

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
NALED

Chemical Code # 418, Document Processing Number (DPN) # 215

SB 950 # 041

August 3, 1987

Revised 1/21/88, 10/12/88, 5/24/89, 2/7/91, 8/25/94, 11/8/94, 1/9/96, 10/2/00, 6/4/04

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effect
Chronic toxicity, dog: No data gap, possible adverse effect
Oncogenicity, rat: No data gap, no adverse effect
Oncogenicity, mouse: No data gap, possible adverse effect
Reproduction, rat: No data gap, no adverse effect
Teratology, rat: No data gap, no adverse effect
Teratology, rabbit: No data gap, no adverse effect
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotoxicity: No data gap, no adverse effect¹

¹ Studies in both rat and hen

Toxicology one-liners are attached.

All record numbers for the above study types through 210694 (Document No. 215-0200) were examined. This includes all relevant studies indexed by DPR as of June 2, 2004.

Revised by [REDACTED], 1/21/88; [REDACTED], [REDACTED], 10/12/88; [REDACTED], [REDACTED], 5/24/89; [REDACTED], 2/7/91, 7/27/94, 11/8/94, 1/9/96, 10/2/00; [REDACTED], 6/4/04.

See "Guidance for the Re-registration of Pesticide Products Containing NALED as the Active Ingredient", US EPA, 6/83. EPA 1-liners dated 1985. [REDACTED], 5/24/89.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

** 064-071 037591-98 (With rebuttal and supplemental information in 098 064051): "Dibrom Chronic Oral Toxicity/Carcinogenicity Study in Rats," (Bio-Research Laboratories, 6/7/84). Naled, purity approximately 92%, administered by gavage to 55 Sprague-Dawley rats/sex/dose at 0, 0.2, 2.0, 10.0 mg/kg/day. **ADVERSE EFFECT**: mammary adenocarcinomas in males, LEL = 2.0 mg/kg/day. Other effects: cholinesterase inhibition in brain, plasma and RBC, NOEL = 0.2 mg/kg/day. Initially unacceptable, insufficient information for assessment (██████████, 3/28/85). Again unacceptable, lacked dose level justification (██████████, 1/24/86). This was satisfied by first rebuttal, but still unacceptable. A review (██████████, 8/3/87) revealed an oncogenic adverse effect (male mammary tumors) and the need for historical tumor incidence for male mammary adenocarcinomas. Now ACCEPTABLE with historical control data supplied in 064051 (██████████, 1/21/88).

EPA One-Liner (1985): Oncogenic NOEL > 10 mg/kg/day (HDT); systemic NOEL > 10 mg/kg/day; ChE NOEL = 0.2 mg/kg/day; Levels of 10 mg/kg/day showed slight RBC ChE inhibition, moderate plasma and brain ChE inhibition. Core Grade = supplementary, minimum.

097 064701, "Addendum to Lifetime Study in Rats with CHEVRON Naled Technical (SX-1278)", (Bio-Research Laboratories Project No. 9394, Ortho Test no. S-1802, May 24, 1983). Dosage formulation analysis indicate that the dosage formulations were homogeneous and stable during the time required to dose animals. Assays of Dibrom technical (93.3% pure) indicate stability when stored in a freezer, but unstable at ambient temperatures. This addendum provides useful information for an ACCEPTABLE study (064-071, 037591-98). (██████████ & ██████████, 10/07/88).

043 022768. Exact duplicate of #037591 above.

032 928896. SBCS31275E, rebuttal to combined rat study, record #037591-98 above; Prior review of report (██████████, 1/24/86) found the lack of dose level justification to be the major deficiency. Rebuttal cites pilot study results and steep dose-response curve for Naled, satisfying this criticism. (██████████, 5/22/87).

098 064051: Second rebuttal (1/6/88) to record #037591-98 above: provided historical control data as requested. Upgraded study to acceptable with adverse effect. (██████████, 1/21/88).

033 928918: Interim report of study with record number 037591-98.

CHRONIC TOXICITY, RAT

See "Combined, Rat," above.

CHRONIC TOXICITY, DOG

**** 087 046846-046847, "One-Year Chronic Oral Toxicity Study in Dogs With Naled Technical", (IRDC, report no: 415-044, 6/10/86). Naled technical, 91.4% pure, by oral gavage at 0, 0.2, 2.0 and 20.0 mg/kg/day to 6 dogs/sex/level for one year; mild testicular degeneration, focal mineralization of spinal cord, anemia, and mild splenic siderosis; plasma, RBC and brain cholinesterase inhibition; overall NOEL = 0.2 mg/kg/day. Originally reviewed as unacceptable, needing dose level justification (██████████ 11/7/86); review of supplemental data by ██████████ (5/22/87) changed status to complete and ACCEPTABLE with a possible adverse effect (testicular degeneration, focal mineralization of the spinal cord and mild splenic siderosis).**

EPA One-Liner not available.

092 055451: "A Four-Week Dibrom Oral Toxicity Study in Dogs", Bio-Research Laboratories, 1/10/87; Supplemental to #046846-7 above, upgraded study status to ACCEPTABLE. (██████████, 5/22/87).

ONCOGENICITY, RAT

See "Combined, Rat," above.

ONCOGENICITY, MOUSE

**** 044 026887-026886, "Lifetime Oral Carcinogenicity Study in Mice", (IRDC, 3/19/84). Naled, 92.7% pure, at 0, 3, 15, 75/50 mg/kg/day by gavage to 60 mice/sex/group for 89 weeks; high dose reduced to 50 mg/kg at 27 weeks due to mortality (i.e. 75 mg/kg > MTD); interim sacrifice of 10 mice/sex/group at 52 weeks; oncogenic NOEL > 75/50 mg/kg/day, toxic NOEL = 15 mg/kg/day, based on mortality at 75 mg/kg/day; ACCEPTABLE. (██████████, 4/1/85; ██████████, 7/15/87).**

EPA One-Liner: Oncogenic NOEL > 75/50 mg/kg/day; Systemic NOEL = 15 mg/kg/day. Core Grade = supplementary, minimum.

REPRODUCTION, RAT

**** 051 027114 (plus record #s 034059-034065 in volumes 057-061), "Two-Generation Reproduction Study in Rats With Dibrom," (Bio/dynamics, 3/22/85). Naled, 91.0% pure, by oral gavage in 0.5% CMC at 0, 2, 6 or 18 mg/kg/day to 15 male and 30 female CD rats/level for two-generations; decreased pup survival and body weights in F_{2b} only at 18 mg/kg; reduced number of pups at birth at 6 & 18 mg/kg in F_{2b} only; reproductive NOEL = 2 mg/kg, no parental NOEL (decreased body weight gain in all treated male groups). Complete and ACCEPTABLE. (█████, 9/9/85).**

EPA One-Liner not available.

018 046120. Summary, Dibrom Residue Tolerance Petition Reproduction Study 3-Generation - Rat. Summary (1 page) reports no abnormalities to 3rd generation parents or litters observed with Dibrom up to and including 25 ppm. No worksheet or formal review. This study is not on file at CDFR and should be submitted. (█████, 5/23/89 and █████, 5/24/89).

TERATOLOGY, RAT

**** 073 037600, "Teratology Study in Rats With Naled Technical," (Science Applications, Inc., 1/18/84). Naled Technical, 91.4% pure, by oral gavage in CMC at 0, 2, 10 and 40 mg/kg/day to 30 CD rats/level days 6-19 (plug=day 0); maternal NOEL = 10 mg/kg/day (cholinergic symptoms and slight but significant decrease in body weight gain at 40 mg/kg during the dosing period); developmental NOEL = 40 mg/kg/day (HDT). Complete and ACCEPTABLE. (█████, 1/17/86).**

EPA One-Liner: Teratogenic NOEL > 40 mg/kg/day (HDT), Fetotoxic NOEL > 40mg/kg/day, Maternal NOEL = 10 mg/kg/day, Core Grade = Minimum

038 000892. Partial duplicate (21 pp.) of 037600 above.

025 023505, "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats," (publication in J. Environ. Sci. Health, B14(6): 563-577, 1979). Fly Killer D, 36% Naled, in corn oil by oral gavage, at 100, 50, 25, or 0 mg/kg/day, unspecified whether expressed as AI or formulated material, to 15-19 pregnant Wistar rats/group; no adverse effects reported. UNACCEPTABLE, not upgradeable, insufficient information for assessment. (█████ 7/29/87).

TERATOLOGY, RABBIT

**** 072 037599, "Teratology Study in Rabbits With Chevron Naled Technical," (Chevron Environmental Health Center, 2/28/85). Naled technical, 92.5% pure, by oral gavage in 0.5% CMC at 0, 0.2, 2 or 8 mg/kg/day to 20 rabbits/level; no adverse effects; maternal NOEL =**

developmental NOEL = 8 mg/kg/day (highest dose tested); originally reviewed by [REDACTED] (1/16/86) as unacceptable, needing justification of dosage levels. Upgraded to ACCEPTABLE by [REDACTED], 5/22/87, upon review of rebuttal (SBCS131275E) and range-finding study (034058) cited below.

EPA One-Liner not available.

056 034058, "Pilot Teratology Study in Rabbits With Chevron Naled Technical (SX-1397)", (SOCAL 2194, Chevron Environmental Health Center, 1/24/85; supplemental to #037599 above). Maternal toxicity at 10 mg/kg, lowest dose tested. Supplemental information upgraded rabbit teratology study, #037599, to ACCEPTABLE. ([REDACTED] 5/22/87).

050 026891: partial duplicate of 037599.

034 928919: "Teratogenic Study With Naled Technical in Albino Rabbits," IBT, 3 pp.--Invalid.

GENE MUTATION

** 105 072239 "Microbial/Mammalian Microsome Plate Incorporation Mutagenicity Assay with Naled Technical (SX-1665)." (Chevron Environmental Health Center, Inc., July 18, 1988, J. Carver) Naled, 93.3%; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation (Aroclor induced); First trial: 0 (DMSO), 0.003, 0.1, 0.33, 0.1 or 0.33 mg/plate, second trial at 0, 0.01, 0.33, 0.1, 0.33 or 1.0 mg/plate; also used E. coli strain WP2 uvrA; triplicate plates each trial; plate incorporation assay; although some colony counts were statistically significant, there were no reproducible results and none were twice the spontaneous rate; no evidence of an adverse effect; ACCEPTABLE with minor variances. ([REDACTED], 5/24/89)

042 022776, "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems," (publication in Mutation Research, 116: 185-216, 1983 - Literature review of Ames assays performed on 228 pesticides). Insufficient information for adverse effects assessment; Brief Summary, results reported as "-" UNACCEPTABLE, not upgradeable. ([REDACTED] 3/28/85).

EPA One-Liner: No specific data on Naled provided; Core Grade = Unacceptable.

042 035744 "Activity of Organophosphorus Insecticides in Bacterial Tests for Mutagenicity and DNA Repair--Direct Alkylation Versus Metabolic Activation and Breakdown. II. O-O-Dimethyl-0-(1,2-dibromo-2,2-dichloroethyl)-phosphate and two O-Ether Derivations of Trichlorfon," (publication in Chem.-Biol. Interactions, 43: 361-370, 1983). Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 with and without activation (male mice) tested; 0.1 and 0.3 ml S9 per ml mix tested; mutagenicity in TA100 claimed, but reversion rate < 2x background - a result usually considered equivocal for TA100. Revertants

appeared to be greater in number with 0.3 than 0.1 but data by graph only. UNACCEPTABLE, not upgradeable. (██████████, 3/28/85 and ██████████, 5/23/89).

EPA One-Liner: Positive with/without mouse MA in TA100 (Ames); Core Grade = Acceptable.

042 035745, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila," (publication in Mutation Research, 28: 405-420, 1975). S. typhimurium (11 strains) tested; mutagenicity in tester strain TA1535 was claimed, but insufficient information for independent assessment. UNACCEPTABLE, not upgradeable. (██████████, 3/18/85).

EPA One-Liner: Reported positive in S. typhimurium strain TA 1535 of 11 bacterial strains tested; Core Grade = NOT ACCEPTABLE.

042, 022774, "Mutagenicity of Pesticides in the Salmonella/Microsome System", (Kor. Jour. Microbiol. Vol. 14, 123-134, 1976 - journal article; abstract and tables in English, remainder untranslated; S. typhimurium (strains TA98, TA100, TA1535 and TA1538); "ambiguous" mutagenicity in strains TA1535 and TA100 reported and negative results with TA1538 and TA98, but insufficient information present for independent assessment; Incomplete (missing detailed protocol information and results in English); UNACCEPTABLE, not upgradeable. (██████████, 3/28/85 and ██████████, 5/23/89).

EPA One-Liner: Reported negative in S. typhimurium strain TA 100; Core Grade = NOT Acceptable.

045 014823, "Pesticide Mutagenicity in Bacillus subtilis and Salmonella typhimurium Detectors," (publication in J. Agric. Food Chem., 29: 268-271, 1981). Naled (no purity information); S. typhimurium (strains TA1535, TA1536, TA1537, TA1538, TA98, and TA100) and B. subtilis (strains TKJ5211 & 6321), with and without rat liver activation; 50, 100 or 300 µg/plate by spot test, 0 to 50 µg/plate with 30 minutes pre-incubation; mutagenicity indicated in S. typhimurium strains TA1535 and TA100 and in B. subtilis strains TKJ5211 and TKJ6321, but insufficient information presented for independent adverse effects assessment; data presented as "+" or graph only; Incomplete (lacking detailed results); UNACCEPTABLE, not upgradeable. (██████████, 4/1/85).

EPA One-Liner: Positive, but only in B. subtilis strain TKJ6321 without activation of 8 bacterial strains tested; Core Grade = Accepted.

075 037603, "Evaluation of Chevron Naled Technical/Dibrom in the Mouse Somatic Cell Mutation Assay," (Litton, 6/84). Naled technical (92.5%) at dosages of 0, 3, 20 or 150 mg/kg by gavage days 8.5-12.5 of gestation to 120-181 plugged female C57B1/6 mice per group; 34 to 38 litters per group; ethyl nitrosourea (i.p.) used as positive control; decreased lactation index at high dose; no evidence of a positive result in the spot test; UNACCEPTABLE - not a FIFRA guideline study. (██████████, 4/1/85 and ██████████, 12/27/86).

EPA One-Liner: Negative for increase in recessive coat color "spot" presumably indicative of mutational events consisting of intragenic base-pair changes, deletions and somatic crossing over. Core Grade = Acceptable.

044 022773. Partial duplicate of (28 pp) 037603 above.

044 022772, "Pilot Evaluation of Chevron Naled Technical in the Mouse Somatic Cell Assay", (Litton, 6/84). NOT REVIEWED.

SBCS31275E: Rebuttal to gene mutation and somatic cell mutation studies in reference to 037603. No new or useful information provided (022772), studies remain UNACCEPTABLE. (██████████, 7/28/87).

042 022775, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila" (DNA repair in E. coli, publication in Mutation Research, 28: 405-420, 1975). E. coli (7 strains) tested; also tested with several strains of Salmonella including TA1535; no mutagenicity indicated, but insufficient information for independent assessment; Incomplete (missing protocol information and detailed results); very poor copy; UNACCEPTABLE, not upgradeable. (██████████, 3/28/85).

EPA One-Liner did not report on E. coli results.

Summary: Several studies have been conducted in bacteria with mixed results in inadequately reported studies. The previous version of this summary indicated that a guideline study was required to address the conflicting results. This has been done. With the submission of # 072239 in 215-105, with sufficient data to make an evaluation, the collective data indicate that Naled is not clearly mutagenic in microbial systems. As noted in the 1-liners, where a notation of a possible effect was made, inadequate data were available for some and equivocal results were reported in others. (██████████, 5/23/89).

CHROMOSOME EFFECTS

** 074 037601, "Mouse Bone Marrow Micronucleus Assay With Chevron Naled Technical (92.0% Purity, SX-1397)," (Chevron, 11/21/84). Male mice dosed at 55, 110 and 220 mg/kg; female mice dosed at 55, 110 and 290 mg/kg; sacrificed 5 mice/sex/group at 24, 48 and 72 hours; PCE/NCE and micronucleated PCE's showed NO ADVERSE EFFECT. Complete, ACCEPTABLE. (██████████, 1/27/86).

No EPA One-Liner available.

050 026893: Partial duplicate of 037601.

** 043 022769, "In Vivo Cytogenetics Study in Rats, Naled Technical (SX-1397)", (EG&G Mason Research Institute, 6/6/83, report MRI-193-CCC-82-82). Naled (no purity information); Sprague-Dawley rats; low-dose (6.17 mg/kg to females; 3.88 mg/kg to males); mid-dose (20.57

mg/kg to females; 12.93 mg/kg to males); and, high-dose (61.7 mg/kg to females; 38.8 mg/kg to males); doses administered in a single oral gavage dose to 4 animals/sex/group/sacrifice interval; rats sacrificed at 6, 24 or 48 hours; NO ADVERSE EFFECT; Complete, ACCEPTABLE. ([REDACTED] 3/26/85).

EPA One-Liner: Negative for chromosome aberrations in bone marrow cells at oral doses of 3.88, 12.93 and 38.80 mg/kg to males, and 6.17, 20.57 and 61.70 mg/kg to females. Insufficient dosage to effect target tissue. Core Grade = Unacceptable.

DNA DAMAGE

** 105 072240, "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography: Naled Technical", (Sitek Research Laboratories, laboratory study No. 0087-5100, 11/9/88). Naled technical, purity 93.3%, tested with rat hepatocytes at concentrations of 0 (DMSO), 1.0, 2.5, 5.0, 7.5, 10, or 50 µg/ml for 18 hours. Under study conditions, Naled did not induce unscheduled DNA synthesis in rat hepatocytes. ACCEPTABLE. ([REDACTED], 5/22/89 and [REDACTED], 5/24/89))

042 022777, "Activity of Organophosphorus Insecticides in Bacterial Tests for Mutagenicity and DNA Repair - Direct Alkylation Versus Metabolic Activation and Breakdown. II. O,O-Dimethyl-0-(1,2-Dibromo-2,2-Dichloroethyl)-Phosphate and Two 0-Ether Derivatives of Trichlorfon," (Chem.-Biol. Interactions, 43: 361-370, 1983, Braun et al.). Naled (no purity information), 10 or 40 µM/plate; Proteus mirabilis strains PG 713 and PG 273; No adverse effect indicated, but insufficient information provided for independent adverse effects assessment; Incomplete (no detailed protocol or results information); UNACCEPTABLE, not upgradeable. ([REDACTED], 3/28/85).

EPA One-Liner: Negative for DNA damage in P. mirabilis; Core Grade = Acceptable.

NEUROTOXICITY

Range-finding Study:

127 130856 "A Range finding Study for A Subchronic Delay Neurotoxicity Study in Laying Hens (*Gallus gallus domesticus*)," (Beavers, J. B. and Foster, J. W., Wildlife International Ltd., Easton, MD; Project ID #: 263-129, VP-10103, 4/29/94). Naled technical (91.7% pure) was administered by gavage at 0 (0.25% carboxymethyl cellulose), 2, 4, 8, and 16 mg/kg daily for 7 days, followed by a 4 day observation period. NOEL = 2 mg/kg (Clinical signs and decreased locomotor activity at ≥ 4 mg/kg and increased mortality were observed at ≥ 8 mg/kg.) **Possible adverse effects:** Signs of cholinesterase inhibition (≥ 4 mg/kg) and increased mortality occur (≥ 8 mg/kg). **These data are supplemental.** ([REDACTED], 7/21/94).

Definitive Studies:

** 126 130839 "A 28-Day Subchronic Delayed Neurotoxicity Study in Laying Hens (*Gallus gallus domesticus*)," (Beavers, J. B. & Foster, J. W., Wildlife International Ltd., Easton, MD; Project ID #: 263-132, VP-10103, 4/29/94). Naled technical (91.7% pure) was administered by gavage to White Leghorn Hens (*Gallus gallus domesticus*--4/dose for NTE & AChE determinations; 10/dose for behavior/pathology) at 0 (vehicle = 0.25% CMC), 0.5, 2.0 & 4.0 mg/kg and positive control hens received TOCP at 0 (vehicle = corn oil), 35 or 45 mg/kg for 28 days. Treatment was followed by a 21 day observation period. The NOEL for brain ChE was re-evaluated and decreased, based upon biological relevance of inhibition values. NOEL = 0.5 mg/kg (There was a significant decrease in brain AChE levels at ≥ 2.0 mg/kg.) Acceptable. No adverse effect. [REDACTED], 1/9/96.

** 108 088863 "Acute Delayed Neurotoxicity Study with Naled Technical in the Domestic Hen," (Redgrave, V., Gopinath, C., Anderson, A., Cameron, D., Rao, R. and Dawe, I., Huntingdon Research Centre, Ltd., England, 7/30/90). Naled technical (Batch NB 10198-41, 98% pure) was used on hybrid brown laying hens at 0 (0.5% sodium carboxymethylcellulose) or 42 mg/kg (40 hens) in a single dose (by gavage), followed by a repeat dose after 21 days in birds showing a negative neurotoxic response. Naled treated birds were protected with atropine sulphate (10 mg/kg) and 2-PAM (50 mg/kg) immediately prior to dosing. A satellite group was maintained for assessing brain ChE and NTE, treated at 0, 8 (5 hens/group) and 42 mg/kg (10 hens) with a single dose and a 24-hour observation period (then sacrifice). TOCP (corn oil) was used as a positive control (500 mg/kg--10 hens in the main group and 5 hens in the satellite). **No adverse effect.** The positive control was functional. **Acceptable.** [REDACTED], 1/3/91.

107 087179 This volume contains a letter from Therese St. Peter (State Regulatory Affairs Manager), dated July 18, 1990. The letter contained information about study 088863 and a discussion of the histopathological effects observed and their conclusions regarding possible adverse effects. In addition, a table is included which shows the results of the grading for neurotoxic effects (also in the main report). [REDACTED], 1/11/91.

076 037604, "The Evaluation of Dibrom As A Potential Neurotoxic Agent Following Oral Administration to Hens Protected by Atropine Sulfate," (FDRL, 11/14/78). Naled technical (no purity information) at 117 mg/kg in a single gavage dose in atropine-protected hens; NOEL = 117 mg/kg (no delayed neurotoxicity at the only dose tested); UNACCEPTABLE, incomplete, unlikely upgradeable (no repeat dosage given in absence of response to first dose). [REDACTED] 1/21/86).

No EPA One-Liner available.

SBCS31275E: Rebuttal to neurotoxicity study referenced above. No new or useful information provided, study remains UNACCEPTABLE. [REDACTED], 7/28/87). No record number. DPR response (letter dated 8/6/87) to rebuttal (Chevron letter dates 11/24/86 and 3/6/87) on hen delayed neurotoxicity study. New Report Status: No change from previous status of unacceptable, but now upgradeable.

034 928895. Partial duplicate of 037604 . [REDACTED], 3/26/85).

045 016194. Partial duplicate (20 pp) of 037604.

143 131952 "A Range-Finding Acute Study of Valent Naled Technical in Rats," (Lamb, I. C., WIL Research Laboratories, Inc., Ashland, OH; Project #: WIL-194006, 2/9/94). Naled technical (92.7% pure) was administered by gavage to Sprague-Dawley Crl:CD BR rats (1-4/sex/dose) at: **Part A:** 0.5, 1, 5, 35, 75, 100, 125 & 150 mg/kg. **Part B:** 300 mg/kg. **Part C:** 600 mg/kg. **Part D:** 50, 450, 500 & 550. **Part E:** 25 & 450 mg/kg (vehicle = 0.5% carboxymethylcellulose). In Part A, post-dosing observation times were 1, 1.5, 2, 3, 4, 5, 6, 7 & 8 hours and Parts B-E observation times were 0.25, 0.5, 0.75, 1, 2 & 3 hours. All animals were observed for a total of 7 days. At 450 mg/kg 1/4 females died on the day of dosing. All animals at ≥ 500 mg/kg died or were killed moribund within 24 hours post-dosing (most within 45 minutes). Animals treated at 0.5-300 mg/kg survived to termination (day 8). Clinical signs showed gait alterations (rocking, lurching, swaying, prostration), whole body tremors, constricted pupils, reduced forelimb/hindlimb grasp, exophthalmos and splayed hindlimbs at ≥ 75 mg/kg, salivation at ≥ 300 mg/kg and hypoactivity at ≥ 450 mg/kg (peak effects at 0.5 hr post-dosing). At ≤ 50 mg/kg, clinical signs were few (gait alterations: rocking, lurching & swaying) were observed at 50 mg/kg (1 male) at 0.5 & 0.75 hr only. Constricted pupils were observed at 0.5, 1, 5 & 35 mg/kg (no dose relationship). Some body weight loss was observed at 450 mg/kg (1 surviving male) & 300 mg/kg (2/2 females). NOEL = 35 mg/kg. These data are supplemental. [REDACTED], 11/3/94.

** 122 129873 "An Acute Neurotoxicity Study of Naled Technical in Rats," (Lamb, I. C., WIL Research Laboratories, Inc., Ashland, OH; WIL-194007, Sponsor #: VP-10102, 7/12/93). Naled technical (purity = 92.7%) was administered by gavage to Sprague-Dawley Crl:CD BR rats at 0 (vehicle = 0.5% carboxymethylcellulose), 25, 100 and 400 mg/kg (12/sex/dose at 0, 25 & 100 mg/kg; 16/sex at 400 mg/kg). Animals were observed for 14 days post-treatment. NOAEL = 25 mg/kg. At 400 mg/kg, both sexes showed increased mortality, and males showed a transient decrease in body weight gain. Clinical signs were observed in both sexes at 400 mg/kg: orange and/or yellow material on various surfaces and red material around the mouth, nose and/or eyes, gait alterations, tremors and hypoactivity (≥ 100 mg/kg, rales & retching). No adverse effects: Effects were observed in the FOB at ≥ 25 mg/kg: Tremors in limbs, reduced hindlimb resistance (≥ 25 mg/kg) and at ≥ 100 mg/kg: sensorimotor activity, neuromuscular, physiological, autonomic, excitability domains in both sexes. These effects were reversed by day 14 to control values. Acceptable. [REDACTED], 6/27/94.

** 125 130838 "A Subchronic (13-Week) Neurotoxicity Study of Naled Technical in Rats," (Lamb, I. C., WIL Research Laboratories, Inc., Project ID: WIL-194008, VP-10104, 4/28/94). Naled technical (92.7% pure) was administered by gavage to Sprague-Dawley, Crl:CD BR rats (10/sex/dose) at 0 (vehicle = carboxymethyl-cellulose), 0.4, 2.0 and 10.0 mg/kg/day for at least 91 days. NOEL = 2.0 mg/kg (At 10 mg/kg, females showed tremors (forelimb/hindlimb and/or whole body). At 10 mg/kg (males) and at ≥ 2.0 mg/kg (females), there was an increase in hair loss. Males at 10 mg/kg showed a mean urination count that was significantly lower than control.) No adverse effect. [REDACTED], 7/21/94.

DEVELOPMENTAL NEUROTOXICITY (includes pilot study and supplementary studies)

215-0194 210688 Moxon, M. E., "Naled: developmental neurotoxicity study in rats," Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, Oct. 8, 2003. Laboratory Study #: CTL/RR0882/REG/REPT. Thirty Alpk:AP_iSD timed-pregnant dams/group were dosed daily by gavage (10 mg/kg corn oil vehicle) with 0, 0.4, 2, or 10 mg/kg/day Naled (95.4% purity) from gestation day 7 through lactation day 7. On PND 5, litters were culled randomly to achieve ideally 4/sex. F1 pups designated for developmental neurotoxicity studies were dosed from PND 8-22. One pup/sex/litter was allocated for one of these in-life assessments: (1) FOB and motor activity, (2) Learning and memory assessment (days 24 and 27), (3) Auditory startle, or (4) Learning and memory (days 59 and 62). Usually one male or one female per litter was utilized for a given test, so most evaluations had 10 rats/sex/group. Microscopy was performed on PND 12 controls and high dose groups, in which only brains were examined. Brain sections, spinal cord sections, eyes, an acceptable set of spinal roots and ganglia, and peripheral nerves were collected from all perfused rats at PND 63. Most of these tissues were embedded in paraffin and stained with H&E, however peripheral nerves were embedded in resin and stained with toluidine blue. All protocol tissues were examined in perfused males and females of control and high dose groups (N = 10/sex/group examined). In addition, intermediate group female brains of perfused rats were examined. Investigators also performed an analysis of the dimensions of the Purkinje cell layer in cerebellar lobe 8 (adjacent to the prepyramidal fissure). They also estimated Purkinje cell density in that region. Dams tolerated the selected dose range, which also did not cause any definitive effects in offspring. Apparent NOEL for dams and for pups (for all parameters which can now be assessed) = 10 mg/kg/day (highest dose tested). DPR needs further information on motor activity, FOB, and water maze to complete this review (see discussion section of DPR review. [REDACTED] 6/2/04.

215-0193 210687 Moxon, M. E., "Naled: preliminary developmental neurotoxicity study in rats," Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, Nov. 10, 2003. Laboratory Study #: CTL/RR0881/REG/REPT. Fifteen timed-mated Alpk:AP_iSD females/group were dosed with 0, 3, 10, or 30 mg/kg/day Naled (purity 95.84%, in 10 ml/kg corn oil vehicle) from gestation day 7 through lactation day 22. Investigators monitored maternal body weight, food consumption, survival, and clinical signs, as well as survival, clinical signs, and body weights of pups. Whole brain and RBC acetylcholinesterase activities were assessed in 5 dams/group on gestation day 22 and lactation day 22, in fetuses (5/group) on gestation day 22, and in pups (5/group) on lactation days 2, 8, 15, and 22. The only definitive clinical sign in dams was "staining around the mouth" in eleven 30 mg/kg/day dams, and in three 10 mg/kg/day dams. Similar staining was seen in one 3 mg/kg/day dam on only one occasion. This latter event was probably incidental, since the single case occurred earlier in the treatment period than any affected dams at higher dose levels. These signs were typically limited to shortly after daily dosing, and most events occurred between the last few days of gestation and the first few days of lactation. One high dose dam died shortly after delivery, with signs of "hunched, pale, piloerection, pinched-in sides, and urine staining." Two additional dams (one each at 10 and 30 mg/kg/day) had total litter losses between lactation days 2 and 5. It is plausible that at least the high dose findings of one death and one total litter loss were treatment-related. Mean dam body weights were comparable between groups during gestation, however high dose dams weighed up to 25 g less than controls during lactation (peak difference on day 12). Excluding the pups in the

total litter lost at 30 mg/kg/day, pup survival was not affected by treatment. Maternal RBC cholinesterase inhibition was dose-related over the entire dose range (73, 50, and 47% of control activity for 3, 10, and 30 mg/kg/day groups, respectively, at gestation day 22; and 75, 48, and 46% of control in corresponding groups at lactation day 22). Maternal brain cholinesterase inhibition in dams appeared to be progressive over time (137, 63, and 28% of control activity for 3, 10, and 30 mg/kg/day groups, respectively, at gestation day 22; and 84, 34, and 19% of control in corresponding groups at lactation day 22). Maternal brain cholinesterase inhibition was only meaningful under these study conditions at 10 to 30 mg/kg/day. The steep dose-response curve for brain cholinesterase inhibition over the range of 10 to 30 mg/kg/day justifies choosing 10 mg/kg/day as the high dose for the definitive developmental neurotoxicity study. Treatment did not affect litter size. Pup body weights were reduced by 5-6 g at 30 mg/kg/day at weaning, although this may have been partially due to comparatively small litter sizes in controls. Pup brain cholinesterase inhibition was limited to 30 mg/kg/day, with significant inhibition only in gestation day 22 male fetuses and in lactation day 2 male pups; the maximum response being a 29% inhibition among male fetuses on gestation day 22. At lactation day 8 and thereafter, no treatment difference in cholinesterase activity was detectable in pups. Pup RBC cholinesterase inhibition followed nearly an identical pattern. This was a satisfactory pilot study. Key NOEL's: 3 mg/kg/day for maternal clinical signs (staining around mouth), < 3 mg/kg/day for maternal RBC cholinesterase inhibition, 3 mg/kg/day for maternal brain cholinesterase inhibition, 10 mg/kg/day for pup body weight decrement, and also for fetal or pup brain and RBC cholinesterase inhibition. "Possible adverse effect" (brain cholinesterase inhibition). [REDACTED] June 4, 2004.

215-0196 210690 Moxon, M. E., "Naled: repeat dose cholinesterase inhibition study in pre-weaning and young adult rats," Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, 10/22/03. Laboratory Study #: CTL/KR1489/REG/REPT. Groups of 5 Alpk:AP₁SD rats/sex were dosed daily with Naled (purity 95.4%, in 10 ml/kg corn oil vehicle, formulations not adjusted for purity) for 7 days prior to sacrifice on day 7, one hour after dosing (timing expected to yield peak response). Pre-weaning rats were initiated on treatment at lactation day 12, whereas young adult rats were initiated on day 42. Dose levels were 0, 0.4, 2, 10, and 30 mg/kg/day, administered by gavage. There were several mortalities, but no clear relationship of deaths nor of clinical signs due to treatment. This study suggests cholinesterase inhibition NOEL's of 0.4 mg/kg/day and 2 mg/kg/day for brain in 18-day males and females, respectively; 2 mg/kg/day and [less than 0.4] mg/kg/day for RBC in 18-day males and females, respectively; 2 mg/kg/day for brain in either sex of day 48 young adult rats (based on consistent but non-statistically significant inhibition of 17% and 16% in males and females at 10 mg/kg/day, and on highly significant inhibition of 66% and 57% in males and females at 30 mg/kg/day), and 2 mg/kg/day for RBC in either sex at day 48, based on 40% and 31% inhibition at 10 mg/kg/day in males and females, respectively. Investigators placed the NOEL for day 18 rats at 2 mg/kg/day (based on brain and RBC inhibition), and for day 48 rats also at 2 mg/kg/day (based on RBC inhibition alone). Investigators did not consider the data to illustrate sex differences. There do not appear to be studies of similar design for comparisons. Small "N" values of 3 to 5 limit the statistical power of the study. Useful supplementary data, indicating a "possible adverse effect" (brain cholinesterase inhibition). [REDACTED] 5/14/04.

215-0199 210693 Twomey, K., “Naled: acute cholinesterase inhibition study in rats,” Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, 6/25/02. Laboratory Study #: CTWAR7139/REG/REPT. Groups of 15 Alpk:AP_rSD rats/sex were dosed once with Naled (purity 95.0%, in 10 ml/kg corn oil vehicle, formulations not adjusted for purity). Dose levels were 0, 5, 25, or 100 mg/kg, administered by gavage. Sets of 5 rats were killed for cholinesterase assays of red blood cells (RBC's) and of brain [each brain divided 5 ways as follows: cerebellum, cerebral cortex, hippocampus, “brain half” (defined as one cerebral hemisphere plus half of the cerebellum), and “remainder” (that which remains after the above samples have been taken)]. Sacrifices were either one hour after dosing (timing expected to yield peak response), or on day 8 or day 15. Generally, only the 100 mg/kg groups were processed for cholinesterase assays on days 8 and 15. There were no treatment-related changes in body weights, brain weights, or clinical signs. NOEL = 5 mg/kg, based on cholinesterase inhibition in RBC's (significant in both sexes), and on cholinesterase inhibition in cerebral cortex (significant in females, non-significantly reduced in males). Cholinesterase inhibition was highly significant for all brain samples and for RBC in both sexes on Day 1, with lesser inhibition at subsequent intervals (sometimes significant). Useful supplementary data. Brain cholinesterase inhibition is a “possible adverse effect”. [REDACTED], 5/14/04.

215-0198 210692 Twomey, K., “Naled: acute cholinesterase inhibition study in rats (1st Study),” Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, 5/30/02. Laboratory Study #: CTL/AR7080/SUM/REPT. Groups of 15 Sprague-Dawley rats/sex/group were dosed once by gavage (in 10 mg/kg corn oil) with 0, 5, 25, or 100 mg/kg/day Naled (purity not stated, but probably 95-96%, based on contemporary studies). Five/sex/group were sacrificed after 1, 8, or 15 days. Basic observations such as clinical signs and body weights were recorded, as well as cholinesterase assays of RBC's and cerebellum at respective sacrifices. Clinical signs were entirely limited to the first 24 hrs, hence “N = 15” for clinical observations. There were no premature deaths. Clinical signs NOEL = 5 mg/kg, based on 2 males with miosis, and 1 female “subdued” at 25 mg/kg (the latter not seen at 100 mg/kg, and thus possibly incidental). Signs at 100 mg/kg were “activity decreased” (9 M, 1 F), fasciculations (10 M, 6 F), lacrimation (3 M), miosis (6 M, 10 F), salivation (7 M, 2 F), splayed gait (6 M, 1 F), tremors (4 M, 9 F), plus occasional signs observed in males (“sides pinched in,” “reduced stability,” “tip toe gait,” and “upward curvature of the spine”). Body weights and brain weights were unaffected at any dose. Investigators considered the cholinesterase NOEL to be 5 mg/kg for both sexes, although there was a significantly decreased RBC cholinesterase activity in 5 mg/kg females on day 1. Individual data were not provided in this short report, and this reviewer does not have an adequate basis to support dismissal of the finding at 5 mg/kg as an incidental event. Thus the cholinesterase NOEL for RBC's is less than 5 mg/kg. Percentage reductions on day 1 for RBC's were 9% (NS) in M and 11% (marginally significant, $p < 0.05$) in F at 5 mg/kg, and significant ($p < 0.01$) at all higher dose levels, specifically 33% and 23% in 25 mg/kg M and F, and 39% for both M and F at 100 mg/kg. The NOEL for cerebellum cholinesterase was 5 mg/kg (M and F). Percentage reductions from control cholinesterase activities at day 1 for cerebellum were 36% and 31% for M and F at 25 mg/kg, and 47% and 52% for 100 mg/kg M and F. There was substantial recovery of cholinesterase activity in RBC's and especially in brain by day 8. Useful supplementary information. Brain cholinesterase inhibition is a “possible adverse effect.” [REDACTED], 5/19/04.

215-0197 210691 Moxon, M. E., “Naled: acute cholinesterase inhibition study in pre-weaning rats,” Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, 10/24/03. Laboratory Study #: CTL/AR7146/REG/REPT . Groups of 5 Alpk:AP_fSD pups/sex were dosed once with Naled (purity 95.4%, in 10 ml/kg corn oil vehicle, formulations not adjusted for purity). Dose levels were 0, 5, 25, or 100 mg/kg, administered by gavage. Ages at treatment were lactation days 8, 15, or 22. Pups were sacrificed 1 hr post-dosing for evaluation of brain and RBC cholinesterase. NOEL for clinical signs was 25 mg/kg (primarily based on tremors at 100 mg/kg in 2/10 on Day 8, in 6/10 on Day 15, and in 10/10 on Day 22, with no apparent sex difference). In addition, 2/5 males and 2/5 females of the high dose pups dosed on Day 8 died within one hour, and “decreased activity” was observed at 100 mg/kg in 3/10 pups on Day 15, and in 3/10 pups on Day 22. NOEL for brain cholinesterase = 5 mg/kg (statistically significant, dose-related reduction of activity at 25 to 100 mg/kg). RBC cholinesterase inhibition NOEL < 5 mg/kg (reduced RBC cholinesterase activity in both sexes at Day 15, and in females at Day 22). Useful supplementary data. Brain cholinesterase is a “possible adverse effect.” [REDACTED], 5/14/04.

215-0195 210689 Milburn, G. M., “Naled: time course of cholinesterase inhibition in pre-weaning and adult rats,” Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, 9/23/03. Laboratory Study #: CTL/AR7309/REG/REPT. Female pups (PND day 15) or young adults (PND 42) were dosed once by gavage (10 ml/kg corn oil vehicle) with 0 or 100 mg/kg Naled (95.4% purity). Groups of 5 were sacrificed after 1, 3, 8, 24, or 72 hr. Clinical signs were usually observed shortly after dosing, hence N = 25 for practical purposes. Most common signs were “activity decreased” (7 pups and 5 adults), “ataxia” (3 pups and 1 adult), and “tremors” (3 pups and 3 adults). Regardless of age, brain cholinesterase was reduced 60-70% between 1 and 8 hours after dosing, and 36-39% at 24 hours. At 72 hr after dosing, pup cholinesterase activity reduction was only 16% (not significant, and perhaps reflecting new tissue growth in addition to enzyme replacement), whereas adult brain cholinesterase activity was still reduced by 40% compared to controls. Also regardless of age, RBC cholinesterase was reduced 50-57% during hours 1 to 8 post-treatment, then 32-42% at 24 or 72 hours. This supplementary study was adequate for its intended purpose. Since only one dose was employed, which was a highly effective dose, no NOEL was sought nor found. Brain cholinesterase inhibition is a “possible adverse effect.” [REDACTED], June 4, 2004.

215-0200 210694 Twomey, K., “Naled: 90 day cholinesterase inhibition study in the rat with recovery groups,” Central Toxicology Laboratory, Alderley Park, Macclesfield, UK, Oct. 11, 2002. Laboratory Study #: CTL/PR1230/REG/REPT. Up to 5 Sprague-Dawley rats/sex/group/interval were dosed daily by gavage (10 mg/kg corn oil vehicle) at 0, 0.4, 2, or 10 mg/kg/day Naled (95.8% purity) for up to 13 weeks. Sacrifice intervals varied as needed, but generally included weeks 9, 14, and 18 (the latter providing the 4-week recovery period). There were no body weight, food consumption, brain weight, or clinical signs responses at any tested dose level. RBC cholinesterase NOEL = 0.4 mg/kg/day (clear dose-response at 2 to 10 mg/kg/day: activities at 10 mg/kg/day were 50% to 62% of control). Brain cholinesterase NOEL = 0.4 mg/kg/day (reduction of cholinesterase activity in female cerebellum at Week 9, and in male and female “brain remainder” at Week 9). Brain cholinesterase mean activities at 10 mg/kg/day during treatment averaged 65% of control levels in cerebellum, and less than 50% of control levels in hippocampus, cerebral cortex, and the remainder of the brain, without consistent sex differences. There was substantial or complete return of cholinesterase activity after 4 weeks

recovery in all tissues examined. Useful supplementary data. Brain cholinesterase inhibition indicates a "possible adverse effect." [REDACTED], June 4, 2004.

MISCELLANEOUS

090 no record #, "Three-Week Aerosol Inhalation Toxicology Study of Chevron Naled Technical (SX-1554) in Rats," (Chevron, 12/11/86, subchronic inhalation (824) rat). Naled technical, 90%, at 0, 3.4, 7.2 and 12.1 microgram/L to 10/sex/dose for 6 hours/day, 5 days/week for 3 weeks; nasal lesions occurred at 3.4, 7.2 and 12.1 µg/L; possible adverse effect: corneal and nasal lesions; supplemental data. ([REDACTED] and [REDACTED], 4/27/87).

133 131243 "Thirteen Week Aerosol Inhalation Toxicity Study of Chevron Naled Technical (SX-1665) in Rats," (Griffis, L., Chevron Environmental Health Center, Richmond, CA; SOCAL 2400, 8/26/86). F-344 rats (12/sex/dose) were exposed to Naled technical (92.1% pure; SX-1665), generated in aerosol, at 0, 0.2, 1.2 and 6.0 µg/L (6 h/day, 5d/week for 13 weeks). In addition, 10 rats/sex (control and 6.0 µg/L) were held for a 6 week recovery.

Dosing Material: Concentration of Naled and BDCA (hydrolysis product) in the chamber, MMAD and GSD of the aerosol were determined. Average Naled concentrations: 0, 0.23, 1.29 & 5.8 µg/L. Average BDCA concentrations: 0, 0.18, 0.31 and 0.93 µg/L. Average MMAD at 5.8 µg/L = 2.4 µm, at 1.29 & 0.23 µg/L < 0.7 µm (most of the Naled was in vapor).

Observations: Toxicity was determined by daily clinical observations, weekly body weights and food consumption, clinical pathologies (end of exposure) and cholinesterase determinations (at 2, 7 & 13 weeks--main group; 12, 15 & 19 weeks--recovery groups), gross necropsy examinations, organ weights and histopathological examinations. There were no treatment-related mortalities. Females at 6.0 µg/L had a significant increase in food consumption during the 2nd half of the study (no effects on body weight). Increased food consumption was sporadic and usually ≤ 10%.

Both sexes showed an increase in clinical signs of cholinesterase inhibition at 6.0 µg/L (salivation, nasal and anogenital discharge, abnormal respiratory sounds). Cholinesterase inhibition was as follows:

1. **Mean RBC ChE:** Significantly decreased in both sexes at ≥ 1.2 µg/L. It remained low in the recovery animals.
2. **Mean Plasma ChE:** Significantly decreased in both sexes at ≥ 1.2 µg/L. Male levels remained low throughout the 6 week recovery period, whereas female levels were reversed at 3 weeks recovery.
3. **Mean Brain ChE:** Significantly decreased at 6.0 µg/L in both sexes (some reversal by 6 weeks recovery but still a significant decrease).

Hematology: MCH were both significantly increased at ≥ 1.2 µg/L. Males showed an increased MCV at 6.0 µg/L and female MCV was increased at ≥ 6.0 µg/L. Females showed an increased A:G ratio at 6.0 µg/L.

Organ Weights: Absolute and relative kidney weights were increased in females at 6.0 µg/L.

Histopathology: Nasal pathology was observed in treated animals:

Effect Observed	Naled Concentration ($\mu\text{g/L}$)							
	Males				Females			
	0	0.2	1.2	6.0	0	0.2	1.2	6.0
<u>Level 1:</u>								
Epithelial Dysplasia	0	0	3	2	0	1	1	3
Epithelial Dystrophy	0	0	1	0	0	0	0	0
Suppurative Exudate	0	3	1	0	0	0	0	0
Epithelial Hyperplasia	0	0	0	1	0	0	0	0
Chronic Rhinitis	0	2	1	1	0	2	3	4
Chronic Inflammation	0	0	0	0	0	0	1	0
<u>Level 2:</u>								
Suppurative Exudate	0	1	0	0	0	0	0	0
Hemorrhage	0	1	0	0	0	0	1	1
Chronic Rhinitis	0	0	1	0	0	0	0	0
<u>Level 3:</u>								
Hemorrhage	0	2	1	0	1	1	2	1
<u>Level 4:</u>								
Hemorrhage	0	4	1	0	1	2	3	1

There were 12/sex/dose examined for histopathology. The report did not note that the nasal effects were treatment-related, however it appears that they occurred almost exclusively in treated animals.

Systemic NOEL < 0.2 $\mu\text{g/L}$ (Increased food consumption, increased MCH, MCV and A:G ratio, increased absolute and relative kidney weights. Possible adverse effect: There was an increase in nasal pathology at all doses and in both sexes of treated animals.) ChE NOEL = 0.2 $\mu\text{g/L}$ (RBC and plasma ChE were significantly decreased at ≥ 1.2 $\mu\text{g/L}$ and brain ChE was significantly decreased at 6.0 $\mu\text{g/L}$.) These data are supplemental. ■■■, 8/17/94.

** 188 177307 “Naled: 28 Day Dermal Toxicity Study in Rats,” (Moxon, M.E.; Central Toxicology Laboratory, AMVAC Chemical Corporation, Cheshire, UK; Study #: LR0584; Document #: CTL/LR-0584/REG/REPT; Report #: CTL/LR0584/Regulatory/Report; 8/23/00). Naled technical (95.84% pure) was dermally applied (occluded) to Crl:CD (SD) BR rats (10/sex/dose, main group; 5/sex/dose, satellite group) at 0 (dried corn oil), 5, 10 and 40 mg/kg/day (6 hours/day) during days 1-5, 8-12, 15-19, 22-24 and 26-28 of the study (21 days total). The satellite group was used to assess brain, erythrocyte and plasma cholinesterase activity. Systemic NOEL = 10 mg/kg (There was a statistically significant decrease in hindlimb grip strength in males at 40 mg/kg. There was a statistically

significant decrease in platelet counts for both sexes at 40 mg/kg. Females showed statistically significant increases in white blood cell, lymphocyte, monocyte and large unstained cell counts at 40 mg/kg. Females, at 40 mg/kg, showed statistically significantly increased plasma calcium, plasma chloride, potassium and APT activity. In males at 40 mg/kg, absolute epididymal weights were significantly decreased. Male relative kidney weights at 40 mg/kg were significantly increased.) Dermal NOEL = 5 mg/kg (Acanthosis and hyperkeratosis were observed in both sexes at ≥ 10 mg/kg by the end of the study. Macroscopically, discoloration and erythema were observed in the area of treated skin at ≥ 10 mg/kg, respectively.) ChE NOEL = 10 mg/kg (There were significant decreases in RBC, plasma and brain ChE in both sexes at 40 mg/kg.) The study is acceptable (no adverse effects). ■■■■, 10/2/00.