generation Females-Lactation					
LD 1-4	0.4±9.2	-1.8±11.9	-4.5±16.7	-6.8±13.2	-14.1±11.6(↓3625)**
LD 4-7	10.2±32.6	3.2±12.6	6.2±13.27	3.4±9.7	-2.6±13.0
LD 7-14	3.0±30.7	6.9±22.8	11.2±21.9	13.8±18.1	-1.1±13.5
LD 1-14	14.5±18.8	8.3±19.1	13.3±25.5	11.8±18.0	-17.6±16.1(↓221)**
F_1 Generation Females-Gestation					
GD 0-6	22.8±16.9	33.3±9.5	33.2±7.5	30.2±12.2	28.6±8.4
GD 6-10	13.0±9.4	10.8±13.7	10.9±7.8	9.6±9.9	13.7±6.2
GD 10-15	24.5±12.0	27.3±18.0	29.6±13.1	28.6±15.9	23.1±8.2
GD 15-20	70.6±20.1	59.1±33.6	70.7±17.2	67.3±22.6	58.3±25.5
GD 0-20	130.9±36.8	129.1±30.5	144.4±29.0	135.7±31.4	123.7±32.3
F_1 Generation Females-Lactation					
LD 1-4	3.6±12.2	5.4±12.1	1.9±10.4	-0.3±11.3	-2.6±9.4
LD 4-7	-0.3±9.1	-0.4±11.5	2.4±11.1	-2.4±11.7	-6.1±14.1
LD 7-14	-4.5±28.1	-7.3±33.1	0.0±22.2	-4.6±18.6	-4.8±16.1
LD 1-14	-1.3±26.5	-2.3±34.3	4.3±26.8	-7.3±21.8	-13.5±18.6

a Data extracted from the Study Report, Tables C10, C12, E10, and E12; pages 199, 201, 449, and 451, MRID 44398101.

** Significantly different from controls at $p \leq 0.01$.

Absolute food consumption (g/animal/day; Table 4e) was decreased ($p \leq 0.05$ or 0.01) in high-dose groups throughout the premating period (P males - ↓9-41%; P females - ↓8-34%; F_1 males - ↓12-59%; F_1 females - ↓14-51%). Overall food consumption for the premating periods (days 1-82 for the P animals; days 1-99 for the F_1 animals) were decreased (P males - ↓16%; P females - ↓13%; F_1 males - ↓25%; F_1 females - ↓23%). The largest decrease in food consumption was observed during the first week of dosing in all groups (↓34-59%, $p \leq 0.01$), suggesting that the diet was unpalatable. Differences in food consumption were observed in other treatment groups, but these were minor and/or sporadic and therefore not considered of toxicological concern. Relative food consumption (g/kg/day) was decreased ($p \leq 0.01$) during the first week in all high-dose groups (↓24-36%) and during the second week in F_1 males (↓17%), but was increased (↑14-18%, $p \leq 0.05$ or 0.01) and/or only slightly decreased (↓2-6%, $p \leq 0.05$ or 0.01) at later periods in all high-dose groups. The decreases during the first and second week were attributed to the unpalatability of the diet formulation; therefore, these and the other differences in relative food consumption observed were not considered of toxicological concern.

There were no differences in absolute food consumption of toxicological concern between treated and control P or F_1 dams during gestation (Table 4f). During lactation, P dams (↓19-26%) and F_1 dams (↓16-26%) ate less ($p \leq 0.05$ or 0.01) than controls at all intervals.

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Table 4e. Selected mean absolute food consumption (g/animal/day); P and F_1 generation males and females during mating and premating.[a]

Study Period	Dose Group (ppm)				
	0	5	20	80	320
P Generation Males					
Day 1-8	26.2±1.8	26.0±3.3	25.7±3.2	25.7±4.4	15.5±3.1(↓41)**
Day 8-15	27.4±2.4	27.4±2.6	27.5±2.4	27.7±2.8	22.0±2.3(↓20)**
Day 15-22	28.6±2.8	28.3±2.8	27.5±2.4	28.1±3.9	23.5±2.5(18)**
Day 50-57	31.6±3.5	32.2±2.9	31.3±2.3	32.2±3.2	28.6±2.2(↓9)**
Day 78-82	33.6±4.4	33.1±4.2	32.4±3.1	33.2±3.4	28.9±2.3(↓14)**
Day 1-82	30.6±3.1	30.5±2.6	30.0±2.0	30.8±2.8	25.8±1.9(↓16)**
P Generation Females					
Day 1-8	18.1±1.6	18.2±1.7	18.1±1.8	17.7±1.7	12.0±2.8(↓34)**
Day 8-15	19.0±1.9	18.9±4.0	19.2±2.0	19.4±1.9	17.3±1.3(↓9)**
Day 15-22	19.8±2.7	20.1±2.3	19.7±2.5	19.5±2.0	17.0±1.4(↓14)**
Day 36-43	21.3±2.4	22.0±2.7	22.4±3.4	21.9±2.9	19.5±1.7(↓8)**
Day 78-82	20.8±2.3	21.5±2.4	20.8±2.4	20.0±2.2	18.9±1.8(↓9)**
Day 1-82	20.5±2.0	21.0±2.0	20.6±2.0	20.6±2.0	17.9±1.5(↓13)**
F_1 Generation Males					
Day 1-8	13.2±1.8	13.9±1.9	12.3±2.5	12.6±2.5	5.4±1.7(↓59)**
Day 8-15	21.0±2.0	21.6±2.3	20.4±1.9	21.1±1.5	9.4±3.1(↓55)**
Day 15-22	26.6±2.3	27.5±2.5	26.2±2.3	27.5±2.1	14.6±3.7(↓45)**
Day 64-71	31.5±3.4	33.3±3.6	32.2±3.0	32.8±2.6	27.6±3.6(↓12)**
Day 1-99	29.7±2.6	30.3±2.8	29.4±2.0	30.0±1.9	22.2±2.4(↓25)**
F_1 Generation Females					
Day 1-8	11.3±2.2	12.2±2.4	11.1±2.3	10.9±3.1	5.5±1.6(↓51)**
Day 8-15	18.3±1.9	20.0±1.6(↑9)**	17.9±2.5	18.9±1.3	10.2±3.3(↓44)**
Day 15-22	20.9±2.1	22.5±1.8(↑8)*	21.2±2.5	21.3±1.5	13.9±3.9(↓33)**
Day 22-29	21.8±2.6	23.5±2.4(↑8)*	21.2±2.5	21.5±1.5	16.8±3.4(↓23)**
Day 43-50	23.0±3.5	25.2±3.0(↑10)**	22.5±2.8	22.5±2.3	19.7±2.1(↓14)**
Day 1-99	22.3±2.5	23.0±2.3	20.6±2.0*	20.9±1.7*	17.1±1.9(↓23)**

a Data extracted from the Study Report, Tables B9, C13, D9, and E13; pages 114, 202, 329, 330, 452, and 453, MRID 44398101. Percent change from controls is presented parenthetically.

* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.

Table 4f. Mean absolute food consumption (g/animal/day); P and F_1 females during gestation and lactation.[a]

Study Period	Dose Group (ppm)				
	0	5	20	80	320
P Generation Females-Gestation					
GD 0-6	25.3±2.9	25.9±2.3	24.4±2.4	25.8±2.1	21.7±1.9(↓14)**
GD 6-10	27.4±4.2	28.7±5.0	26.8±3.0	28.2±3.1	26.2±2.4
GD 10-15	24.8±3.4	27.5±4.0*(↑11)	25.3±2.9	24.2±5.2	23.7±2.2
GD 15-20	26.6±5.1	28.7±2.1	27.9±3.6	28.2±4.3	27.1±3.1
GD 0-20	26.0±3.0	27.7±3.2*(↑7)	26.0±2.2	26.5±2.1	24.4±1.9
P Generation Females-Lactation					
LD 1-4	35.1±10.1	30.2±7.6	27.8±4.6*	32.3±9.6	25.9±4.4(↓26)**
LD 4-7	40.5±6.0	41.5±8.2	40.5±7.4	41.4±6.3	32.8±5.4(↓19)**
LD 7-14	55.1±6.6	54.2±9.6	54.4±8.2	55.7±7.0	42.3±6.5(↓23)**
LD 1-14	48.0±5.3	46.1±8.2	45.9±4.6	47.1±6.5	36.3±5.2(↓24)**
F_1 Generation Females-Gestation					
GD 0-6	22.9±4.7	27.4±3.9(↑20)**	26.1±2.6(↑14)*	24.3±4.1	22.1±2.9
GD 6-10	25.3±3.5	27.4±6.5	26.6±3.0	25.1±2.6	23.1±3.6
GD 10-15	25.3±4.3	28.9±4.7*(↑14)	27.2±3.0	26.9±3.7	23.1±2.3
GD 15-20	26.2±4.2	27.5±3.5	28.0±3.3	26.9±5.0	25.4±4.0
GD 0-20	24.8±3.0	28.0±3.0(↑13)**	26.9±2.3(↑8)*	25.8±2.6	23.6±2.8
F_1 Generation Females-Lactation					
LD 1-4	31.9±4.8	32.7±4.2	34.4±7.2	33.3±8.1	26.9±3.2(↓16)*
LD 4-7	41.9±3.8	41.9±4.3	44.3±7.5	40.3±6.7	32.2±4.7(↓23)**
LD 7-14	54.3±6.6	56.5±7.2	54.5±8.7	54.4±8.2	40.4±5.6(↓26)**
LD 1-14	46.2±4.2	47.6±4.3	47.1±6.7	46.4±6.7	35.4±4.2(↓23)**

a Data extracted from the Study Report, Tables C15, C17, E15, and E17; pages 204, 206, 456, and 458, MRID 44398101. Percent change from controls is presented parenthetically.

* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.

3. **Test substance intake:** The mean intake of deltamethrin (mg/kg/day) in the P and F_1 animals for the premating, gestation, and lactation periods was calculated using food consumption and diet concentration (Tables 5a and b). During the premating period, P females consumed 11-33% more of the test substance than the corresponding males; F_1 females consumed 0-21% more than the F_1 males. These values were considered to be representative of the compound intake for the entire study.

Table 5a. Compound intake during the premating period[a]

Test Group	Dose (ppm)	Overall achieved dosages (mg/kg/day)			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	0	0	0	0
Low-dose	5	0.3	0.4	0.4	0.4
Mid-dose	20	1.3	1.5	1.4	1.7
High-mid-dose	80	5.4	6.1	5.8	6.7
High-dose	320	21.2	23.5	24.9	27.2

a Data extracted from Study Report, Tables B1, C1, D1, and E1; pages 106, 185, 413, and 428, MRID 44398101.

Table 5b. Compound intake during the gestation and lactation period[a]

Test Group	Dose (ppm)	Overall achieved dosages (mg/kg/day)			
		P Dams		F_1 dams	
		Gestation	Lactation	Gestation	Lactation
Control	0	0	0	0	0
Low-dose	5	0.3	0.6	0.3	0.6
Mid-dose	20	1.4	2.5	1.4	2.4
High-mid-dose	80	5.7	10.6	5.2	9.7
High-dose	320	23.0	37.3	21.8	35.0

a Data extracted from Study Report, Tables C1and E1; pages 186, 187, 429, and 430, MRID 44398101.

4. Reproductive function:

a. Estrous cycle length and periodicity: No observations were made pertaining to estrous cycle length and periodicity.

b. Sperm and male reproductive organ measures in males: No observations were made pertaining to sperm measures. One male in each of the 5, 80, and 320 ppm P groups and one 5 ppm F_1 male had flaccid and purple testes and reduced testes weights. The observations were not dose-dependent and the incidences (3.3%) were within historical control range (unilateral or bilateral small flaccid testes - 0-6.7%) and therefore the observations were considered incidental.

5. Reproductive performance: There were no differences of toxicological concern observed in the reproductive performance of the P or F_1 adults (Tables 6a and b). The 5 ppm F_1 dams had decreased ($p \leq 0.05$ or 0.01) mating (↓24%) and pregnancy (↓35%) indices relative to concurrent controls, but the effect was not dose-dependent and therefore not considered of toxicological concern. High-dose F_1 dams had increased ($p \leq 0.05$ or 0.01) mating (↑20%) and pregnancy (↑50%) indices and high-dose F_1 sires had an increased impregnation index (↑76%), but these increases in fertility were not considered of toxicological concern.

Table 6a. Reproductive performance of P dams.[a]

Observation	Dose Group (ppm)				
	0	5	20	80	320
P Generation - Litter F_1					
Male Mating Index-%	90.0	89.6	83.3	93.3	100.0
Male Impregnation Index - %	76.7	69.0	76.7	73.3	86.2
Male Fertility Index - %	85.2	76.9	92.0	78.6	86.2
Female Mating Index-%	100.0	96.7	96.7	93.3	100.0
Female Pregnancy Index - %	83.3	73.3	83.3	73.3	86.2
Female Fertility Index-%	83.3	75.9	86.2	78.6	86.2
Gestation Index-%	100.0	95.4	96.0	100.0	100.0
Mean days to mating	NR	NR	NR	NR	NR
Gestation Length (days)	23.3	23.2	23.1	23.1	22.9
Number of Litters	25	21	24	22	25

a Data extracted from the study report, Tables B11, C19, and C20, pages 116, 208, and 209, MRID 44398101.
NR Not reported.

Table 6b. Reproductive performance of F_1 dams.[a]

Observation	Dose Group (ppm)				
	0	5	20	80	320
F_1 Generation - Litter F_2					
Male Mating Index-%	66.7	63.3	90.0	76.7	100.0
Male Impregnation Index - %	56.7	43.3	70.0	66.7	100.0(↑76)**
Male Fertility Index - %	85.0	68.4	77.8	87.0	100.0
Female Mating Index-%	83.3	63.3(↓24)**	93.3	93.3	100.0(↑20)*
Female Pregnancy Index - %	66.7	43.3(↓35)*	70.0	76.7	100.0(↑50)**
Female Fertility Index-%	80.0	68.4	75.0	82.1	100.0
Gestation Index-%	95.0	84.6	100.0	100.0	88.9
Mean days to mating	NR	NR	NR	NR	NR
Gestation Length (days)	23.2	22.8	23.1	23.3	22.9
Number of Litters	19	11	21	23	8

a Data extracted from the study report, Tables D11, E19, and E20, pages 333, 460, and 461, MRID 44398101. Percent change from controls is presented parenthetically.
NR Not reported.
* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.

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6. **Parental postmortem results**

a) **Organ weights:** There were no changes in organ weights of toxicological concern. The differences ($p \leq 0.05$ or 0.01) relative to concurrent controls were considered incidental due to the fact that the changes were not dose-dependent, due to decreased terminal body weights (↓13-20%, $p \leq 0.01$), and/or there was no associated histopathological or gross pathological evidence to corroborate a treatment-related effect. For example, high-dose P males had increased relative (to body) left epididymis (↑18%), testes (↑10-14%), seminal vesicles with fluid (↑21%), pituitary (↑13%) and brain (↑15%) weights. High-dose P females had decreased absolute right ovary (↓23%), nongravid uterus (↓30%), and pituitary (↓12%) weights; increased relative (to body) brain weights (↑21%); and decreased relative (to brain) nongravid uterus (↓28%) and pituitary (↓15%) weights. High-dose F_1 males had decreased absolute epididymides (↓16%) and testes (↓12%) weights, increased relative (to body) testes (↑7-10%), seminal vesicles with fluid (↑21%), and brain (↑22%) weights; and decreased relative (to brain) epididymides (↓13%) and testes (↓9%) weights. High-dose F_1 females had decreased absolute right ovary (↓21%), and nongravid uterus (↓37%) weights; increased relative (to body) brain weights (↑19%); and decreased relative (to brain) right ovary (↓21%) and nongravid uterus weights (↓37%).

b) **Pathology:**

1) **Macroscopic examination:** Treatment-related gross pathological findings (Table 7) were limited to the high-dose F_1 rats that died during the study. These animals demonstrated cerebral congestion and/or blood clots (males - 9/28 treated vs. 0/30 controls; females - 12/28 treated vs. 0/30 controls). Some of the deceased animals demonstrated stomachs and/or intestines distended with gas and/or food, but these findings were attributed to autolysis and were not considered of toxicological concern.

Table 7. Select necropsy observations in F_1 adult rats fed deltamethrin.[a]

Observation	Dietary Level (ppm)				
	0	5	20	80	320
F_1 Males-Premating					
Total examined	30	30	30	30	28
Brain: congested, dark, red	0	0	0	0	1
Cerebrum and Cerebellum: red	0	0	0	0	1
Subdural blood clot	0	0	0	0	3**
Blood clot in cerebral fissure	0	0	0	0	2
Epidural blood clot along the medial fissure	0	0	0	0	3**
Total # of animals with brain pathologies	0	0	0	0	9
F_1 Females-Premating					
Total examined	30	30	30	30	28
Brain: blood clots	0	0	0	0	12**
Brain: red to dark red	0	0	0	0	3**
Brain: congested	0	0	0	0	1
Total # of animals with brain pathologies	0	0	0	0	12

a Data extracted from the Study Report, Tables D3 and E3, pages 321 and 440, MRID 44398101.

2) Microscopic examination: There were no treatment-related histopathological findings in the tissues specified for examination in the P or F_1 adults. The brain was not examined.

B. OFFSPRING

1. Viability and clinical signs: An increase in mortality relative to concurrent controls in the high-dose F_1 pups (13/200 treated vs. 0/184 controls, $p \leq 0.01$) from PND 8 to 14 caused a decrease in the lactation index (↓8%, $p \leq 0.01$) for this group. The increases (↑1-7%, $p \leq 0.05$ or 0.01) in the livebirth and Day 4 viability indices of the 5, 80, and 320 ppm groups were not considered of toxicological concern. There were no differences of toxicological concern in the F_2 litters. High-dose mortality was increased from day 8-14 (1/64 in treated vs. 0/151 in controls, $p \leq 0.01$), but only one pup died, so the difference was not considered of toxicological concern. Increases occurred in livebirth indices in all F_2 treatment groups, but were not considered of toxicological concern. Viability indices are shown in Tables 8a and b. There were no differences in clinical signs in the F_1 or F_2 pups.

Table 8a. F_1 generation mean litter size and viability.[a]

Observation	Dose Group (ppm)				
	0	5	20	80	320
Mean litter size					
Day 1	13.9±2.8	13.5±4.6	13.0±4.3	13.9±3.6	15.2±2.5
Day 4[b]	12.9±4.4	13.2±4.6	12.2±4.6	13.8±3.6	14.7±2.1
Day 4[c]	7.4±1.8	7.5±1.6	7.3±2.0	7.7±0.9	8.0±0.0
Day 7	7.4±1.8	7.4±1.6	7.2±2.0	7.6±1.0	7.8±0.6
Day 14	7.4±1.8	7.4±1.6	7.2±2.0	7.6±1.0	7.3±1.4
Day 21	7.3±1.8	7.4±1.6	7.2±2.0	7.6±1.0	7.3±1.4
Number live pups					
Day 1	337	283	312	305	379
Day 4[b]	314	278	292	303	367
Day 4[c]	184	157	176	170	200
Day 7[d]	184	156	174	168	196
Day 14[d]	184	156	174	168	183
Day 21	183	156	174	168	183
Number deaths					
Days 1-4[d]	23	5	20	2	12
Days 8-14	0	0	0	0	13**
Days 4-21[d]	1	1	2	2	17
Viability indices (%)					
Stillborn	1.7	0.0	1.9	0.6	0.5
Livebirth	98.2	100.0**	97.8	99.3*	99.5**
Viability (Day 4)[b]	93.2	98.2**	93.6	99.3**	96.8**
Lactation	99.4	99.4	99.4	98.8	91.5(↓8%)**
Sex ratio (% male)[b]	52.0	56.9	49.7	49.3	49.2

a Data extracted from the Study Report, Table C21, pages 210 and 212, MRID 44398101. Percent change from controls is presented parenthetically.

* or ** Significantly different from controls at $p \leq 0.05$ or 0.01

b Before culling

c After culling

d Calculated by the reviewers from data extracted from the Study Report, Table C21, page 210.

Table 8b. F_2 generation mean litter size and viability.[a]

Observation	Dose Group (ppm)				
	0	5	20	80	320
Mean litter size					
Day 1	14.7±3.4	13.8±4.1	14.4±4.0	14.0±4.3	13.5±3.2
Day 4[b]	14.4±3.1	13.4±3.7	14.3±4.0	13.7±4.2	13.2±3.1
Day 4[c]	8.0±0.0	7.7±0.9	7.7±1.3	7.6±1.3	8.0±0.0
Day 7	7.9±0.2	7.7±0.9	7.7±1.3	7.6±1.3	8.0±0.0
Day 14	7.9±0.2	7.7±0.9	7.7±1.3	7.6±1.3	7.9±0.4
Day 21	7.9±0.2	7.7±0.9	7.7±1.3	7.6±1.3	7.9±0.4
Number live pups					
Day 1	280	152	303	321	108
Day 4[b]	274	147	300	316	106
Day 4[c]	152	85	162	175	64
Day 7[d]	151	85	162	175	64
Day 14[d]	151	85	162	175	63
Day 21	151	85	162	174	63
Number deaths					
Days 1-4[d]	6	5	3	5	2
Days 8-14	0	0	0	0	1**
Days 4-21[d]	1	0	0	1	1
Viability indices (%)					
Stillborn	0.3	0.6	0.3	0	0.9
Livebirth	97.9	99.3**	99.7**	100.0**	99.1*
Viability (Day 4)[b]	97.8	96.7	99.0	98.4	98.1
Lactation	99.3	100.0	100.0	99.4	98.4
Sex ratio (% male)[b]	47.0	53.8	47.6	54.5	52.4

a Data extracted from the Study Report, Table E21, pages 463-465, 467, and 468, MRID 44398101.
* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.
b Before culling.
c After culling.
d Calculated by the reviewers from data extracted from the Study Report, Table E21, pages 463 and 464.

2. <u>Body weights and gains</u>: Body weights (Table 9) were decreased ($p \leq 0.05$ or 0.01) relative to concurrent controls in high-dose F_1 pups (↓14-25%) for PNDs $4_{(precull)}$-21, and in high-dose F_2 pups (↓12-24%) for PNDs 7-21. Overall body weight gains were not analyzed by the investigator, but were reduced 28% and 27% for PNDs 1-21 in high-dose F_1 and F_2 pups, respectively.

Table 9. Mean F_1 and F_2 pup weights and body weight gains (g).[a]

Postnatal Day	Dose Group (ppm)				
	0	5	20	80	320
F_1 litters					
Day 1	6.7±0.9	7.1±0.6	6.8±0.7	6.6±0.7	6.4
Day 4[b]	10.4±1.4	10.4±1.4	9.8±1.9	10.2±1.7	8.9±1.1(↓14)**
Day 4[c]	10.5±1.5	10.5±1.4	9.9±1.9	10.2±1.6	9.0±1.2(↓14)**
Day 7	16.9±2.5	17.4±1.9	16.4±2.8	16.9±2.1	13.7±2.2(↓19)**
Day 14	34.1±4.8	34.2±3.9	34.0±5.1	35.1±3.3	26.8±3.5(↓21)**
Day 21	52.5±7.0	53.4±5.4	52.9±8.0	53.6±4.9	39.3±5.0(↓25)**
Gain (0-21)[d]	45.8	46.3	46.1	47.0	32.9(↓28)
F_2 litters					
Day 1	6.5±0.5	6.5±0.6	6.4±0.6	6.6±0.6	6.3±0.6
Day 4[b]	9.5±1.4	10.0±1.1	9.9±1.2	10.0±1.0	9.1±1.4
Day 4[c]	9.7±1.4	10.1±1.0	10.0±1.2	10.2±1.0	9.1±1.4
Day 7	16.2±2.2	17.5±1.8	17.0±1.8	16.9±1.3	14.2±2.1(↓12)*
Day 14	34.1±3.3	37.8±3.9**	36.2±3.4	35.3±2.5	27.2±3.7(↓20)**
Day 21	53.1±3.8	58.0±7.6	56.8±3.8*	56.0±4.5	40.1±6.4(↓24)**
Gain (0-21)[d]	46.6	51.5	50.4	49.4	33.8(↓27)

a Data extracted from the Study Report, Tables C21 and E21; pages 211 and 466, MRID 44398101.. Percent change from controls is presented parenthetically.
* or ** Significantly different from controls at $p \leq 0.05$ or 0.01.
b Before culling.
c After culling.
d Calculated by the reviewers from data extracted from the Study Report, Table C21 and E21, pages 211 and 466.

3. **Sexual maturation (F_1):** Not determined.

4. **Offspring postmortem results:**

a) **Organ weights:** Not determined.

b) **Pathology**

1) **Macroscopic examination:** There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

2) **Microscopic examination:** Not performed.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: Deltamethrin at 320 ppm caused clinical signs, reduced body weights, and decreased food consumption in both P and F_1 males and females, and increased mortality in the P females and F_1 males and females. The NOAEL for systemic toxicity is 80 ppm. Deltamethrin at up to 320 ppm did not affect mating performance or fertility in either generation. The NOAEL for reproductive toxicity is 320 ppm. In the F_1 pups, deltamethrin at 320 ppm caused increased deaths, a reduced lactation index, and reduced body weights at birth and throughout the lactation period. In the F_2 pups, deltamethrin at 320 ppm caused reduced body weights throughout the lactation period. The NOAEL for offspring toxicity is 80 ppm.

B. REVIEWER'S DISCUSSION: In this 2-generation reproduction study, deltamethrin was administered in the diet continuously to Sprague-Dawley rats (30/sex/dose) at dose levels of 0, 5, 20, 80, or 320 ppm (equivalent to 0, 0.3/0.4, 1.3/1.5, 5.4/6.1, or 21.2/23.5 mg/kg/day in the P animals [M/F] and 0, 0.4/0.4, 1.4/1.7, 5.8/6.7, or 24.9/27.2 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at approximately 6 weeks of age and lasted for at least 82 days prior to mating. F_1 pups selected (30/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents on PND 21 and continuously throughout the rest of the study. F_1 animals were administered the test article for at least 86 days prior to mating to produce the F_2 litters. Mating to produce a second F_{2b} generation was not performed. Exposure of all animals to the test material was continuous throughout the study.

The analytical data indicated that the variation between nominal and actual dosage to the study animals and formulation stability were acceptable.

1. Parental toxicity: There were no differences in food efficiency. There was no evidence of histopathological changes in the organs specified for examination. The brain was not examined. There were no differences of toxicological concern in organ weights.

Treatment-related mortality occurred in high-dose P females (1 rat), F_1 males (17) and F_1 females (19). Clinical signs observed in these rats included: ataxia, impaired righting reflex, and stained abdomen, nose, mouth, neck, and chest, hyperactivity, splayed limbs, vocalization, excess salivation, and enophthalmos. Necropsy findings included: black, red, and/or brown material in the gastrointestinal tract, stomach erosions, enlarged adrenals, cerebral congestion, and blood clots in the brain.

Treatment-related clinical signs observed ($p \leq 0.01$) in the high-dose P males were lesions on the head, neck, or forelimbs (11/30 treated vs. 1/30 controls) and alopecia (8/30 treated vs. 2/30 controls). In the high-dose P females, clinical signs observed ($p \leq 0.01$) were limited to ataxia (22/25 treated vs. 0/25 controls) and hypersensitivity (3/25 treated vs. 0/25 controls) during lactation. In the high-dose F_1 males, clinical signs observed were ataxia (28/28 treated vs. 0/30 controls), impaired righting reflex (23/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (10/28 treated vs. 1/30 controls), hyperactivity (9/28 treated vs. 0/30 controls), splayed limbs (8/28 treated vs. 0/30 controls), vocalization (7/28

treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red, dried, and/or yellow substance on nose, mouth, neck, chest, fur, and/or abdomen (13/28 vs. 0/30 treated). In the high-dose F_1 females, clinical signs observed during premating were ataxia (27/28 treated vs. 0/30 controls), impaired righting reflex (25/28 treated vs. 0/30 controls), urine-stained abdominal fur (15/28 treated vs. 0/30 controls), skin lesions (6/28 treated vs. 1/30 controls), hyperactivity (8/28 treated vs. 0/30 controls), splayed limbs (3/28 treated vs. 0/30 controls), vocalization (7/28 treated vs. 0/30 controls), excessive salivation (4/28 treated vs. 0/30 controls), and a red or brown, wet, dried, and/or yellow substance on nose, mouth, neck, chest, fur, and/or abdomen (14/28 vs. 0/30 treated). During gestation and lactation, F_1 females demonstrated ($p \leq 0.01$) skin lesions (1/9 treated vs. 0/25 controls), foot splay (6/8 treated vs. 0/20 controls), and ataxia (2/8 treated vs. 1/20 controls).

Body weights were decreased ($p \leq 0.01$) throughout the premating period in high-dose P males (↓13-16%), P females (↓7-11%), F_1 males (↓23-49%), and F_1 females (↓15-47%). Body weights were decreased ($p \leq 0.05$ or 0.01) in P females for GDs 0-15 (↓7-11%) and for LDs 1-14 (↓7-16%). In F_1 females, body weights were decreased ($p \leq 0.05$ or 0.01) throughout gestation (↓11-15%) and LDs 1-14 (↓11-15%).

Body weight gains were decreased ($p \leq 0.01$) during premating in high-dose P males (↓16-89 in 4/12 weeks), F_1 males (↓26-75% in 4/14 weeks), and F_1 females (↓30-81% in 3/14 weeks); and highly variable in P females (↓30-↑300% in 5/12 weeks). Body weight gains for the overall premating periods (1-82 days for P; 1-99 days for F_1) were decreased in all high-dose groups (P males - ↓24%; P females - ↓20%; F_1 males - ↓24%; F_1 females - ↓22%).

Absolute food consumption was decreased ($p \leq 0.05$ or 0.01) in all groups throughout the premating period (P males - ↓9-41%; P females - ↓8-34%; F_1 males - ↓12-59%; F_1 females - ↓14-51%). Overall food consumption for the premating periods (days 1-82 for the P animals; days 1-99 for the F_1 animals) were decreased (P males - ↓16%; P females - ↓13%; F_1 males - ↓25%; F_1 females - ↓23%). The largest decrease in food consumption was observed during the first week of dosing in all groups (↓34-59%, $p \leq 0.01$), suggesting that the diet was unpalatable. During lactation, P dams (↓19-26%) and F_1 dams (↓16-26%) ate less ($p \leq 0.01$) than controls at all intervals.

Treatment-related gross pathological findings were limited to the high-dose F_1 rats that died during the study. These animals demonstrated cerebral congestion and/or blood clots (males - 9/28 treated vs. 0/30 controls; females - 12/28 treated vs. 0/30 controls).

There were no treatment-related findings at any of the lower doses.

The LOAEL for parental systemic toxicity is 320 ppm in males and females (equivalent to 21.2/23.5 mg/kg/day [M/F]) based on increased mortality and clinical signs, decreased body weights, body weight gains, and absolute food consumption, and gross pathological findings in both sexes. The NOAEL is 80 ppm (equivalent to 5.4/6.1 mg/kg/day [M/F]).

2. Reproductive/offspring toxicity: There were no differences of toxicological concern in reproductive performance. Sexual maturation and developmental parameters were not measured.

The LOAEL for reproductive toxicity is greater than 320 ppm (equivalent to >21.2/23.5 mg/kg/day [M/F]. The NOAEL is equal to or greater than 320 ppm (equivalent to ≥24.9/27.2 mg/kg/day [M/F].

No treatment-related differences in clinical signs were observed at any time in the F_1 and F_2 litters. There were no treatment-related findings of toxicological concern at necropsy of the F_1 or F_2 litters.

An increase in mortality in the high-dose F_1 pups (13/200 treated vs. 0/184 controls, $p \leq 0.01$) from PND 8 to 14 caused a decrease in the lactation index (↓8%, $p \leq 0.01$) for this group.

Body weights were decreased ($p \leq 0.05$ or 0.01) relative to concurrent controls in high-dose F_1 pups (↓14-25%) for PNDs $4_{(precull)}$-21, and in high-dose F_2 pups (↓12-24%) for PNDs 7-21. Overall body weight gains were not analyzed by the investigator, but were reduced 28% and 27% for PNDs 1-21 in high-dose F_1 and F_2 pups, respectively.

There were no treatment-related findings at any of the lower doses.

The LOAEL for offspring systemic/developmental toxicity is 320 ppm (equivalent to 24.9/27.2 mg/kg/day [M/F]) based on increased pup mortality and decreased body weights and body weight gains. The NOAEL is 80 ppm (equivalent to 5.8/6.7 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS# 870-3800; OECD# 416) for a multigenerational reproductive toxicity study in the rat.

C. STUDY DEFICIENCIES: No deficiencies were noted.

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DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §84-2, Bacterial Gene Mutation (*Salmonella typhimurium*) and DNA Damage (*Escherichia coli*) Assays

Work Assignment No. 4-02-189K (MRID 42475902)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S.
Signature: David A. McEwen
Date: 7/1/02

Secondary Reviewer
Ronnie J. Bever, Jr., Ph.D.
Signature: Ronnie J. Bever Jr.
Date: 7/1/02

Program Manager
Mary L. Menetrez, Ph.D.
Signature: Mary L Menetrez
Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D.
Signature: Steven Brecher
Date: 7/3/02

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** SWF
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 010078 for previous review.

STUDY TYPE: *In vitro* Bacterial Gene Mutation (*Salmonella typhimurium*)/ Mammalian Activation Gene Mutation Assay; OPPTS 870.5100 [§84-2]; OECD 471 (formerly OECD 471 & 472). Other Genotoxicity: Bacterial DNA Damage in *Escherichia coli* (Pol A_1^-); OPPTS 870.5500 [§84-2]; OECD None

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (purity not reported)

SYNONYMS: RU 22974; (S)-α-cyano-3-phenoxybenzyl (1R,3S)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Chantot, J.F., R. Glomot, L. Penasse, et al. (1980) Detection of a mutagenic potency of decamethrin (RU22974) bacterial tests. Roussel Uclaf, Department of Toxicology, Romainville, France. Laboratory Report No.: RU/TOX/80.21.01/A, January 21, 1980. MRID 42475902. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In this study (MRID 42475902), two different bacterial assays were performed. In a DNA damage assay, *E. coli* strains W3110 (Pol A^+), WP2 ($uvrA^+$, $exrA^+$), p3478 (Pol A_1^-), and CM611 ($uvrA^-$, $exrA^-$) were exposed to deltamethrin (purity not reported; Lot/Batch #: not reported) in DMSO at concentrations of 0, 1250, 2500, or 5000 µg/mL for 18 hours. The well diffusion method was used. In a gene mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to deltamethrin (purity not reported; Lot/Batch #: not reported) in DMSO at concentrations of 0, 2, 10, 50, 200, 500, 1000, or 5000 µg/plate in the presence and absence of S9-activation in an Ames assay. Acceptable strain specific positive controls were used.

In the DNA damage assay, deltamethrin was tested up to the limit dose (5000 µg/mL). No treatment-related increases in the difference between zones of inhibition were observed in any treatment group compared to the concurrent controls. The positive controls induced the appropriate response. **There was no evidence that DNA damage was induced.**

In the gene mutation assay, deltamethrin was tested up to the limit of solubility (>200 µg/plate +/-S9). No treatment-related increases in the number of revertants/plate were observed in any bacterial strain at any dose level in the presence or absence of S9-activation compared to solvent controls. The positive controls induced the appropriate response. **There was no evidence of induced mutant colonies over background in the presence of S9.**

The study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) and (OPPTS 870.5500) for other genotoxic mutagenicity (bacterial DNA damage) data. Although the test article purity was not reported, the technical compound was tested to the limit dose and/or the limit of solubility.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §84-2, Chromosome Aberration Assay in Chinese Hamster Ovary Cells

Work Assignment No. 4-02-189I (MRID 41651027)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S. — Signature: David A. McEwen — Date: 7/1/02

Secondary Reviewer
Ronnie J. Bever, Jr., Ph.D. — Signature: Ronnie J. Bever Jr. — Date: 7/1/02

Program Manager
Mary L. Menetrez, Ph.D. — Signature: Mary L. Menetrez — Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D. — Signature: Steven Brecher — Date: 7/3/02

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EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/08

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: *In vitro* Mammalian Cytogenetics [Chromosome Aberration in CHO cells] OPPTS 870.5375 [§84-2]; OECD 473.

PC CODE: 097805 **DP BARCODE:** D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: RU 22974; (S)-α-cyano-3-phenoxybenzyl (1R,3S)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Putman, D.L. and M.J. Morris (1989) Chromosome aberration assay of deltamethrin in Chinese hamster ovary (CHO) cells. Microbiological Associates, Inc., Rockville, MD. Laboratory Study No.: T8418.337003, February 23, 1989. MRID 41651027. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a chromosome aberration assay (MRID 41651027), Chinese hamster ovary (CHO) cells were exposed to deltamethrin (99.2% a.i.; Lot/Batch #: 8B-0153B3) in acetone at concentrations of 0, 9.5, 19, 38, 75, or 150 µg/mL in the presence and absence of S9-activation for 16 (-S9) or 2 (+S9) hours. Cells were harvested at 18 hours (-S9) or 8 and 12 hours (+S9) after initiation of treatment.

Deltamethrin was tested up to the limit of solubility (≥75 µg/mL, +/-S9). Cytotoxicity was observed at ≥38 µg/mL (-S9) and at 150 µg/mL (+S9, 12 hr harvest). No statistically significant increases in aberration frequency were observed at any dose in the presence or absence of S9-activation compared to controls. Positive controls induced the appropriate response. **There was no evidence of chromosome aberration induced over background.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §84-2, Unscheduled DNA Synthesis in Primary Rat Hepatocytes

Work Assignment No. 4-02-189J (MRID 41651028)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall II
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
David A. McEwen, B.S. — Signature: David A. McEwen — Date: 7/01/02

Secondary Reviewer
Ronnie J. Bever, Jr., Ph.D. — Signature: Ronnie J. Bever Jr. — Date: 7/1/02

Program Manager
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez — Date: 7/3/02

Quality Assurance
Steve Brecher, Ph.D. — Signature: Steven Brecher — Date: 7/3/02

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Nancy McCarroll **Signature:** Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 09/11/02

Work Assignment Manager: Sanyvette Williams-Foy **Signature:** [illegible]
Registration Action Branch 2, Health Effects Division (7509C) **Date** 9/24/02

Template version 11/01

TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT See TXR# 009425 for previous review.

STUDY TYPE: Other Genotoxicity: Unscheduled DNA Synthesis in Primary Rat Hepatocytes/ Mammalian Cell Cultures; OPPTS 870.5550 [§84-2]; OECD 482

PC CODE: 097805

DP BARCODE: D283537
SUBMISSION NO.: S545023

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: RU 22974; (S)-α-cyano-3-phenoxybenzyl (1R,3S)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Curren, R.D. (1989) Unscheduled DNA synthesis of deltamethrin in rat primary hepatocytes. Microbiological Associates, Inc., Rockville, MD. Laboratory Study No.: T8418.380, March 13, 1989. MRID 41651028. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In an unscheduled DNA synthesis assay (MRID 41651028), primary rat hepatocyte cultures were exposed to deltamethrin (99.2% a.i.; Lot/Batch #: 8B-0153B3) in acetone for 18-20 hours at concentrations of 0, 4.2, 13, 42, 130, 420, 1300, or 4200 µg/mL.

Deltamethrin was tested up to the limit of solubility (≥130 µg/mL). No cytotoxicity (as indicated by decreased lactate dehydrogenase activity) was observed at any dose. No treatment-related increases in mean net nuclear grains (NNG) or percent of cells under repair (≥ 5 grains/nuclei) were observed at any dose compared to controls. The positive controls induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.5550; OECD 482) for other genotoxic mutagenicity data.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §81-8(a), Neurotoxicity Screening Battery in Rats

Work Assignment No. 2-01-43A (formerly 1-01-43A) MRID 44557901

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer
Kimberly Woodard, B.S.

Signature: Mary Menetrez for Kimberly Woodard
Date: 11/26/99

Secondary Reviewer
Kelley Van Vreede, M.S.

Signature: Kelley Van Vreede
Date: 11/29/99

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 11/26/99

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 11/29/99

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This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Waheeda Mani Tehseen, Ph.D. **Signature:** Stephen C. Dapson for
OPP-HED Registration Action Branch III (7509C) **Date** 09/25/2002
EPA Secondary Reviewer: Meta Bonner **Signature:** Stephen C Dapson
Registration Action Branch 3 (7509C) **Date** 09/25/2002
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** Ghazi Dannan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 09/25/2002

TXR# 0050424

DATA EVALUATION RECORD

STUDY TYPE: Neurotoxicity Screening Battery in Rats
OPPTS Number: 870.6200 OPP Guideline Number: §81-8(a)

DP BARCODE: D245495 SUBMISSION CODE: S541415
P.C. CODE: 097805 TOX. CHEM. NO.: 463B

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Nemec, M. (1998). An Acute Neurotoxicity Study of Deltamethrin in Rats. WIL Research Laboratories, Inc. Ashland, Ohio. Laboratory Study No. WIL-274002. March 18, 1998. MRID 44557901. Unpublished.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE 19808.

EXECUTIVE SUMMARY: In this acute neurotoxicity screening battery (MRID 44557901), deltamethrin (99.2% a.i.) was administered as a single dose by gavage to 12 Crl:CD (SD)BR rats/sex/dose at levels of 0, 5, 15, or 50 mg/kg. All animals were subjected to the functional observational battery (FOB) and motor activity measurements during the pretest interval and on study days 0 (≈3 hours after dosing), 7, and 14. Animals were checked twice daily for mortality and moribundity. All surviving animals were perfused *in situ* at study termination, and five animals/sex from the control and high-dose groups were subjected to neuropathological evaluation.

Body weight, body weight gains, brain weights, and neuropathological findings were unaffected by the test substance in all dose groups.

One male and one female in 50 mg/kg group died on day 0 (3-3.5 hours post-dosing). Pale lungs and red matting on external surfaces were observed in the male. Mottled lungs, ocular opacity, and red/yellow matting on external surfaces were observed in the female.

At 50 mg/kg, the following treatment-related clinical findings (total occurrences/number of animals) were observed on days 1, 2, and/or 3: (i) rocking, swaying, or lurching (males- 2/2, females- 3/2); (ii) dried yellow staining on the ventral abdominal area (males- 3/3, females- 6/6); (iii) dried yellow staining on the urogenital area (females- 9/7); and (iv) dried tan staining around the mouth (males- 3/2).

Treatment-related effects were observed on day 0 during the home cage, handling, open field, sensory, neuromuscular, and physiological observations, and were mostly dominant in the high-dose groups.

At 50 mg/kg, significant (vs. controls) signs of toxicity noted during the **home cage observations** included altered posture, clonic convulsions, tonic convulsions, slight tremors, increased cage biting, and alterations palpebral closure were observed in both sexes. Statistical significant signs of toxicity noted during the **handling observations** included increase displayed freezing upon removal from the cage, reduced ease of handling in the hand, slight to severe salivation, slight lacrimation, and slightly soiled fur in males and females. Statistical significant signs of toxicity observed in both sexes during the **open field observations** included impaired mobility, alterations in gait, impaired gait score, clonic and tonic convulsions, low arousal and writhing, as well as decreased rearing, grooming, urination, and increased time-to-first step. Both sexes showed decreased rearing activity (100%) and increased time-to-first step (3240%). Signs of toxicity seen during the **sensory observations** included alterations in approach, touch, startle, and tail pinch responses, olfactory orientation, lack of forelimb and hindlimb extension, and air righting reflex. During the **neuromuscular observations**, the following significant decreases were observed in the animals: (i) forelimb grip strength (males-45%; females- 29%); (ii) hindlimb grip strength (males-38%; females-27%); (iii) rotarod performance (males-79%; females-87%); and (iv) hindlimb footsplay (males-32%). During the **physiological observations**, body temperatures were decreased in the males (7%) and females (8%). Catalepsy times were increased in the males (1080%) and in the females (2683%).

On days 7 and 14, observations in treated animals were similar to observations made for control animals with the exception of increased ($p<0.01$) hindlimb footsplay in 50 mg/kg males on day 7.

Several effects were observed in animals on day 0 at 15 mg/kg. This included slight salivation in one male and slightly soiled fur for one female during **handling observations**; slightly impaired mobility for one male during **open field observations**; and no reactions to approach response (2 females) and touch response (2 females) **during sensory observations**. None of these effects were observed in the control animals.

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Under the conditions of this study, the NOAEL for male and female rats is 5 mg/kg. The LOAEL is 15 mg/kg based on salivation, soiled fur, impaired mobility, no reaction to approach and no reaction to touch response observed in the FOB.

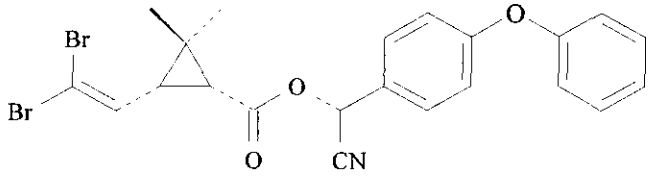
This acute oral neurotoxicity study is classified as **Acceptable/ Guideline** and satisfies the guideline requirement for an acute oral neurotoxicity study [OPPTS 870.6200(§81-8)] in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Deltamethrin
   Description: White powder
   Lot/Batch #: 4N0397B
   Purity (w/w): 99.2% a.i.
   Stability of compound: Stable for up to 5 days at room temperature.
   CAS #: 52918-63-5
   Structure:



2. Vehicle: Mazola® corn oil

3. Test animals: Species: Rat
   Strain: Sprague-Dawley Crl:CD® BR
   Age and weight at the start of dosing: 43 days old; 159-237 g (males), 127-186 g (females)
   Source: Charles River Breeding Laboratories, Inc., Portage, Michigan
   Housing: Individually, in stainless steel wire mesh cages
   Diet: Certified Rodent Chow 5002 (Purina), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 72-74° F
   Humidity: 36-46%
   Air changes: Not reported
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: 18 days

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B. STUDY DESIGN

1. In life dates - start: 12/4/95 end: 3/1/96

2. Animal assignment - The rats (12/sex/group) were randomly assigned (stratified by weight) to the test groups shown in Table 1.

Table 1. Study design.[a]

Test Group	Dose Levels (mg/kg)	Animals Assigned[b]	
		Male	Female
Control	0	12	12
Low	5	12	12
Mid	15	12	12
High	50	12	12

a Data were obtained from study report, page 21.
b All animals were perfused *in situ*, and 5 rats/sex/dose in the control and high dose group were subjected to neuropathological examinations.

3. Dose rationale - Dose levels were based on results of an acute range-finding study (WIL-274001, AgrEvo Study No. 53013A. Acute Oral Toxicity Study of Deltamethrin in Albino Rats. WIL Research Laboratories, Inc., Ashland, Ohio). No further information concerning the range-finding study was presented in this study report.

4. Dose preparation and analysis- For each dose level, the specified amount of test material was weighed and placed into a container to which the appropriate amount of corn oil was added to achieve the required concentration and volume. The preparation was mixed continuously throughout the sampling and dosing periods with a magnetic stirrer and stir bar. The test material and control articles were administered to non-fasted animals. The formulations were prepared once for homogeneity and stability analyses and twice for dosing and were stored at room temperature. Homogeneity, stability (5 days at room temperature) and concentration analyses were conducted. The top, middle, and bottom of the formulations were sampled for homogeneity. The middle of all formulations (including the control) was sampled for stability and concentration analyses.

Results:
Homogeneity (range as mean % of nominal): 96.0-99.4% with relative standard deviations (RSDs) of 0.33-1.9%.

Stability (range as mean % of Day 0): 97.6-103% with RSDs of 1.2-1.6%.

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Concentration analysis (range as mean % of nominal): 93.6-99.3% with RSDs of 0.33-1.8%.

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. Estimated time-to-peak effect

The time of peak effect was based on results of an acute range-finding study (WIL-274001, AgrEvo Study No. 53013A. Acute Oral Toxicity Study of Deltamethrin in Albino Rats. WIL Research Laboratories, Inc., Ashland, Ohio). No further information concerning the range-finding study was presented in this study report. There is, however, information in the published literature indicating that the peak effect occurs 1- 4 hours after dosing (Crofton et al., 1995; Crofton and Reither 1984)[1], thus supporting 3 hours as an appropriate time to perform the day 0 monitoring.

6. Statistics - For body weight, body weight gain, brain weights and dimensions, and continuous FOB data, a one-way analysis of variance (ANOVA) was performed. If significant differences were indicated by the ANOVA, then a Dunnett's test was used to compare control and treated groups. Locomotor activity was analyzed using a two way repeated measures (ANOVA). If significant, a one-way ANOVA was performed at each time point. If significance at a time point was observed, Dunnett's multiple T-test was used. The one-tailed Kolmogorov-Smirnov test was used to compare histopathological data between the high-dose and controls.

C. METHODS.

1. Observations

A. Clinical signs - All animals were examined twice daily for mortality and/or moribundity and once daily for clinical signs.

B. Functional observational battery (FOB) and motor activity - Animals were tested prior to dosing, approximately 3 hours after dosing on day 0 (time of peak effect), and on days 7 and 14. The FOB tests were performed by the same technicians (when possible) who were blind to animal treatment. The FOB was performed in a sound

[1]Crofton, KM, Kehn, LS, Gilbert, ME. (1995). Vehicle and route dependent effects of pyrethroid insecticide, deltamethrin, on motor function in the rat. Neurotoxicol and Terata 17:489-495.

Crofton, KM and Reiter, LW. (1984). Effects of two pyrethroids in motor activity and the acoustic startle response in the rat. Toxicol and Appl Phamacol 75: 318-328.

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proof room with a white noise generator at 70 ± 10db, except for the home cage observations which were performed in the animal room. The FOB assessment included the following parameters:

Home Cage Observations	Open Field Observations	Neuromuscular Observations
Posture	Mobility	Hindlimb foot-splay
Convulsions/Tremors	Rearing	Grip strength, hindlimb & forelimb
Feces consistency	Convulsions/Tremors	Hindlimb extensor strength
Biting	Grooming	Rotarod performance
Palpebral (Eyelid) closure	Bizarre/Stereotypic behavior	
	Time to first step (seconds)	
Handling Observations	Gait	**Physiological Observations**
	Arousal	
Ease of removal from cage	Urination/Defecation	Catalepsy
Lacrimation/Chromodacryorrhea	Gait Score	Body temperature
Piloerection	Backing	Body weight
Palpebral closure		
Red/crusty deposits	**Sensory Observations**	
Eye prominence		
Ease of handling in hand	Forelimb extension	
Salivation	Approach response	
Fur appearance	Startle response	
Respiratory rate/character	Pupil response	
Mucous membranes/Eye/Skin color	Air righting reflex	
	Tail pinch response	
Muscle tone	Eyeblink response	
	Olfactory orientation	
	Hindlimb extension	
	Touch response	

Following each administration of the FOB, motor activity was assessed using the Digiscan 'Micro' Animal Activity System (Omnitech Electronics, Inc., Columbus, OH) that utilizes a series of infrared beams per cage to measure total activity (counts). Motor activity was evaluated over a 40 minute period and the number of beam interruptions was tabulated over 4 subsessions, each lasting 10 minutes.

C. Positive and Historical Control Data - Summaries (Appendix E, Volume 3 of the study report) were provided of four neurotoxicity studies performed on rats to generate positive control data, validate the laboratory's procedures and apparatus, and verify the ability of the observers to perform the FOB and assess motor activity, neurotoxicity and behavioral effects. The chemicals used in these studies included the following: d-amphetamine sulfate (0, 0.5, 1.0, or 2.0 mg/kg, administered as a single i.p. injection); chlorpromazine hydrochloride (0, 2.5, 5.0, or 10 mg/kg, administered as a single i.p. injection); carbaryl (0, 2, 10, or 50 mg/kg, administered as a single i.p. injection); acrylamide (0, 5, 10, or 20 mg/kg, administered 5 days/week for 4 weeks);

trimethyltin chloride (7.5 mg/kg, administered as a single i.p. injection); and 3,3'-iminodipropionitrile (IDPN, 0 or 2000 mg/kg administered as a single dose by gavage).

Clinical signs of peripheral neuropathy such as altered hindlimb extensor and/or grip strength were observed after administration of acrylamide and carbaryl. Other clinical signs such as alterations in posture and rearing were observed in animals treated with d-amphetamine sulfate and chlorpromazine hydrochloride. Differences were noted in gait, gait score, mobility, and startle response after administration of chlorpromazine hydrochloride, carbaryl, and IDPN. Signs of central neuropathy, such as tremors and convulsions, were also observed in animals treated with carbaryl. Signs of autonomic system involvement, such as lacrimation, were observed in the animals treated with chlorpromazine hydrochloride. Histopathological evidence of peripheral and central nervous system changes were noted following administration of acrylamide and trimethyltin chloride. Increased motor activity was observed in the d-amphetamine sulfate treated animals and decreased activity was observed in the chlorpromazine hydrochloride treated animals. Motor activity was recorded by the Digiscan "Micro" Animal Motor Activity System.

FOB historical control data for male and female Charles River rats over several test intervals of up to 21 days were summarized in Appendix G of MRID 44557901. Although concurrent control data were used in the evaluation of the present study, the historical control data were used to indicate whether or not deviations from the control group values had occurred in the past.

Historical control data for motor activity from subchronic studies with male and female Charles River rats were summarized in Appendix H of MRID 44557901. Data from 22 studies were provided for 40-minute sessions over intervals of pretest to day 28.

Historical control data providing information on the types and incidences of central and peripheral nervous system lesions observed in untreated male and female Charles River rats were presented in Appendix I of MRID 44557901.

2. Body weight - All animals were weighed prior to treatment and on study days 0, 7, 14, and 15 (prior to necropsy).

3. Sacrifice and pathology - After 15 days, all surviving animals were euthanized by CO_2 inhalation and then perfused *in situ*. Central and peripheral nervous system tissues from all animals were dissected and preserved. Absolute brain weights (without olfactory bulb) and dimensions were recorded after removal. In the control and high-dose groups, 5 animals/sex/dose were subjected to neuropathological examinations. The following

peripheral and central nervous system tissues were embedded in paraffin or plastic, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Nervous system tissues examined:

Central Nervous System		
Brain		
Midbrain	Forebrain	Center of cerebrum
Cerebellum and pons	Medulla oblongata	
Spinal cord		
Cervical swellings C3-C7	Lumbar swellings T13-L4	
Other		
Gasserian ganglion/Trigeminal nerves	Lumbar dorsal root ganglion at T13-L4	Lumbar dorsal root fiber at T13-L4
Lumbar ventral root fiber at T13-L4	Cervical dorsal root ganglion at C3-C7	Cervical dorsal root fiber at C3-C7
Cervical ventral root fiber at C3-C7	Optic Nerves	Eyes
Peripheral Nervous System		
Sciatic nerves (mid-thigh region and sciatic notch)	Peroneal nerves	Tibial nerve
Sural nerve	Forelimbs	Tail

II. RESULTS

A. Clinical Observations

1. Mortality - One male and one female in the 50 mg/kg group died on day 0 (3-3.5 hours post-dosing). Pale lungs and red matting on external surfaces were observed in the male and mottled lungs, ocular opacity, and red/yellow matting on external surfaces were observed in the female. No other mortalities occurred in any other treated group.

2. Clinical signs - Selected clinical signs are presented in Table 2. In the 50 mg/kg treatment group animals, treatment-related clinical findings (total occurrences/number of animals) were observed on days 1, 2, and/or 3: (i) rocking, swaying, or lurching (males- 2/2, females- 3/2); (ii) dried yellow staining on the ventral abdominal area (males- 3/3,

females- 6/6); (iii) dried yellow staining on the urogenital area (females- 9/7); (iv) dried tan staining around the mouth (males- 3/2).

Table 2. Selected clinical signs (days 1, 2, and/or 3) in rats dosed with deltamethrin by gavage. [a]

Clinical Sign	Dose (mg/kg)							
	Males				Females			
	0	5	15	50	0	5	15	50
Animal rocks, lurches, or sways	0	0	0	2 (2)	0	0	0	3 (2)
Dried yellow staining on ventral abdominal area	0	0	0	3 (3)	0	0	0	6 (6)
Dried yellow staining on urogenital area	0	0	0	1 (1)	0	0	0	9 (7)
Dried tan staining around mouth	0	0	0	3 (2)	0	0	0	1 (1)

a Data obtained from the study report, Table 1 , pages 45 through 48; n=12. Data is presented as [# of incidences (# of infected animals)].

3. Functional Observational Battery (FOB) - Treatment-related effects were observed on day 0 during the home cage, handling, open field, sensory, neuromuscular, and physiological observations, and were mostly dominant in the high-dose groups. Selected FOB results for day 0 are shown in Tables 3 - 8 (data presented as % incidence).

   At 50 mg/kg, signs of toxicity noted during the **home cage observations** (Table 3) included altered posture, convulsions, tremors, alterations in biting, and palpebral closure. All males and females displayed altered posture, including flattened posture, sitting with the head lowered, and sleeping. Clonic convulsions (repetitive movement of the mouth and jaws), tonic convulsions, including contraction of extensors and emprosthotonus, and slight tremors were observed in both sexes. Alterations in palpebral closure and increased incidences of cage biting were observed in both sexes. Signs of toxicity noted during the **handling observations** (Table 4) included alterations in ease of removal from the cage, ease of handling in the hand, salivation, lacrimation, and fur appearance. Both sexes displayed freezing upon removal from the cage, as well as reduced ease of handling in the hand. Slight lacrimation was observed in the males and females. Slight and severe salivation was observed in both sexes. In addition, slightly soiled fur was noted in males and females. Signs of toxicity observed during the **open field observations** (Table 5) included alterations in mobility, gait, gait score, convulsions, and behavior, as well as decreased rearing, grooming, and urination, and increased time-to-first step. Both sexes displayed impaired mobility. Alterations in gait observed in males and females included splayed or dragging hindlimbs, body drags or sways, hunched body, and ataxia. Gait score was impaired in all animals. Clonic convulsions (repetitive movement of the mouth and jaws), tonic convulsions, including contraction of extensors, emprosthotonus, and opisthotonus, and slight tremors were observed in males and females. Low, somewhat

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stuporous arousal and writhing were also observed in these animals. Both sexes showed decreased rearing activity (100%) and increased time-to-first step (3240%). Signs of toxicity seen during the **sensory observations** (Table 6) included alterations in approach, touch, startle, and tail pinch responses, olfactory orientation, forelimb and hindlimb extension, and air righting reflex. The air righting reflex was deleteriously affected in both sexes and included landing on the back and/or side, and a slight lack of coordination. Males and females also lacked forelimb and hindlimb extension. During the **neuromuscular observations** (Table 7), the following significant decreases were observed in the animals: (i) forelimb grip strength (males-45%; females-29%); (ii) hindlimb grip strength (males-38%; females-27%); (iii) rotarod performance (males-79%; females-87%); and (iv) hindlimb footsplay (males-32%). During the **physiological observations** (Table 8), body temperatures were decreased in the males (7%) and females (8%). Catalepsy times were increased in the males (1080%) and in the females (2683%).

On days 7 and 14, observations in treated animals were similar to observations made for control animals with the exception of increased ($p<0.01$) hindlimb footsplay in 50 mg/kg males on day 7.

Most effects as mentioned above were observed in high-dose animals; however, several effects were also noted in animals in the 15 mg/kg group. Treatment-related effects on day 0 noted at 15 mg/kg included slight salivation in one male and slightly soiled fur for one female during **handling observations**; slightly impaired mobility for one male during **open field observations**; and no reactions to approach response (2 females) and touch response (2 females) during **sensory observations**. None of these effects were observed in the control animals.

Table 3. Selected home cage observations (day 0) in rats dosed with deltamethrin by gavage.[a]

Observations	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Males					
Animals tested	12	12	12	11	192
Posture					
Asleep, lying on side or curled up	6(50%)	3 (25%)	4 (33%)	0*	68 (35%)
Sitting, head held low	0	0	0	1 (9%)	1 (0.5%)
Flattened, limbs may be extended	0	0	0	10* (91%)	NA
Convulsions (clonic%)					
Repetitive movement of mouth/jaws	0	0	0	2 (18%)	NA
Convulsions (tonic%)					
Contraction of extensors	0	0	0	1 (9%)	NA
Emprosthotonus	0	0	0	9* (82%)	NA
Tremors					
Slight (1.5 mm%)	0	0	0	2 (18%)	NA
Biting					
Biting of cage	0	0	0	9* (82%)	NA
Palpebral closure					
Eyelids slightly drooping	1 (8%)	1 (8%)	1 (8%)	10* (91%)	3 (2%)
Drooping eyelids (half-closed%)	1(8%)	0	1 (8%)	1 (9%)	7 (4%)
Females					
Animals tested	12	12	12	11	192
Posture					
Asleep, lying on side or curled up	6 (50%)	5 (42%)	2 (17%)	0*	56 (29%)
Sitting, head held low	0	0	0	1 (9%)	1 (0.5%)
Flattened, limbs may be extended	0	0	0	10* (91%)	NA
Convulsions (clonic%)					
Repetitive movement of mouth/jaws	0	0	0	3 (27%)	NA
Convulsions (tonic%)					
Contraction of extensors	0	0	0	1 (9%)	NA
Emprosthotonus	0	0	0	9* (82%)	NA
Tremors					
Slight (1.5 mm%)	0	0	0	3(27%)	NA

Table continues

Observations	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Biting					
Biting of cage	0	0	0	3 (27%)	NA
Palpebral closure					
Eyelids slightly drooping	0	0	0	9* (82%)	3 (2%)
Drooping eyelids (half-closed%)	0	0	1 (8%)	1 (9%)	3 (2%)

a Data obtained from the study report, Table 6, pages 59 through 62; NA = not observed. Data is presented as [# affected animals (percent as calculated by reviewers)].

* Statistically different from controls; $p<0.05$.

Table 4. Selected handling observations (day 0) in rats dosed with deltamethrin by gavage.[a]

Observation	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Males					
Animals tested	12	12	12	11	192
Ease of removal from cage Freezes	0	0	0	6*(55%)	1(0.5%)
Ease of handling in hand Moderately low (slight resistance%)	0	0	0	5*(45%)	21(11%)
Salivation Slight Severe	0 0	0 0	1(8%) 0	1(9%) 10* (91%)	3(2%) NA
Fur appearance Slightly soiled	0	0	0	10*(91%)	1 (0.5%)
Lacrimation Slight	0	0	0	2(18%)	0
Females					
Animals tested	12	12	12	11	192
Ease of removal from cage Freezes (with/without vocalization%)	0	0	0	5*(45%)	NA
Ease of handling in hand Moderately low (slight resistance%)	2(17%)	0	0	5(45%)	23(12%)
Salivation Severe	0	0	0	10*(91%)	NA
Fur appearance Slightly soiled	0	0	1(8%)	10*(91%)	NA
Lacrimation Slight	0	0	0	4*(36%)	2(1%)

a Data obtained from the study report, Table 14, page 93 through 98; NA = not observed. Data is presented as [# affected animals (percent as calculated by reviewers)].

* Statistically different from controls; $p<0.05$.

Table 5. Selected open field observations (day 0) in rats dosed with deltamethrin by gavage. [a]

Observation	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Males					
Animals tested	12	12	12	11	192
Mobility					
Slightly impaired	0	0	1(8%)	1(9%)	NA
Moderately impaired	0	0	0	8*(73%)	NA
Totally impaired	0	0	0	2(18%)	NA
Gait					
Hunched body	0	0	0	2(18%)	NA
Body drags and sways	0	0	0	2(18%)	NA
Hindlimbs splayed or dragging	0	0	0	7*(64%)	NA
Gait score					
Considerable impairment	0	0	0	2(18%)	NA
Severe impairment	0	0	0	9*(82%)	NA
Convulsions (clonic%)					
Repetitive movement of mouth and jaws	0	0	0	5*(45%)	NA
Convulsions (tonic%)					
Contraction of extensors	0	0	0	1(9%)	NA
Opisthotonus	0	0	0	1(9%)	NA
Emprosthotonus	0	0	0	2(18%)	NA
Tremors					
Slight (1.5mm%)	0	0	0	2(18%)	NA
Arousal					
Low, somewhat stuporous	3(25%)	1(8%)	1(8%)	10*(91%)	4(2%)
Bizarre/stereotypic behavior					
Writhing	0	0	0	7* (64%)	NA
Rearing activity (# occurrences/2 min.%)	4.3	3.7	4.0	0.0** (↓100%)	6.4
Time to first step (sec%)	0.5	0.5	0.5	16.7**(13240 %)	0.6
Grooming (# occurrences/2 min.%)	1.0	1.0	1.2	0.0	0.3
Urination (# occurrences/2 min.%)	1.4	1.0	0.5	0.0	0.3

(Table continues)

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Observation	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Females					
Animals tested	12	12	12	11	192
Mobility					
Slightly impaired	0	0	0	1(9%)	NA
Moderately impaired	0	0	0	9*(82%)	NA
Totally impaired	0	0	0	1(9%)	NA
Gait					
Ataxia, excessive sway	0	0	0	1(9%)	3(2%)
Body drags and sways	0	0	0	3(27%)	NA
Hindlimbs splayed or dragging	0	0	0	7*(64%)	NA
Gait Score					
Considerable impairment	0	0	0	2(18%)	2(1%)
Marked impairment	0	0	0	1(9%)	NA
Severe impairment	0	0	0	8*(73%)	NA
Convulsions (clonic%)					
Repetitive movement of mouth and jaws	0	0	0	5*(45%)	NA
Convulsions (tonic%)					
Opisthotonus	0	0	0	1(9%)	NA
Emprosthotonus	0	0	0	3(27%)	NA
Tremors					
Slight (1.5mm%)	0	0	0	1(9%)	1(0.5%)
Arousal					
Low, somewhat stuporous	0	0	0	10*(91%)	1(0.5%)
Bizarre/stereotypic behavior					
Writhing	0	0	0	8*(73%)	NA
Rearing activity (# occurrences/2 min.%)	11.2	8.6	9.9	0.0**(↓100%)	8.5
Time to first step (sec.%)	0.5	0.5	0.5	16.7(↑3240%)	0.4

a Data obtained from the study report, Table 22 , pages 142 through 145; NA = not observed. Data is presented as [# affected animals (percent as calculated by reviewers)].

* or** Statistically different from controls at p<0.05 or 0.01

Table 6. Selected sensory observations (day 0) in rats dosed with deltamethrin by gavage.[a]

Observation	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Males					
Animals tested	12	12	12	11	192
Approach response					
No reaction	2(17%)	1(8%)	1(8%)	10*(91%)	5(3%)
Touch response					
No reaction	5(42%)	2(17%)	1(8%)	10*(91%)	2(1%)
Tail pinch response					
No reaction	0	0	0	7*(64%)	NA
Olfactory orientation					
No reaction	0	0	0	8*(73%)	1(0.5%)
Air righting reflex					
Slightly uncoordinated	0	0	0	1(9%)	3(2%)
Lands on side	0	0	0	6*(55%)	1(0.5%)
Lands on back	0	0	0	4*(36%)	NA
Forelimb extension					
No forelimb extension	1(8%)	0	0	2(18%)	0
Hindlimb extension					
No hindlimb extension	0	0	0	2(18%)	0
Females					
Animals tested	12	12	12	11	192
Approach response					
No reaction	0	0	2(17%)	8*(73%)	5(3%)
Touch response					
No reaction	0	0	2(17%)	9*(82%)	2(1%)
Startle response					
No reaction	0	0	0	2(18%)	NA
Slight reaction (i.e. ear flick%)	9(75%)	6(50%)	7(58%)	1*(9%)	74(39%)
More energetic response	3(25%)	6(50%)	5(42%)	8*(73%)	116(60%)
Tail pinch response					
No reaction	0	0	0	8*(73%)	NA
Olfactory orientation					
No reaction	0	0	0	7*(64%)	4(2%)
Air righting reflex					
Slightly uncoordinated	0	0	0	3(27)	6(3)
Lands on back	0	0	0	3(27)	NA
Lands on side	0	0	0	5*(45)	NA

(Table continues)

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Observation	Dose (mg/kg)				
	0	5	15	50	Historical Controls
Forelimb extension					
No forelimb extension	0	0	0	2(18%)	0
Hindlimb extension					
No hindlimb extension	0	0	0	2(18%)	2(1%)

a Data obtained from the study report, Table 30, pages 186 through 189. Data is presented as [# affected animals (percent as calculated by reviewers)].

* Statistically different from controls; p<0.05

Table 7. Selected neuromuscular observations at day 0 in rats dosed with deltamethrin by gavage. [a]

Observation	Dose (mg/kg)							
	Males				Females			
	0	5	15	50	0	5	15	50
Forelimb grip strength	642.4	661.0	690.9	353.1**(↓45%)	622.8	556.9	641.6	440.1**(↓29%)
Hindlimb grip strength	315.4	282.0	297.9	195.3**(↓38%)	266.6	276.9	276.4	195.4*(↓27%)
Rotarod performance	88.6	120.0	110.4	18.6**(↓79%)	83.2	84.3	78.2	10.5** (↓87%)
Hindlimb footsplay	66.8	62.7	70.8	45.3** (↓32%)	61.8	61.0	55.2	51.8(↓16%)

a Data obtained from the study report, Table 38, pages 222 and 223. Percentage difference from controls calculated by reviewer is parenthetical.

* Statistically different from controls at p<0.05.

** Statistically different from controls at p<0.01.

Table 8. Selected physiological observations at day 0 in rats dosed with deltamethrin by gavage. [a]

Observation	Dose (mg/kg)							
	Males				Females			
	0	5	15	50	0	5	15	50
Body temperature (°C)	38.4	38.3	38.3	35.6** (↓7%)	38.6	38.6	38.4	35.5**(↓8%)
Catalepsy time(s)	1.0	0.7	5.0	11.8 (↑1080%)	0.6	0.6	0.6	16.7** (↑2683)

a Data obtained from the study report, Table 45, pages 240 and 241. Percentage difference from controls calculated by reviewers is parenthetical.

* Statistically different from concurrent controls; $p<0.01$.

4. Motor activity - Total activity data are summarized in Table 9 and ambulatory activity data are summarized in Table 10. Increases ($p<0.05$) in mean total motor activity (54%) and mean ambulatory motor activity (92%) were observed in the high-dose males on day 0. The increases were due mainly to increases in ambulatory activity counts during subsessions 2, 3, and 4 and in total activity counts during subsession 4. There were large variations in individual animal data (total activity counts- 532-3697; ambulatory counts- 188-3246) for high-dose males. In addition, increased total motor activity (35%) and ambulatory motor activity (29%) were observed during the pretest interval in these animals. Therefore, it was considered that no treatment-related changes were noted in any of the treated groups in the motor activity tests.

TABLE 9. Total (0-40-minute) motor activity (counts ±SD) for male and female rats administered *Deltamethrin* by gavage

Dose (mg / kg)	Males				Females			
	Predose	Day 0	Day 7	Day 14	Predose	Day 0	Day 7	Day 14
0	1116±273.4	1239±395.6	1111±487.5	1211±366.5	1318±415.2	1423±420.9	1570±457.1	1603±433.5
5	1076±440.1 (-4%)[a]	1159±392.9 (-6%)	984±353.8 (-11%)	1085±417.3 (-10%)	1401±454.9 (6%)	1295±401.6 (-9%)	1699±592.4 (8%)	1807±534.5 (13%)
15	1178±328.1 (6%)	1074±367.3 (-13%)	1092±584.9 (-2%)	1106±485.0 (-9%)	1564±606.7 (19%)	1174±587.6 (-17%)	1654±404.8 (5%)	1666±584.2 (4%)
50	1509*±335.4 (35%)	1912*±1114 (54%)	1439±460.9 (30%)	1453±383.0 (20%)	1478±622.1 (12%)	1343±1208.8 (-6%)	1691±391.5 (8%)	1494±514.4 (-7%)

*$p<0.05$. Data taken from Tables 48-51, pp. 248-263, MRID 44557901.

[a]Percent of control, calculated by reviewer.

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TABLE 10. Mean (0-40-minute) ambulatory activity (counts ±SD) for male and female rats administered Deltamethrin by gavage

Dose (mg/kg)	Males				Females			
	Predose	Day 0	Day 7	Day 14	Predose	Day 0	Day 7	Day 14
0	608±188.4	703±242.7	633±281.5	750±251.0	709±229.4	824±252.1	943±313.0	974±305.9
5	548±278.4 (-10%)[a]	626±187.4 (-11%)	557±212.1 (-12%)	616±246.6 (-18%)	758±243.4 (7%)	732±239.0 (-11%)	1001±417.1 (6%)	1093±346.9 (12%)
15	619±154.0 (2%)	564±188.3 (-20%)	669±362.4 (6%)	647±330.8 (-14%)	840±354.7 (18%)	621±314.5 (-25%)	988±250.4 (5%)	1027±352.9 (5%)
50	786±209.2 (29%)	1352*±923.2 (92%)	864±355.5 (36%)	833±274.8 (11%)	774±352.5 (9%)	1039±1149.5 (26%)	934±209.5 (-1%)	866±320.9 (-11%)

*p<0.05. Data taken from Tables 48-51, pp. 249-263, MRID 44557901.
[a]Percent of control, calculated by reviewer.

B. Body weight and body weight gain

When compared to concurrent controls, no differences in body weights were observed in any treated group. Body weight gains were decreased (20%, p<0.01) relative to controls in the 50 mg/kg males during the day 0-7 interval; however this finding was considered to be incidental. No differences from controls in body weight gains were observed in any other treatment group.

C. Sacrifice and pathology

1. Brain weight - No treatment-related differences from controls were observed regarding brain weights and dimensions.

2. Microscopic pathology - No treatment-related neuropathological changes were observed in the 5 animals/sex in the high-dose which were subjected to histopathological examinations. Limited microscopic findings included digestion chambers in the sciatic nerve (with axonal degeneration) and tibial nerve of one high-dose male, and digestion chambers in the sciatic and peroneal nerves of one high-dose female. The authors considered these effects incidental to treatment since "spontaneous nerve fiber degeneration, characterized by digestion chambers, has been previously noted in the central and peripheral nervous systems of control and treated rats." This effect is present in the historical control data from this laboratory.

III. DISCUSSION

A. Investigator's conclusions

Deltamethrin elicits neurotoxic effects at 50 mg/kg, based on mortality, clinical signs, and differences from controls during the home cage, handling, open field, sensory, neuromuscular, and physiological FOB observations. Potential neurotoxic effects occurred at 15 mg/kg. No neuropathological changes or differences in brain weights/dimensions and were noted throughout the study. The NOAEL for this study was 5 mg/kg.

B. Reviewer's discussion

In this acute neurotoxicity screening battery, deltamethrin was administered as a single dose by gavage to 12 Crl:CD (SD)BR rats/sex/dose at levels of 0, 5, 15, or 50 mg/kg. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

Motor activity, body weight, body weight gains, brain weights, and neuropathological findings were unaffected by the test substance.

One 50 mg/kg male and one 50 mg/kg female died on day 0 (3-3.5 hours post-dosing). Pale lungs and red matting on external surfaces were observed in the male. Mottled lungs, ocular opacity, and red/yellow matting on external surfaces were observed in the female.

In the 50 mg/kg animals, the following treatment-related clinical findings (total occurrences/number of animals) were observed on days 1, 2, and/or 3: (i) rocking, swaying, or lurching (males- 2/2, females- 3/2); (ii) dried yellow staining on the ventral abdominal area (males- 3/3, females- 6/6); (iii) dried yellow staining on the urogenital area (females- 9/7); and (iv) dried tan staining around the mouth (males- 3/2). At 15 mg/kg, treatment-related clincial signs included: slight salivation, slightly soiled fur and slightly impaired mobility were seen in single male and female rats. When compared to the effects observed at 50 mg/kg, the effects at 15 mg/kg, while limited (slight salivation, slightly soiled fur and slightly impaired mobility in single male or female rats), are similar to those noted at 50 mg/kg. One of the signs (impaired mobility) was consistently seen in the submitted studies and published articles (Crofton et al., 1995; Crofton and Reither 1984).

During the functional observational battery, treatment-related effects were observed on day 0 during the home cage, handling, open field, sensory, neuromuscular, and physiological observations, and were mostly dominant in the high-dose groups. At 50 mg/kg, signs of toxicity noted during the **home cage observations** included altered posture, convulsions, tremors, alterations in biting, and palpebral closure. All males and females displayed altered posture, including flattened posture, sitting with the head lowered, and sleeping. Signs of toxicity seen during the **handling observations** included alterations in ease of removal from the cage, ease of handling in the hand, salivation, lacrimation, and fur appearance. Signs of toxicity observed during the **open field observations** included alterations in mobility, gait, gait score, convulsions, and behavior, as well as decreased rearing, grooming, and urination, and increased time-to-first step. Signs of toxicity seen during the **sensory observations** included

alterations in approach, touch, startle, and tail pinch responses, olfactory orientation, forelimb and hindlimb extension, and air righting reflex. During the **neuromuscular observations**, the following significant decreases were observed in the animals: (i) forelimb grip strength (males-45%; females- 29%); (ii) hindlimb grip strength (males-38%; females-27%); (iii) rotarod performance (males-79%; females-87%); and (iv) hindlimb footsplay (males-32%). During the **physiological observations**, body temperatures were decreased in the males (7%) and females (8%). Catalepsy times were increased in the males (1080%) and in the females (2683%).

Several effects were observed in animals on day 0 at 15 mg/kg. This included slight salivation in one male and slightly soiled fur for one female during handling observations; slightly impaired mobility for one male during open field observations; and no reactions to approach response (2 females) and touch response (2 females) during sensory observations. None of these effects were observed in the control animals. When compared to the effects observed at 50 mg/kg, the effects at 15 mg/kg, while limited (slight salivation, slightly soiled fur and slightly impaired mobility in single male or female rats and no reaction to approach or touch in 2 females), are similar to those noted at 50 mg/kg. One of the signs (impaired mobility) was consistently seen in the submitted studies and published articles (Crofton et al., 1995; Crofton and Reither 1984).

On days 7 and 14, observations in treated animals were similar to observations made for control animals with the exception of increased ($p>0.01$) hindlimb footsplay in 50 mg/kg males on day 7.

Under the conditions of this study, the NOAEL for male and female rats is 5 mg/kg. The LOAEL is 15 mg/kg based on salivation, soiled fur, impaired mobility, no reaction to approach and no reaction to touch response observed in the FOB.

C. Study deficiencies -
– No Flagging statement was provided in the report. This deficiency does not invalidate the study.

D. Classification -
This acute oral neurotoxicity study is classified as **Acceptable/ Guideline** and satisfies the guideline requirement for an acute oral neurotoxicity study [OPPTS 870.6200(§81-8)] in rats.

DATA EVALUATION RECORD

DELTAMETHRIN

Study Type: §82-7, Subchronic (13-Week) Oral Dietary Neurotoxicity Study in Rats

Work Assignment No. 2-01-43B (formerly 1-01-43B) MRID 44557902

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer Kimberly Woodard, B.S.	Signature: Mary Menetrez for Kimberly Woodard Date: 11/28/99
Secondary Reviewer Kelley Van Vreede, M.S.	Signature: Kelley Van Vreede Date: 11/29/99
Program Manager Mary L. Menetrez, Ph.D.	Signature: Mary L Menetrez Date: 11/28/99
Quality Assurance Steve Brecher, Ph.D.	Signature: Steven Brecher Date: 11-29/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

DELTAMETHRIN **Subchronic Oral Neurotoxicity (§82-7)**

EPA Reviewer: Waheeda Mani Tehseen, Ph.D. **Signature:** Stephen C. Dapson for
OPP-HED Registration Action Branch III (7509C) **Date** 09/25/2002
EPA Secondary Reviewer: Meta Bonner **Signature:** Stephen C. Dapson for
Registration Action Branch 3 (7509C) **Date** 09/25/2002
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** Ghazi A. Dannan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 09/25/2002

SCD 09/25/2002

TXR # 0050424

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Neurotoxicity [Feeding] - rat
OPPTS Number: 870.6200 OPP Guideline Number: §82-7
DP BARCODE: D245495 SUBMISSION CODE: S541415
P.C. CODE: 097805 TOX. CHEM. NO.: 463B

TEST MATERIAL (PURITY): Deltamethrin (99.2% a.i.)

SYNONYMS: (s)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Nemec, Mark. (1998) A Subchronic (13-week) Neurotoxicity Study of Deltamethrin in Rats. WIL Research Laboratories, Inc. Ashland, Ohio. Laboratory Study Number WIL-274003. March 19, 1998. MRID 44557902. Unpublished.

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE, 19808.

EXECUTIVE SUMMARY: In this subchronic neurotoxicity study (MRID 44557902), deltamethrin (Batch No.: 4N0397B, 99.2% purity) was administered to 10 Charles River (Crl:CD®[SD]BR) rats/sex/dose at dietary levels of 0, 50, 200, or 800 ppm for 13 weeks. Based on analytical measurements, doses were 0, 4, 14, and 54 mg/kg/day for males and 0, 4, 16, and 58 mg/kg/day for females. Body weights were recorded weekly and clinical observations were recorded daily. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all animals/sex/group pretreatment and once/week during weeks 3, 7, and 12. At study termination, all surviving animals were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5 rats/sex in the control and high-dose groups were subjected to histopathological evaluation of the central and peripheral nervous system tissues.

Brain weights and dimensions, motor activity, and neuropathological findings were unaffected by the test substance at all dose levels.

Three males (days 13, 25, and 47; 3/10 = 30%) and two females days (22 and 90; 2/10 = 20%) in the 800 ppm treatment group died before the end of the study, motility did not occur in other groups. Findings in these rats included emaciation (one male) dark red stomach and intestinal contents (two males and one female) gas-distended stomach (one male), enlarged lymph nodes (one male and one female), pale spleen (one male) and mottled lungs (one female). A third female appeared to have experienced mechanical trauma and was euthanized *in extremis* (day 91). This female had a broken incisor, an abrasion of the tongue, swollen gingiva, and red matting on the entire head, ventral surface, limbs and tail. No explanation of the mechanical trauma was given.

Clinical findings noted at the high-dose throughout the study included (i) rocking, swaying, or lurching, (ii) hypersensitivity to noise, (iii) impaired righting reflex, (iv) piloerection, (v) seizures, (vi) altered posture, (vii) convulsions, and (viii) soiled fur.

Significant decreases in body weights (males: 26-35% and females: 10-17%), body weight gains (males: 50-102% and females: 48-114%) and food consumption (males:18-45% and females: 11-25%) were observed at the high dose throughout the study.

Results of the FOB indicated no treatment-related findings during the home cage observations; however, treatment-related effects were noted at the high-dose (800 ppm) during the handling, open field, sensory, and neuromuscular observations. Findings noted during the **handling observations** included slightly soiled fur, altered palpebral closure, salivation, pale mucous membranes, pale eyes, and pale skin in the females. During the **open field observations**, animals showed impaired mobility, body drags or sways, splayed or dragging hindlimbs, impairment of gait score, side to side rocking, and gait alterations (ataxia, excessive sway), and walking on tiptoes. Signs of neurotoxicity were noted during the **sensory observations** such as slightly uncoordinated air righting reflex in the males and females, and landing on the side or back in females. During the **neuromuscular observations**, decreased forelimb and hindlimb grip strength were observed in the males. Reduced hindlimb resistance (animal shows some weakness) was observed in the males and females, and an absence of hindlimb resistance was observed in the females.

At the low dose (500 ppm) there were no effects on body weight, FOB parameters or motor activity and there were no treatment-related lesions in the brain or central or peripheral nervous system tissues. At the mid dose (200 ppm) there were single incidences of effects in males as indicated by the FOB (soiled fur and impaired mobility), but no effects on body weight or motor activity and no treatment-related lesions in the brain or central or peripheral nervous system tissues.

The neurotoxicity LOAEL is 800 ppm (equivalent to 54 mg/kg/day in males and 58 mg/kg/day in females) based on mortality, clinical signs of toxicity, FOB findings, and decreased body weights, body weight gains, and food consumption. The neurotoxicity NOAEL is 200 ppm (equivalent to 14 mg/kg/day in males and 16 mg/kg/day in females).

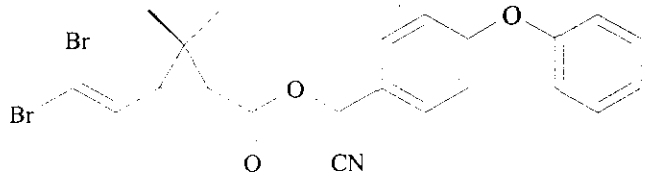
The submitted study is classified as **Acceptable/Guideline (§82-7)** and satisfies the guideline requirements for a subchronic neurotoxicity screening battery in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Deltamethrin
   Description: White powder
   Lot/Batch #: 4N0397B
   Purity (w/w): 99.2% a.i.
   Stability of compound: The compound was stable in the diet for 10 days at room temperature.
   CAS #: 52918-63-5
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain: Crl:CD® (SD)BR
   Age and weight at the start of dosing: 42 days old; 157-234 g (males), 137-193 g (females)
   Source: Charles River Laboratories, Inc., Portage, Michigan, 49801.
   Housing: Individually, in stainless steel wire mesh cages
   Diet: Certified Rodent Lab Diet 5002 (PMI Feeds, Inc.), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   - Temperature: 71.1-72.9° F
   - Humidity: 41.7-55.0%
   - Air changes: Not reported
   - Photoperiod: 12 hours light/12 hours dark

   Acclimation period: 14 days

B. STUDY DESIGN

1. In life dates - start: 7/16/96 end: 10/18/96

2. Animal assignment - The rats (10/sex/group) were randomly assigned (stratified by weight) to the test groups shown in Table 1.

Table 1. Study design.[a]

TABLE 1: Study design. [a]					
Test group	Dietary Level (ppm)	Dose (mg/kg/day)		Number of animals	
		Male	Female	Male	Female
1 (Control)	0	0	0	10	10
2 (low-dose)	50	4	4	10	10
3 (mid-dose)	200	14	16	10	10
4 (high dose)	800	54	58	10	10

a Data taken from pp. 21 and 28, MRID 44557902.

3. Dose rationale - Dose levels selected were based on the results of previous 90-day and 2-year studies. Data from these studies were not provided in the study report.

4. Test material preparation and analysis - Diets were prepared in the following manner. The appropriate amount of test material for each group was weighed in a tared glass vessel. This was transferred to a Hobart mixer along with 1 kg of rodent chow. The premix was mixed for 5 minutes and then transferred to and mixed in a V-twin mixer for 10 minutes along with enough feed to achieve the appropriate concentration for each group. An intensifier bar was used during the first and last 3 minutes of the mixing procedure. The test and control diets were placed in properly labeled storage bags.

   One hundred gram samples were taken for homogeneity, stability and concentration analyses. For homogeneity analysis, duplicate samples were taken from the top, middle, and bottom of the diet preparations prior to dosing. For stability analysis, samples were taken from the middle of all preparations and stored at room temperature for 10 days. For concentration analysis, samples were collected weekly from the middle of all preparations. Samples from six different weeks were analyzed for concentration. Samples taken for homogeneity and concentration analyses were stored frozen prior to analysis. Analysis was by liquid chromatography with UV detection.

   Results - Homogeneity (range as mean % of nominal): 94.7-105% with relative standard deviations (RSD) of 0.04-3.6%

   Stability (range as mean % of Day 0): 96.5-108% with RSD of 0.63-8.0%

   Concentration analysis (range as mean % of nominal): 88.3 -113% with RSD of 0.71-10.0%

   The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. Statistics - Food consumption, body weight, body weight gain, brain weight and dimensions, and continuous FOB data were subjected to a one-way analysis of variance (ANOVA). If significant differences were indicated by the ANOVA, then Dunnett's test was used to compare the control and treated groups. Discontinuous FOB data were analyzed using Fisher's Exact test. Locomotor activity data were analyzed using a two way repeated measures ANOVA. If significant, a one-way ANOVA was performed at each time point. If significance was observed at a time point, Dunnett's multiple T-test was used.

C. METHODS.

1. Observations

A. Clinical signs - All animals were examined twice daily for mortality and/or moribundity and once daily for clinical signs.

B. Functional observational battery (FOB) and locomotor activity - All animals (10/sex/group) were subjected to FOB and motor activity measurements one week prior to treatment and at study weeks 3, 7, and 12. The following FOB observations were performed by trained technicians who were blind to the animal group assignment:

Home Cage Observations

Posture
Convulsions/tremors
Feces consistency
Biting
Palpebral (eyelid) closure

Handling Observations

Ease of removal from cage
Lacrimation/Chromodacryorrhea
Piloerection
Palpebral closure
Red/crusty deposits
Eye prominence
Ease of handling in hand
Salivation
Fur appearance
Respiratory rate/character
Mucous membranes/eye/skin color
Muscle tone

Open Field Observations

Mobility
Rearing
Convulsions/tremors
Grooming
Bizarre/stereotypic behavior
Time to first step (seconds)
Gait
Arousal
Urination/defecation
Gait Score
Backing

Sensory Observations

Forelimb extension
Approach response
Startle response
Pupil response
Air righting reflex
Tail pinch response
Eyeblink response
Olfactory orientation
Hindlimb extension
Touch response

Neuromuscular Observations

Hindlimb foot-splay
Grip strength, hindlimb & forelimb
Hindlimb extensor strength
Rotarod performance

Physiological Observations

Catalepsy
Body temperature
Body weight

C. Positive and Historical Control Data - Summaries (Appendix E, Volume 3, of the study report) were provided of four neurotoxicity studies performed on rats to generate positive control data, validate the laboratory's procedures and apparatus, and validate the ability of the observers to perform the FOB and assess motor activity, neurotoxicity and behavioral effects. A study conducted in 1990 with D-amphetamine sulfate and chlorpromazine hydrochloride (WIL-99026) showed that rats treated with these chemicals had increases and decreases in motor activity, respectively. Control motor activity over a 24-hour period was recorded to show the natural daily activity of male and female rats. The effects of these chemicals on FOB observations were also recorded. An acute study with carbaryl (WIL-99032, 1990) provided evidence of the ability to detect convulsions, autonomic signs, reduced responsiveness, and reduced arousal and locomotor activity. Positive control data that indicated the ability to detect central and peripheral nervous system pathology were also provided in the study report. A repeated dose study with rats using acrylamide (WIL-99034, 1991) provided evidence of the ability to detect limb weakness and peripheral nervous system pathology. In the same study, acute administration of trimethyltin chloride provided evidence of the ability to detect central nervous system pathology. Finally, an inter-observer reliability study with eight technicians (WIL-99035, 1991) showed that the technicians could similarly and consistently detect major behavioral signs in rats administered 3'-3- iminodiproprionitrile.

FOB historical control data for male and female Charles River rats over several test intervals of up to 21 days were summarized in Appendix G of MRID 44557902. Although concurrent control data were used in the evaluation of the present study, the historical control data were used to indicate whether or not deviations from the control group values had occurred in the past.

Historical control data for motor activity from subchronic studies with male and female Charles River rats were provided in Appendix H of MRID 44557902. Data from up to 45 studies (pretest) were provided for 40-minute sessions over intervals of pretest to week 13.

Historical control data from 17 acute and 21 subchronic studies were presented in Appendix I of MRID 44557902. This data provided information on the types and incidences of central and peripheral nervous system lesions observed in untreated male and female Charles River rats.

2. Body weight - All animals were weighed one week prior to treatment, at weekly intervals during the study, upon FOB administration, and prior to study termination.

3. Food and compound intake - Food consumption for each animal was measured at weekly intervals throughout the treatment period, beginning one week prior to treatment. Mean compound intake was calculated as mg/kg/day.

4. Motor activity

Motor activity was measured following each FOB session. Total motor activity was measured for 40 minutes in an automated, computerized Digiscan "Micro" Animal Activity System (Omnitech Electronics, Inc.). Data were automatically collected in one-minute intervals; because placement of the animal in the cage may have taken place any time within the first minute interval, the data were actually collected for 41 minutes with the first minute of data deleted. Total motor activity was measured as the number of times one or two adjacent infrared photobeams were interrupted during the 40 minutes and during each of four 10-minute subsessions. Ambulatory motor activity (interruption of three or more consecutive photobeams) was also automatically recorded. Data were presented on total motor and ambulatory activities over the 40-minute sessions and over each of the 10-minute intervals. The testing of treatment groups was done according to replicate sequence.

5. Sacrifice and pathology - At study termination (week 13) all surviving animals were euthanized by CO_2 inhalation and perfused *in situ*. In the control and high-dose groups, 5 animals/sex/dose were subjected to neuropathological examinations. Central and peripheral nervous system tissues from these animals were dissected and preserved. Brain weights (without olfactory bulb) and dimensions were recorded after removal. The following peripheral and central nervous system tissues were embedded in paraffin or plastic, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Central Nervous System		
Brain		
Midbrain	Forebrain	Center of cerebrum
Cerebellum and pons	Medulla oblongata	
Spinal cord		
Cervical swellings C3-C7	Lumbar swellings, T13-L4	
Other		
Gasserian ganglion/Trigeminal nerves	Lumbar dorsal root ganglion at T13-L4	Lumbar dorsal root fiber at T13-L4
Lumbar ventral root fiber at T13-L4	Cervical dorsal root ganglion at C3-C7	Cervical dorsal root fiber at C3-C7
Cervical ventral root fiber at C3-C7	Optic Nerves	Eyes
Peripheral Nervous System		
Sciatic nerve (mid-thigh region and sciatic notch)	Peroneal nerve	Forelimbs
Tail	Sural nerve	Tibial nerve

II. RESULTS

A. Observations

1. Mortality - Three males (days 13, 25, and 47) and two females days (22 and 90) in the 800 ppm treatment group died before the end of the study. Findings in these rats included emaciation (one male) dark red stomach and intestinal contents (two males and one female) gas-distended stomach (one male), enlarged lymph nodes (one male and one female), pale spleen (one male) and mottled lungs (one female). A third female appeared to have experienced mechanical trauma and was euthanized *in extremis* (day 91). This female had a broken incisor, an abrasion of the tongue, swollen gingiva, and red matting on the entire head, ventral surface, limbs and tail. No explanation of the mechanical trauma was given.

2. Clinical signs - Selected clinical signs are presented in Table 2. Treatment-related clinical signs were observed primarily both in males and females in the 800 ppm treatment group. These consisted of gait alterations (rocking, lurching or swaying, walking with hindlimbs splayed, walking on tiptoes and/or writhing) through most of the treatment period, and hypersensitivity to noise (weeks 1-9). Sporadic impaired righting reflex was observed during weeks 2-9 in 10 males and 8 females in this group. Less commonly observed clinical signs in this treatment group consisted of piloerection, convulsions, popcorn seizures, altered posture, and matting/staining on various body surfaces. These clinical signs are tallied in more detail under the results of the FOB.

   Signs were less common in the 200 ppm group. Gait alterations (rocks, lurches or sways) were observed in 4 males and 2 females, hypersensitivity to noise was observed in 1 male and 2 females and piloerection was observed in 1 male. In the 50 ppm group, single instances of gait alterations, hypersensitivity to noise, and piloerection were observed at the mid-point of the study. These observations of altered FOB parameters in the lower dose groups were reported by a single alternate observer. Most of these signs were not noted in these particular animals in either group during the FOB. Therefore, only the clinical signs observed in the high-dose animals were considered to be treatment-related.

Table 2. Selected clinical signs in rats dosed with deltamethrin for 13 weeks.

Clinical Sign	Males (mg/kg)				Females (mg/kg)			
	0	50	200	800	0	50	200	800
Animal rocks, lurches, or sways	0	0	4(5)	10(586)	0	1(1)	2(2)	10(618)
Hypersensitivity to noise	0	0	1(1)	10(104)	0	1(1)	2(2)	10(132)
Impaired Righting Reflex	0	0	0	10(105)	0	0	0	8(74)
Piloerection	0	1(1)	1(1)	7(35)	0	0	0	3(3)
Popcorn seizure	0	0	0	2(4)	0	0	0	2(3)
Altered posture	0	0	0	2(16)	0	0	0	2(4)
Convulsions	0	0	0	2(4)	NO	NO	NO	NO
Tan matting on ventral neck	0	0	0	3(38)	0	0	0	4(24)
Tan matting on ventral abdominal area	0	0	0	3(47)	0	0	0	4(77)
Tan matting ventral on thoracic area	0	0	0	3(33)	0	0	0	3(15)
Tan matting on urogenital area	0	0	0	3(40)	0	0	0	4(75)

a Data obtained from the study report, Table 1 , pages 42 through 52; n=10; NO = not observed. Data are presented as [# affected animals (# incidences)].

3. Functional Observational Battery - Results of the FOB indicated no treatment-related findings during the home cage observations. However, treatment-related effects were observed during the handling, open field, sensory, neuromuscular, and physiological observations and for the most part were isolated to the high dose.

   Home cage observations: All groups were comparable during the pretest evaluation and at test weeks 3, 7 and 12. Only one female in the 800 ppm group had slightly drooping eyelids during the week 12 observation.

   Handling observations: Selected findings noted during the handling observations at weeks 7 and 12 are presented in Table 3. Although various findings occurred in only a low number of the males and females, all were greater than the historical control incidences.

   At week 3, the following signs of neurotoxicity were observed in the 800 ppm males (none of these signs were observed in any concurrent control): (i) slight piloerection [22% treated vs. 0% historical controls (HC)]; (ii) slightly soiled fur (33% treated vs. 3.7% HC); (iii) red deposits around the mouth (11% treated vs. 0.9% HC); and (iv) crusty deposits

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around the mouth (11% treated vs. 0% HC). At week 3 in the 200 ppm males, slightly soiled fur (10% treated vs. 3.7% HC) was observed. With the exception of soiled fur none of these signs of neurotoxicity were observed during the week 7 and 12 observation periods, and therefore were not considered to be of toxicological importance.

At weeks 7 and 12 in the high-dose females, slightly soiled fur (11% and 22%, respectively) was observed. At week 12 the high-dose females showed altered palpebral closure (11%), salivation (11%), pale mucous membranes (11%), pale eyes (11%), and pale skin (11%) (none of these were observed in any concurrent or historical control).

No treatment-related differences from controls were observed in the high-dose males at any time point or in the high dose females at week 3. No treatment-related differences from controls were observed in the 50 or 200 ppm groups during the handling observations.

Table 3. Selected handling observations at weeks 7 and 12 in female rats dosed with deltamethrin for 13 weeks.[a]

Observation	Dose (ppm)				
	0	50	200	800	Historical Controls
Week 7					
Total Animals	10	10	10	9	110
Slightly soiled fur	0	0	0	1 (11%)	0
Week 12					
Total Animals	10	10	10	9	110
Slightly soiled fur	0	0	0	2 (22%)	0
Altered palpebral closure	0	0	0	1 (11%)	0
Salivation	0	0	0	1 (11%)	0
Pale mucous membranes	0	0	0	1 (11%)	0
Pale eyes	0	0	0	1 (11%)	0
Pale skin	0	0	0	1 (11%)	0

a Data obtained from the study report, Tables 16 through 41, pages 105 through 140. Percentage incidence calculated by the reviewer.

Open field observations: Selected findings noted during the open field observations at week 3 are presented in Table 4a. At week 3, slightly impaired mobility (56%) and gait alterations (ataxia, excessive sway) (67%) were observed in the 800 ppm males ($p<0.05$). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included the following: (i) moderately impaired mobility (33%); (ii) body drags or sways (11%); (iii) hindlimbs splayed or dragging (11%); (iv) slight impairment of gait score (33%); (v) considerable impairment of gait score (22%); (vi) marked impairment of gait score (11%); (vii) severe impairment of gait score (11%); and (viii) bizarre/stereotypic behavior (side to side rocking) (33%).

At week 3 the 800 ppm females displayed slightly impaired ($p<0.05$) mobility (44%). Findings which were not statistically significant, not observed in any concurrent control animal, and were biologically and toxicologically significant included the following: (i) alterations in gait (ataxia, excessive sway) (22%); (ii) slight impairment of gait score (33%) and (iii) considerable impairment of gait score (11%).

Table 4a. Selected open field observations at week 3 in rats dosed with deltamethrin for 13 weeks. [a,b,c]

Observation	Males (ppm)			Females (ppm)		
	0	800	Historical Controls	0	800	Historical Controls
Number tested	10	9	107	10	9	107
Mobility						
Normal	10 (100%)	1* (11%)	107 (100%)	10 (100%)	5* (56%)	107 (100%)
Slightly impaired	0	5* (56%)	NO	0	4* (44%)	NO
Moderately impaired	0	3 (33%)	NO	NO	NO	NO
Gait						
Normal	10 (100%)	1* (11%)	107 (100%)	10 (100%)	7 (78%)	105 (98.1%)
Ataxia, excessive sway	0	6* (67%)	NO	0	2 (22%)	NO
Body drags and sways	0	1 (11%)	NO	NO	NO	NO
Hindlimbs splayed or dragging	0	1 (11%)	NO	NO	NO	NO
Gait Score						
Normal	10 (100%)	2* (22%)	107 (100%)	10 (100%)	5* (56%)	106 (99.1%)
Slight impairment	0	3 (33%)	NO	0	3 (33%)	1 (0.9%)
Considerable impairment	0	2 (22%)	NO	0	1 (11%)	NO
Marked impairment	0	1 (11%)	NO	NO	NO	NO
Severe impairment	0	1 (11%)	NO	NO	NO	NO
Bizarre/stereotypic behavior						
None (absent)	10 (100%)	6 (67%)	107 (100%)	10 (100%)	9 (100%)	107 (100%)
Side to side rocking	0	3 (33%)	NO	NO	NO	NO

a Data obtained from the study report, Tables 24 , pages 151 through 154 and Appendix G, pages 1386 through 1440; NO = not observed.

b Percentage incidence calculated by the reviewer.

c No differences from the control data were observed in the 50 and 200 ppm groups; thus the data were not presented.

* Statistically different from controls; $p<0.05$

Selected findings noted during the open field observations at week 7 are presented in Table 4b. In the 800 ppm males, the open field observations ($p<0.05$) included: (i) gait alterations (ataxia, excessive sway) (86%), (ii) slight impairment in gait score (71%) and (iii) side to side rocking (86%). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included slightly impaired mobility (43%) and moderately impaired mobility (29%).

In the 800 ppm females, slightly impaired mobility (44%), gait alterations (ataxia, excessive sway) (67%), and side to side rocking (44%) were observed at week 7. Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included the following: (i) moderately impaired mobility (33%); (ii) slight impairment of gait score (22%); and (iii) considerable impairment of gait score (22%).

Table 4b. Selected open field observations at week 7 in rats dosed with deltamethrin for 13 weeks.[a,b,c]

Observation	Males (ppm)			Females (ppm)		
	0	800	Historical Controls	0	800	Historical Controls
Number tested	10	7	40	10	9	40
Mobility						
Normal	10 (100%)	2* (29%)	40 (100%)	10 (100%)	2* (22%)	40 (100%)
Slightly impaired	0	3 (43%)	NO	0	4* (44%)	NO
Moderately impaired	0	2 (29%)	NO	0	3 (33%)	NO
Gait						
Normal	10 (100%)	1* (14%)	40 (100%)	10 (100%)	3* (33%)	40 (100%)
Ataxia, excessive sway	0	6* (86%)	NO	0	6* (67%)	NO
Gait Score						
Normal	10 (100%)	2* (29%)	40 (100%)	10 (100%)	5* (56%)	40 (100%)
Slight impairment	0	5* (71%)	NO	0	2 (22%)	NO
Considerable impairment	0	NO	NO	0	2 (22%)	NO
Bizarre/stereotypic behavior						
None (absent)	10 (100%)	1* (14%)	40 (100%)	10 (100%)	5* (56%)	40 (100%)
Side to side rocking	0	6* (86%)	NA	0	4* (44%)	NO

a Data obtained from the study report, Table 26, pages 159 through 162 and Appendix G, pages 1386 through 1440; NO = not observed.
b Percentage incidence calculated by the reviewer.
c No differences in the control data were observed in the 50 and 200 ppm groups; thus the data were not presented.
* Statistically different from controls; $p<0.05$

Selected findings noted during the open field observations at week 12, are presented in Table 4c. At week 12 in the 800 ppm males, the following observations ($p<0.05$) were noted: (i) slightly impaired mobility (71%); (ii) gait alterations (ataxia, excessive sway) (86%); (iii) slight impairment in gait score (71%); and (iv) side to side rocking (71%). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included moderately impaired mobility (14%) and considerable impairment of gait score (14%).

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At week 12, the following observations were noted in the 800 ppm females ($p<0.05$): (i) slightly impaired mobility (56%); (ii) gait alterations (ataxia, excessive sway) (56%); (iii) slight impairment of gait score (56%); and (iv) side to side rocking (78%). Findings which were not statistically significant, not observed in any concurrent control animal, and were biologically and toxicologically significant included the following: (i) moderately impaired mobility (33%); (ii) walking on tip toes (11%); (iii) body drags and sways (11%); and (iv) considerable impairment of gait score (33%).

Table 4c. Selected open field observations at week 12 in rats dosed with deltamethrin for 13 weeks.[a,b,c]

Observation	Males (ppm)			Females (ppm)		
	0	800	Historical Controls	0	800	Historical Controls
Number tested	10	7	40	10	9	40
Mobility						
Normal	10 (100%)	1* (14%)	40 (100%)	10 (100%)	1* (11%)	40 (100%)
Slightly impaired	0	5* (71%)	NO	0	5* (56%)	NO
Moderately impaired	0	1 (14%)	NO	0	3 (33%)	NO
Gait						
Normal	10 (100%)	1* (14%)	40 (100%)	10 (100%)	2* (22%)	39 (97.5%)
Ataxia, excessive sway	0	6* (86%)	NO	0	5* (56%)	NO
Body drags and sways	NO	NO	NO	0	1 (11%)	NO
Walks on tiptoes	NO	NO	NO	0	1 (11%)	1 (2.5%)
Gait Score						
Normal	10 (100%)	1* (14%)	40 (100%)	10 (100%)	1* (11%)	39 (97.5%)
Slight impairment	0	5* (71%)	NO	0	5* (56%)	1 (2.5%)
Considerable impairment	0	1 (14%)	NO	0	3 (33%)	NO
Bizarre/stereotypic behavior						
None (absent)	10 (100%)	2* (29%)	40 (100%)	10 (100%)	2* (22%)	40 (100%)
Side to side rocking	0	5* (71%)	NO	0	7* (78%)	NO

a Data obtained from the study report, Table 28, pages 167 through 170 and Appendix G, pages 1386 through 1440; NO = not observed.

b Percentage incidence calculated by the reviewer.

c No differences in data from the controls were observed in the 50 and 200 ppm groups; thus the data were not presented.

* Statistically different from controls; $p<0.05$

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At week 7, decreased rearing in the 800 and 50 ppm males (70% each) and increased defecation in the 50 ppm males (70%) were observed. These findings were not dose-dependent and considered not to be treatment-related. No treatment-related differences from controls were observed in the 200 and 50 ppm groups during the open field observations.

Sensory observations: Selected findings noted during the sensory observations at weeks 3, 7, and 12 are presented in Table 5. At week 3, slightly uncoordinated air righting reflex (44%) was observed in the 800 ppm males. In the 800 ppm males, findings (p = not statistically significant) included slightly uncoordinated air righting reflex at week 7 (29%) and at week 12 (43%).

In the 800 ppm females, the following findings (p = not statistically significant) were noted: (i) slightly uncoordinated air righting reflex at weeks 7 and 12 (11% each week, respectively); (ii) landing on side at week 7 (11%); and (iii) landing on back at week 12 (22%). No treatment-related differences from controls were observed in the 800 ppm females at week 3.

No treatment-related differences from controls were observed in the 200 and 50 ppm groups during the sensory observations.

Table 5. Selected sensory observations (air righting reflex) in rats dosed with deltamethrin for 13 weeks.[a,b,c]

Observation	**Males** (ppm)			**Females** (ppm)		
	0	800	Historical Controls	0	800	Historical Controls
Week 3						
Number tested	10	9	107	10	9	107
Normal	10 (100%)	5* (56%)	104 (97.2%)	10 (100%)	9 (100%)	106 (99.1%)
Slightly uncoordinated	0	4* (44%)	3 (2.8%)	0	NO	1 (0.9%)
Week 7						
Number tested	10	7	40	10	9	40
Narmal	10 (100%)	5 (71%)	38 (95.0%)	10 (100%)	7 (78%)	39 (97.5%)
Slightly uncaardinAted	0	2 (29%)	2 (5.0%)	0	1 (11%)	1 (2.5%)
Lands an side	NO	NO	NO	0	1 (11%)	NO
Week 12						
Number tested	10	7	40	10	9	40
Normal	10 (100%)	4 (57%)	40 (100%)	10 (100%)	6 (67%)	40 (100%)
Slightly uncoordinated	0	3 (43%)	NO	0	1 (11%)	NO
Lands on back	NO	NO	NO	0	2 (22%)	NO

a Data obtained from the study report, Tables 32 through 36, pages 192 through 210 and Appendix G, pages 1386 through 1440; NO = not observed.

b Percentage incidence calculated by the reviewer.

c No treatment-related differences from the controls were observed in the 50 and 200 ppm groups; thus the data were not presented.

* Statistically different from controls; $p<0.05$

Neuromuscular observations: Selected findings noted during the neuromuscular observations are presented in Tables 6a and 6b. At week 3, reduced hindlimb resistance (animal shows some weakness) (89%) and decreased fore- and hindlimb grip strength (↓34%, each) were observed in the 800 ppm males ($p<0.05$). In the 800 ppm males, decreased forelimb grip strength (↓25%, p= not statistically significant) was observed at week 7. In addition, reduced hindlimb resistance (animal shows some weakness) was observed at weeks 7 and 12 (43% and 28%, respectively) in these animals.

In the 800 ppm females, findings ($p<0.05$) included reduced hindlimb resistance (animal shows some weakness) at week 3 (67%) and at week 12 (44%). Findings which were toxicologically important but not statistically significant included reduced hindlimb resistance (animal shows some weakness) at week 7 (33%) and absence of hindlimb resistance (22%) at week 12.

Increased ($p<0.05$ or 0.01) hindlimb gripstrength was observed in the 50 ppm males at weeks 3 and 12 (↑20-35%); however, because gripstrength increased as opposed to decreased and did not occur consistently over time (not present in week 7), it was considered not to be of toxicological concern. No treatment-related differences from controls were observed in the 50 and 200 ppm groups during the neuromuscular observations.

Table 6a. Selected neuromuscular observations (hindlimb extensor strength) in rats dosed with deltamethrin for 13 weeks. [a,b]

Observation	Males (ppm)					Females (ppm)				
	0	50	200	800	Historical Controls	0	50	200	800	Historical Controls
Week 3										
Number tested	10	10	10	9	107	10	10	10	9	107
Resistance reduced	0	0	0	8*(89%)	NO	1	2	0	6* (67%)	1(0.9%)
Resistance present	10	10	10	1* (11%)	107 (100%)	9	8	10	3* (33%)	106 (99.1%)
Week 7										
Number tested	10	10	10	7	40	10	10	10	9	40
Resistance reduced	0	0	0	3 (43%)	NO	0	0	0	3 (33%)	NO
Resistance present	10	10	10	4 (57%)	40 (100%)	10	10	10	6 (67%)	40 (100%)
Week 12										
Number tested	10	10	10	7	40	10	10	10	9	40
Resistance reduced	0	0	0	2 (28%)	NO	0	0	1	4* (44%)	NO
Resistance present	10	10	10	5 (71%)	40 (100%)	10	10	9	3* (33%)	40(100%)
Resistance absent	NO	NO	NO	NO	NO	0	0	0	2 (22%)	NO

a Data obtained from the study report, Tables 40 through 44, pages 221 through 230 and Appendix G, pages 1386 through 1440; NO = not observed.

b Percentage incidence calculated by the reviewer.

* Statistically different from concurrent controls; $p<0.05$

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Table 6b. Selected neuromuscular observations in male rats dosed with deltamethrin for 13 weeks.[a]

Treatment Week	Dose (ppm)				
	0	50	200	800	Historical Controls
Mean Forelimb Grip Strength					
Week 3	980.0	1144.9	1007.5	651.0* (↓34%)	936.2
Week 7	915.0	1091.6	938.4	683.3* (↓25%)	1243.1
Week 12	814.9	1120.8	864.2	850.1	1355.2
Mean Hindlimb Grip Strength					
Week 3	583.5	705* (↑20%)	615.9	383.3** (↓34%)	602.5
Week 7	572.4	709.2	611.6	459.4	741.7
Week 12	498.3	675.7** (↑35%)	565.0	379.7	956.0

a Data obtained from the study report, Tables 40 through 44, pages 221 through 230 and Appendix G, pages 1386 through 1440.
b Percentage difference from concurrent controls calculated by the reviewer.
* or ** Statistically different from concurrent controls; p<0.05 or 0.01.

Physiological observations: In the 800 ppm group, mean body weights were decreased (p<0.05 or 0.01) at weeks 3, 7, and 12 in the males (↓28-35%) and females (↓12-17%), and were consistent with the data presented in Table 7a. Catalepsy time in the 800 ppm females was increased at week 3 (↑100%, p<0.05); however, this finding was not consistent over time nor was it observed in the males. Therefore, this difference was considered to be incidental and not treatment-related. No other treatment-related effects were noted in the 200 and 50 ppm groups.

4. Motor activity - No treatment-related effects were noted in the 800, 200 and 50 ppm groups (Table 7).

No significant differences from the controls were observed at weeks 7 and 12.
At week 3, the following inter-group differences attained statistical significance (p<0.05), but occurred only in one sex, were incidental, and/or not dose-dependent, and were therefore not of toxicological significance:

mean ambulatory activity

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- in the 800 ppm females, during interval 1 (↑28%)
- in the 200 ppm females, during interval 1 (↑20%)
- in the 50 ppm females, during interval 1 (↑33%) and interval 4 (↑106%)
- in the 50 ppm females, total count (↑39%)

mean total activity

- in the 800 ppm females, during interval 1 (↑46%) and interval 2 (↑48%)
- in the 800 ppm females, total count (↑37%)
- in the 200 ppm females, during interval 1 (↑19%)
- in the 50 ppm females, during interval 1 (↑25%) and interval 4 (↑93%)
- in the 50 ppm females, total count (↑35%)

Table 7. Total count of motor and ambulatory activities of rats administered deltamethrin in the diet for 13 weeks[a]

Parameter	Dose (ppm)			
	0	50	200	800
Males				
Motor activity				
pretreatment	1718±390.0	1401±504.5	1464±514.3	1432±330.5
week 3	1957±355.1	1749±635.4	1461±270.3	1563±566.5
week 7	1837±309.7	1618±381.4	1596±362.6	1722±570.0
week 12	1714±247.4	1680±343.5	1485±321.2	1979±426.1
Ambulatory activity				
pretreatment	953±178.8	787±271.7	837±335.8	847±230.1
week 3	1185±205.0	1086±423.9	880±190.5	817±326.1
week 7	1134±196.8	998±246.4	994±260.2	983±289.6
week 12	1089±132.6	1036±265.5	926±235.2	1067±244.8
Females				
Motor activity				
pretreatment	1184±328.0	1552±364.0	1154±364.9	1382±504.0
week 3	1425±281.0	1920±304.0*	1554±218.4	1957±411.1*
week 7	1590±302.8	1729±339.8	1541±372.4	1614±372.9
week 12	1760±430.4	1936±256.7	1783±306.9	1620±674.6
Ambulatory activity				
pretreatment	653±221.5	873±241.3	669±230.0	740±225.0
week 3	862±209.0	1198±178.2*	935±168.7	1015±223.1
week 7	1001±196.2	1111±252.6	971±284.9	901±269.9
week 12	1175±293.2	1264±157.5	1192±281.2	944±358.4

a Data taken from Tables 50-53, pages 247-262, MRID 44557902.
* Statistically significantly different from control group, $p<0.05$, Dunnett's test.

B. Body weight and body weight gain

Selected body weights and body weight gains are presented in Tables 7a and 7b, respectively. Decreases ($p<0.05$ or 0.01) in body weights were observed in high-dose males and females

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throughout the study (↓26-35% and ↓10-17%, respectively). Decreased ($p<0.05$ or 0.01) body weight gains were observed in high-dose males and females throughout the study (↓50-102% and ↓48-114%, respectively). Differences from controls in body weights and body weight gains were considered to be treatment-related. No treatment-related differences from controls in body weight and body weight gains were observed in any other treated group.

Table 7a. Body weights (g) at selected intervals in rats dosed with deltamethrin for 13 weeks.[a]

Treatment week(s)	Dose (ppm)			
	0	50	200	800
Males				
1	270	270	261	201**(↓26%)
3	366	380	359	238**(↓35%)
7	467	500	454	338**(↓28%)
10	519	564	505	373**(↓28%)
13	562	611	541	399*(↓29%)
Females				
1	190	187	189	171*(↓10%)
3	231	230	225	197**(↓15%)
7	271	277	270	238*(↓12%)
10	292	294	288	255*(↓13%)
13	311	313	304	257**(↓17%)

a Data obtained from the study report, Tables 4, pages 53 through 64.
* or ** Significantly different from controls at $p< 0.05$ or 0.01.

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Table 7b. Body weights gains (g) at selected intervals in rats dosed with deltamethrin for 13 weeks.[a]

Treatment week(s)	Dose (ppm)			
	0	50	200	800
Males				
0-1	60	59	55	-1**(↓102%)
1-2	52	60	54	14**(↓73%)
7-8	18	28*(↑56%)	20	9 (↓50%)
8-9	20	22	16	6*(↓70%)
10-11	16	19	12	8*(↓50%)
12-13	13	13	10	6 (↓54%)
Females				
0-1	22	22	23	4**(↓82%)
1-2	23	20	18	12**(↓48%)
6-7	7	13	9	-1*(114%)
8-9	11	7	10	4*(↓64%)
11-12	12	10	6	2**(↓83%)
12-13	2	1	3	-5 (↓350%)

a Data obtained from the study report, Tables 4, pages 53 through 64.
* or ** Significantly different from controls at $p < 0.05$ or 0.01.

C. Food and compound intake/water consumption

1. Food consumption - Food consumption at selected intervals in male and female rats treated with deltamethrin are presented in Table 8. Decreased ($p<0.05$ or 0.01) food consumption was observed in high-dose males and females throughout the study (↓18-45% and ↓11-25%, respectively). No treatment-related differences from controls were observed in any other treated group.

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Table 8. Food consumption (g/animal/day) at selected intervals in rats dosed with deltamethrin for up to 13 weeks.[a]

Treatment week(s)	Dose (ppm)			
	0	50	200	800
Males				
0-1	28	27	26	16**(↓43%)
1-2	29	29	28	16**(↓45%)
5-6	28	31	28	23**(↓18%)
9-10	27	30	27	22**(↓19%)
11-12	27	30	26	21**(↓22%)
12-13	26	28	26	21**(↓19%)
Females				
0-1	20	20	20	15**(↓25%)
1-2	20	20	19	15**(↓25%)
5-6	21	22	21	18**(↓14%)
9-10	19	19	19	17*(↓11%)
11-12	20	19	19	15**(↓25%)
12-13	18	17	18	15**(↓17%)

a Data obtained from the study report, Tables 4 , pages 65 through 70.
* or ** Significantly different from controls at $p < 0.05$ or 0.01.

2. Compound consumption - The achieved mean dosages based on nominal dietary concentrations, actual body weights, and actual food consumption are shown in Table 1.

D. Sacrifice and pathology

1. Gross Pathology - Three males and two females in the 800 ppm treatment group died before the end of the study. Findings in these rats included emaciation (one male) dark red stomach and intestinal contents (two males and one female) gas-distended stomach (one male), enlarged lymph nodes (one male and one female), pale spleen (one male) and mottled lungs (one female). Other than the emaciation, the study author considered these observations common findings in animals that die. A third female appeared to have experienced mechanical trauma and was euthanized *in extremis*. This female had a broken incisor, an abrasion of the tongue, swollen gingiva, and red matting on the entire head, ventral surface, limbs and tail. No explanation of the mechanical trauma was given.

1. Organ weight - No treatment-related differences from controls were observed regarding brain weights and dimensions.

2. Microscopic pathology - No treatment-related neuropathological changes were observed. In high-dose females, minimal retinal dysplasia (2/5 treated vs. 1/5 controls) and minimal retinal degeneration (1/5 treated vs. 1/5 controls) were observed. Because these changes occurred similarly in controls, they were not considered treatment-related.

III. DISCUSSION

A. Investigator's conclusions - The study author concluded that deltamethrin, at a dietary concentration of 800 ppm, elicits clinical signs of toxicity, neurotoxic effects (based on FOB data), mortality, and decreased body weights, body weight gains, and food consumption. The NOAEL for this study was 200 ppm.

B. Reviewer's discussion - In this subchronic neurotoxicity screening battery, deltamethrin was administered for 13 weeks to 10 Crl:CD (SD)BR rats/sex/dose at dietary concentrations of 0, 50, 200, or 800 ppm (equivalent to [M/F] 0/0, 4/4, 14/16, or 54/58 mg/kg/day). The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

No treatment-related findings were observed in the 50 or 200 ppm groups. Brain weights and dimensions, motor activity, and neuropathological findings were unaffected by the test substance.

Three males (days 13, 25, and 47) and two females days (22 and 90) in the 800 ppm treatment group died before the end of the study. Findings in these rats included emaciation (one male) dark red stomach and intestinal contents (two males and one female) gas-distended stomach (one male), enlarged lymph nodes (one male and one female), pale spleen (one male) and mottled lungs (one female). A third female appeared to have experienced mechanical trauma and was euthanized *in extremis* (day 91). This female had a broken incisor, an abrasion of the tongue, swollen gingiva, and red matting on the entire head, ventral surface, limbs and tail. No explanation of the mechanical trauma was given..

Males and females showed various clinical findings at the high-dose throughout the study, which included (i) rocking, swaying, or lurching, (ii) hypersensitivity to noise, (iii) impaired righting reflex, (iv) piloerection, (v) seizures, (vi) altered posture, (vii) convulsions, and (viii) soiled fur.

Significant decreases in body weights were observed in high-dose males and females throughout the study (↓26-35% and ↓10-17%, respectively). Significantly decreased body weight gains were also observed in high-dose males and females throughout the study (↓50-102% and ↓48-114%, respectively). In addition, decreased ($p<0.05$ or 0.01) food consumption was observed in high-dose males and females throughout the study (↓18-45% and ↓11-25%, respectively).

Results of the FOB indicated no treatment-related findings during the home cage

observations. However, treatment-related effects were noted during the handling, open field, sensory, and neuromuscular observations.

Several findings were noted during the handling observations. At weeks 7 and 12 in the high-dose females, slightly soiled fur (11% and 22%, respectively) was observed (this finding was not observed in any concurrent or historical control). At week 12 the following were observed in the high-dose females (none of these were observed in any concurrent or historical control): (i) altered palpebral closure (11%); (ii) salivation (11%); (iii) pale mucous membranes (11%); (iv) pale eyes (11%); and (v) pale skin (11%).

During the open field observations, slightly impaired mobility (56%) and gait alterations (ataxia, excessive sway) (67%) were observed in the 800 ppm males at week 3 ($p<0.05$). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included the following: (i) moderately impaired mobility (33%); (ii) body drags or sways (11%); (iii) hindlimbs splayed or dragging (11%); (iv) slight impairment of gait score (33%); (v) considerable impairment of gait score (22%); (vi) marked impairment of gait score (11%); (vii) severe impairment of gait score (11%); and (viii) bizarre/stereotypic behavior (side to side rocking) (33%). At week 3 the 800 ppm females displayed slightly impaired ($p<0.05$) mobility (44%). Findings which were not statistically significant, not observed in any concurrent control animal, and were biologically and toxicologically significant included the following: (i) alterations in gait (ataxia, excessive sway) (22%); (ii) slight impairment of gait score (33%); and (iii) considerable impairment of gait score (11%).

Many findings indicative of neurotoxicity were noted during the open field observations at week 7. In the 800 ppm males, the following observations ($p<0.05$) were made: (i) gait alterations (ataxia, excessive sway) (86%); (ii) slight impairment in gait score (71%); and (iii) side to side rocking (86%). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included slightly impaired mobility (43%) and moderately impaired mobility (29%). In the 800 ppm females, slightly impaired mobility (44%), gait alterations (ataxia, excessive sway) (67%); and side to side rocking (44%) were observed at week 7. Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included the following: (i) moderately impaired mobility (33%); (ii) slight impairment of gait score (22%); and (iii) considerable impairment of gait score (22%).

At week 12, additional findings were noted during the open field observations. In the 800 ppm males, the following observations ($p<0.05$) were made: (i) slightly impaired mobility (71%); (ii) gait alterations (ataxia, excessive sway) (86%); (iii) slight impairment in gait score (71%); and (iv) side to side rocking (71%). Findings which were not statistically significant, not observed in any concurrent or historical control animal, and were biologically and toxicologically significant included moderately impaired mobility (14%) and considerable impairment of gait score (14%). The following observations were noted in the 800 ppm females ($p<0.05$): (i) slightly impaired mobility (56%); (ii) gait alterations (ataxia, excessive sway) (56%); (iii) slight impairment of gait score (56%); and (iv) side to side rocking (78%). Findings which were not statistically significant, not observed in any concurrent control animal, and were biologically and toxicologically significant included the following: (i)

moderately impaired mobility (33%); (ii) walking on tip toes (11%); (iii) body drags and sways (11%); and (iv) considerable impairment of gait score (33%).

Signs of neurotoxicity were noted during the sensory observations. At week 3, slightly uncoordinated air righting reflex (44%) was observed in the 800 ppm males. In the 800 ppm males, findings (p = not statistically significant) included slightly uncoordinated air righting reflex at week 7 (29%) and at week 12 (43%). In the 800 ppm females, the following findings (p = not statistically significant) were noted: (i) slightly uncoordinated air righting reflex at weeks 7 and 12 (11% each, respectively); (ii) landing on side at week 7 (11%); and (iii) landing on back at week 12 (22%). No treatment-related differences from controls were observed in the 800 ppm females at week 3.

During the neuromuscular observations, reduced hindlimb resistance (animal shows some weakness) (89%) and decreased fore- and hindlimb grip strength (↓34%, each) were observed in the 800 ppm males at week 3 ($p<0.05$). Also in the 800 ppm males, decreased forelimb grip strength (↓25%, p= not statistically significant) was observed at week 7. Reduced hindlimb resistance (animal shows some weakness) was observed at weeks 7 and 12 (43% and 28%, respectively) in these animals as well. In the 800 ppm females, findings ($p<0.05$) included reduced hindlimb resistance (animal shows some weakness) at week 3 (67%) and at week 12 (44%). Findings which were toxicologically important but not statistically significant included reduced hindlimb resistance (animal shows some weakness) at week 7 (33%) and absence of hindlimb resistance (22%) at week 12.

The neurotoxicity LOAEL is 800 ppm (equivalent to 54 mg/kg/day in males and 58 mg/kg/day in females) based on mortality, clinical signs of toxicity, FOB findings, and decreased body weights, body weight gains, and food consumption.
The neurotoxicity NOAEL is 200 ppm (equivalent to 14 mg/kg/day in males and 16 mg/kg/day in females).

The submitted study is classified as **acceptable (§82-7)** and satisfies the guideline requirements for a subchronic neurotoxicity screening battery in rats.

C. Study deficiencies -

The high dose in this study was clearly neurotoxic and the mid dose, although considered a NOAEL by the reviewer, may be close to a LOAEL. Although doses were appropriately well spaced, it would have been useful to administer a dietary treatment dose between 200 and 800 ppm..

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DATA EVALUATION RECORD - SUPPLEMENT

DELTAMETHRIN

Study Type: §85-1a; Metabolism Study in Rats

Work Assignment No. 4-02-189 L (MRID 41677401)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Ronnie J. Bever Jr., Ph.D. — Signature: Ronnie J. Bever Jr. Date: 7/2/02

Secondary Reviewer:
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez Date: 7/2/02

Program Manager:
Mary L. Menetrez, Ph.D. — Signature: Mary L Menetrez Date: 7/2/02

Quality Assurance:
Steven Brecher, Ph.D. — Signature: Steven Brecher Date: 7/3/02

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EPA Reviewer: Nancy McCarroll — **Signature:** [signature]
Toxicology Branch, Health Effects Division (7509C) — **Date** 09/11/02
EPA Secondary Reviewer: Alberto Protzel, PhD. — **Signature:** [signature]
Toxicology Branch], Health Effects Division (7509C) — **Date** 9/11/02
EPA Work Assignment Manager: Sanyvette Williams-Foy, D.V.M. — **Signature:** [signature]
Toxicology Branch, Health Effects Division (7509C) — **Date** 9/24/07

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TXR#: 0050424

DATA EVALUATION RECORD - SUPPLEMENT
See TXR #009425 for the previous review.

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 (§85-1); OECD 417.

PC CODE: 097805

DP BARCODE: D283537
SUBMISSION NO.: S545023

TEST MATERIAL (RADIOCHEMICAL PURITY): [^{14}C-benzyl] deltamethrin and [^{14}C-dimethyl] deltamethrin (>95%)

TEST MATERIAL (UNLABELED PURITY): Deltamethrin (99.3%)

SYNONYM: (S)-α-cyano-3-phenoxybenzyl-(1R, 3R)-cis-3(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Bosch, A. (1990) Metabolism of ^{14}C-Deltamethrin in rats. Hazleton Laboratories America, Inc., Madison, WI. Laboratory Project No.: HLA 6187-108, July 9, 1990. MRID 41677401. Unpublished.

SPONSOR: Hoechst-Roussel Agri-Vet Company, Somerville, NJ

EXECUTIVE SUMMARY: In a rat metabolism study (MRID 41677401), [^{14}C-benzyl] deltamethrin (Lot no. X6819A, >95% radiochemical purity) in corn oil was administered as a single gavage dose at 0.55 or 5.50 mg/kg to 5 Crl:CD (SD) BR rats/sex/dose. [^{14}C-dimethyl] deltamethrin (Lot no. X7506A, >95% radiochemical purity) was administered similarly. Two control groups, each with a single male and female rat, received the vehicle (assumed by the reviewer). In addition, 5 rats/sex/dose for each radiolabeled compound received 14 days of non-radiolabeled compound (Lot No. 7B0235B, 99.3%) at 0.55 mg/kg followed by the labeled compound (0.55 mg/kg) on Day 15.

Absorption was ≥31.2% based on urinary excretion. Absorption was very rapid as excretion was virtually complete within 6 hours after dose administration (data not provided). Biliary duct canulation or i.v. injection were not performed to allow a more accurate estimation of absorption. Furthermore, blood kinetics were not reported. Differences in the excretion profile due to sex, treatment regime (single vs repeated), or radiolabel were slight or absent. Seven days following administration, 31.2-56.3% dose was recovered in the urine and 35.7-58.5% was excreted in the feces. Less than 2% dose was recovered in the tissues and carcass. Overall recovery of the dosed radioactivity was 84.2-96.2%.

Concentrations of radioactivity (ppm) in the tissues were <0.01 ppm at 0.55 mg/kg and <0.05 ppm at 5.50 mg/kg, except in the fat (concentration not reported). In general, the concentration in fat was proportional to the dose.

Metabolism of deltamethrin occurred through cleavage of the ester bond to form m-phenoxybenzoic acid (mPBA) and (1R-cis)-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane carboxylic acid (Br_2CA) and through hydroxylation at the 4' position of the mPBA moiety in the intact molecule or after cleavage. Glucuronidation and sulfation occurred during phase II metabolism.

The parent was found in the feces at 46% dose in the 5.50 mg/kg females treated with [^{14}C-benzyl] deltamethrin and 17-35% dose in both sexes and radiolabels at all doses. A minor metabolite, 4' hydroxy deltamethrin, was found (3-6% dose) in the feces of animals treated with [^{14}C-benzyl] deltamethrin. In the urine of animals treated with [^{14}C-benzyl] deltamethrin, the major metabolite was mPBA- 4'-sulfate (30-49% dose), and the minor metabolite was mPBA (2-4% dose). In the urine of animals treated with [^{14}C-dimethyl] deltamethrin, the major metabolites were Br_2CA (4-10% dose) and its glucuronide conjugate (22-38% dose). The amount of radioactivity that was isolated but not identified was 10.8-32.1% dose. Consequently, it is possible that major metabolites were not successfully isolated and characterized.

This study is classified **acceptable/guideline** and satisfies the requirements for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

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