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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 19 1987

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Naled - Review of 90-Day Inhalation
Data, Submitted under Accession No.'s
265678, 265679 and 265680.

TB Project 7-0223

EPA ID # 239-1633

Caswell 586

TO: William H. Miller/Gary Otakis, PM 16
Registration Division (TS-767c)

FROM: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Judy W. Hauswirth, Ph.D., Acting Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Registrant: Chevron Chemical

Action Requested: Review and evaluate the following study,
submitted under cover letter of October 16, 1986, in response
to the Naled Registration Standard (issued June 30, 1983):

Thirteen- Week Aerosol Inhalation Toxicology Study of
Chevron Naled Technical (SX-1655) in Rats. SOCAL 2400.
(Chevron Project No. 2438, conducted at Chevron's Environ-
mental Health Center; dated August 26, 1986).

TB Conclusions: CORE- MINIMUM

ChEI NOEL = 0.23 $\mu\text{g}/\text{L}$

ChEI LOEL = 1.29 $\mu\text{g}/\text{L}$ (RBC in females; plasma
in both sexes)

Systemic NOEL = 1.29 $\mu\text{g}/\text{L}$

Systemic LOEL = 5.8 $\mu\text{g}/\text{L}$ (clinical signs of
ChE inhibition)

The TOXICOLOGY BRANCH DATA REVIEW is attached.

Attachment (1)

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TOXICOLOGY BRANCH DATA REVIEW

Reviewed by: Irving Mauer, Ph.D. *[Signature]* TB Project: 7-0228
Toxicology Branch
Hazard Evaluation Division Date: 03-13-87

Through: Judith W. Hauswirth, Ph.D., Acting Head
Section VI, Toxicology Branch *[Signature]*
Hazard Evaluation Division 7/10/87

Chemical: NALED

Caswell: 586
EPA Chem: 034401

Study Type: Subchronic (90-day) Inhalation - Rat

Citation: Thirteen-Week Aerosol Inhalation Toxicology Study
of Chevron Naled Technical (SX-1655) in Rats. SOCAL
2400.

Accession Nos.: 265678/265679/265680

MRID: N/A

Sponsor: Chevron Chemical

Testing Lab.: Chevron Environmental Health Center

Study No.: SOCAL 2400 (S-2438)

Study Date: August 26, 1986

Test Material: Naled Technical (92.13 ai), a clear straw-colored
liquid.

Procedures:

A copy of the Materials and Methods (pp. 3 to 12, Vol. I of the Final Report) is attached to this review as Appendix A; no significant deviations from FIFRA Testing Guideline No. 158.135.82-4 were found. [A QA/GLP statement recording periodic inspections of animals and raw clinical data was included in the Final Report.]

Briefly, groups (12/sex) of young (46-day-old) adult male, (weighing 123 to 150 g) and female (97 to 114 g) Fischer-344 rats were exposed in 1 m³ chambers 6 hours/day, 5 days/week for 13 weeks to filtered air (control group) or aerosols of test material at nominal concentrations of 0.2, 1.2, and 6.0 ug/L. Additional groups of control and high-dose animals (10 per sex) were allowed to recover for a 6-week nontreatment period ("satellite" groups).

A full roster of observations and determinations was recorded for all groups, which included necropsy examinations, organ weights, and histopathology.

Results:

The report states that initial target concentrations selected for this study were 0.5, 2.0, and 8 $\mu\text{g/L}$. On study day 16 (after the 13th exposure), however, these targets were changed to 0.2, 1.2, and 6 $\mu\text{g/L}$, based upon the results of cholinesterase assays (see below).

During the period of exposure, daily monitoring of chamber environments (supply and exhaust air flow, static pressure, temperature and relative humidity [RH]) revealed relatively constant chamber conditions throughout the 90 days; overall average temperatures ranged from 21.9 to 23.8 $^{\circ}\text{C}$, RH's from 51 to 60%, and exhaust flows from 318 to 328 L/min. Routine sampling of chamber atmospheres disclosed the following overall average concentrations of naled, bromodichloroacetaldehyde (BDCA, a hydrolysis product), and dichlorvos (DDVP, a minor constituent of the technical):

Nominal Conc. ($\mu\text{g/L}$)	Naled ($\mu\text{g/L}$) \pm SD	BDCA ($\mu\text{g/L}$) \pm SD	DDVP ($\mu\text{g/L}$) \pm SD
0.2	0.23 \pm 0.12	0.18 \pm 0.04	0.01 \pm 0.01
1.2	1.29 \pm 0.48	0.31 \pm 0.08	0.05 \pm 0.02
6.0	5.80 \pm 1.2	0.93 \pm 0.22	0.09 \pm 0.07

As found in the analytical report, included as an addendum and discussed by the study investigators, the greater ratios of BDCA and DDVP to naled at lower naled concentrations were probably due to higher volatility at these levels, resulting in proportionately greater interaction with water vapor generating the hydrolysis product, as well as preferential vaporization of dichlorvos during aerosol generation (because of its higher volatility relative to naled). This explanation is supported by the particle size distribution results which indicate that, although respirable at all three exposure levels, the size distribution was much smaller at the lower concentrations; MMAD mean and range were 2.4/1.8-3.0 μm with a GSD of 2.4 μm at the high-dose, but ranged from 1.0 to 1.5 μm to less than the cut-off, 0.7 μm , at the mid-dose, and was consistently $< 0.7 \mu\text{m}$ at the low-dose. Thus, rough estimates of the proportion of naled per se actually present in the three exposure chambers as aerosol varied from approximately 20% at the low-concentration, to 30% at the mid-concentration, and 60% at the highest-concentration.

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Two animals died during this study, neither in the opinion of the investigators due to compound-related effects. A low-dose female died during orbital bleeding procedures one day prior to scheduled sacrifice on study day 91, probably from "excessive ether anesthesia"; a satellite control female was killed 3 weeks prior to her scheduled sacrifice because of severe ocular inflammation caused by orbital bleeding a week prior.

Clinical signs of cholinesterase inhibition (tremors, salivation, nasal discharge, abnormal respiration, and anogenital staining) were increased in incidence and severity only in high-dose animals (Table 1). Although also increased at lower dosages during the treatment period, they were of mild to low severity. These signs of toxicity were only occasionally observed in high-dose satellite animals during the 6 weeks without treatment, and apparently disappeared by the end of the recovery period.

TABLE 1

Summary of Selected (Naled Exposure-Related) Clinical Observations
(Percent Animals Affected)*

Observation	Sex:	Dose Group (ug/L)							
		0		0.2		1.2		6.0	
	No. Animals Examined:	M	F	M	F	M	F	M	F
		22	22	12	12	12	12	22	22
Tremors		0	0	0	0	0	0	9	13
Salivation		4	0	41	8	41	33	100	86
Nasal discharge		13	13	58	33	33	8	100	100
Abnormal respiration		0	0	16	0	16	0	86	72
Anogenital staining**		-	0	-	8	-	8	-	40

*Extracted from Appendices C and D of the Final Report.

**No observations recorded for males.

A high incidence of eye defects (including corneal opacities, discharge, swelling, exophthalmia and gross damage) was observed in all groups, ascribed by the authors as traumatic injuries resulting from orbital bleeding procedures (and confirmed histologically). Ophthalmological examination at the end of the 13-week exposure period did not reveal any difference between control and treated groups.

Weekly mean body weights of naled exposed animals were not significantly different from controls at any time point except for study day 42, when an average decrease of 15 grams ($p < 0.05$) was recorded for high-dose males. Thereafter, consistent but statistically insignificant decreases (ranging from 9 to 13 grams) were recorded for this group to the end of the exposure period. Mean food consumption values were comparable for all male groups throughout the study, but consistently significant increases in food intakes by high-dose females for 6 of the last 7 weeks of exposure were recorded. Although the authors suggest this correlated with slightly greater increases in mean body weights for this group compared to controls, this is not reflected in their summary tabulation (Report Table 8).

Determinations of circulating cholinesterase activities in plasma and erythrocytes revealed significant inhibition in mid and high-dose naled exposed males and/or females, with erythrocyte values being the more severely affected during the 13 weeks of exposure (Table 2). Tissue values (measured in brain) were depressed only in high-dose groups.

Dose-related depression of RBC values was noted early (as measured on study days 15 and 49) for both sexes, with the greatest inhibition of specific activity observed in high-dose animals (7 to 10% of controls) after 7 weeks (Report Table 10). During the early treatment period, inhibition approached 40 to 50 percent in mid-dose males (1.2 ug/L), and was recorded as statistically significant ($p < 0.05$). At the end of the exposure period, however, inhibition was significant only at the highest dose (15 to 30% of controls), but only marginal (70-75%) in mid-dose females; mid-dose male values were at control levels. Two weeks after the end of exposures, high-dose satellite group values had returned to 60 to 68% of controls, and by 6 weeks post-treatment were slightly above control values.

Less severe (and less variable) inhibition was recorded for plasma cholinesterase activity throughout the exposure period, but persisted to the end of treatment in both sexes exposed to 1.2 ug/L naled (approximately 70-80% of controls), and was 40 to 50% less than controls in high-dose animals. Complete recovery to control values occurred within 3 weeks following cessation of

TABLE 2

Representative Values for Cholinesterase Inhibition
(as Percent of Control) by Inhalation Exposure to Naled Aerosol¹

Compartment (Tissue) Sampled	Type of Activity ²	Main Dose Groups (ug/L) (After 13 weeks exposure/6 animals/group)						Satellite (6.0 ug/L) Group Recovery After (Weeks)			
		0.2		1.2		6.0		2-3		6	
		M	F	M	F	M	F	M	F	M	F
Erythrocyte (RBC)	Whole	113.1	112.2	106.0	75.4	**	**	**	**	114.0	117.6
	Specific	102.4	106.4	101.7	68.4	**	**	**	**	112.9	117.4
Plasma	Whole	99.5	102.7	74.4	84.4	**	**	*	*	79.0	105.2
	Specific	97.2	103.1	71.6	89.3	**	**	80.9	100.0	75.1	103.9
Brain	Whole	103.6	105.7	100.3	96.5	**	**	--	--	93.4	94.8
	Specific	105.2	110.1	101.0	95.9	**	**	--	--	94.4	91.1

¹Extracted from Tables 10, 12, and 14 of the Final Report.

²Whole: Activity determined in IU/unit tissue (mL blood or plasma; g brain).

Specific: Activity determined in IU x 10⁻³/mg total protein.

*Significantly different from control (p < 0.05).

**Significantly different from control (p < 0.01).

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naled exposure in high-dose satellite females, but significant depression of plasma values (75-80% of controls) persisted in males even after 6 weeks posttreatment.

After 13 weeks exposure to naled, brain cholinesterase was significantly depressed only in high-dose animals (approximately 55-60% of controls), and recovery was "essentially complete" (91 to 95%) by 6 weeks in satellite animals exposed only to 6.0 ug/L naled.

Although slight but statistically significant changes were recorded in some hematological parameters for both sexes during the 13 weeks exposure to naled (e.g., red blood cell values for mean cell volume and mean cell hemoglobin), these were within normal limits, and thus not considered exposure related (Report Table 16). Erythrocyte counts and hematocrits were not different from controls in any test group. Similarly, the few sporadic increases in serum chemistry values as recorded in Table 17 of the Report (serum albumin in low- and mid-dose but not high-dose males; albumin/globulin ratio in high-dose males only) are not considered toxicologically significant.

Except for numerous gross abnormalities around the eyes, lacrimal glands and surrounding skull musculature distributed equally in all groups, no treatment-related pathologic changes were recorded in main study or satellite animals (Appendix N of the Report). Microscopic examination confirmed that the ocular lesions were a result of trauma induced by frequent orbital bleeding procedures. No other lesions referable to naled exposure were described (Appendix N).

Organ weight data, as summarized in Report Table 18 (from individual values in Appendix O), revealed only two statistically significant differences from controls in treated (main study) animals: slightly greater left testis/body weight ratio in high-dose males; greater mean relative weight for both kidneys in low- and high-dose, but not mid-dose females. No differences from control organ weight values were recorded in high-dose satellite animals.

Report Conclusions:

The investigators concluded that treatment-related effects of 13 weeks exposure to naled aerosols were attributable to cholinesterase inhibition, especially evident at the highest exposure concentration (nominally 6.0 ug/L, but analyzed as 5.8 ug/L), and resulting in clinical signs of toxicity and severe inhibition of cholinesterase activities in both circulating and tissue-bound enzymes. Marginal effects on cholinesterase activities (and no clinical signs) were found at the next lowest

exposure (1.2 $\mu\text{g/L}$, analyzed as 1.29 $\mu\text{g/L}$), while the lowest exposure (0.2 $\mu\text{g/L}$, analyzed as 0.23 $\mu\text{g/L}$) was a no-effect level. Except for minor inhibition of plasma cholinesterase in high-dose males, no other exposure-related effects were found in satellite animals examined 6 weeks after exposure.

Minimum. Except for a few minor reporting deficiencies, apparently not affecting the conduct or results of this subchronic study, TB agrees with the study authors' conclusions, and ascribes the following effect levels by aerosol exposure of rats to naled technical:

Attachment

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APPENDIX A

Naled toxicology review

Page _____ is not included in this copy.

Pages 10 through 19 are not included in this copy.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients
 - ☐ Identity of product impurities
 - ☐ Description of the product manufacturing process
 - ☐ Description of product quality control procedures
 - ☐ Identity of the source of product ingredients
 - ☐ Sales or other commercial/financial information
 - ☐ A draft product label
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 - ☐ Information about a pending registration action
 - ☒ FIFRA registration data
 - ☐ The document is a duplicate of page(s) _____
 - ☐ The document is not responsive to the request
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