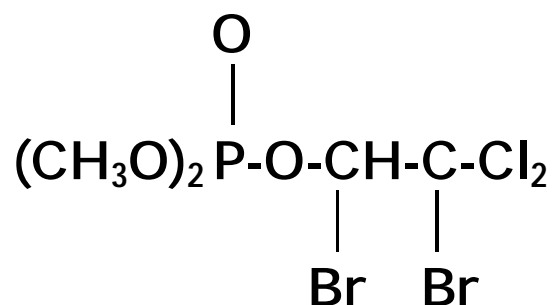


NALED

RISK CHARACTERIZATION DOCUMENT



 **California Environmental Protection Agency**
Department of Pesticide Regulation

November 1999

RCD 99-03

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION**

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RISK CHARACTERIZATION DOCUMENT

Volume I

**Health Assessment Section
Medical Toxicology Branch
Department of Pesticide Regulation
California Environmental Protection Agency**

November 11, 1999

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I. SUMMARY

This document (Volume I) contains the human health risk assessment for naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and its metabolite, dichlorvos (DDVP). The determination of occupational and residential exposures to naled is discussed in Volume II conducted by the Worker Health and Safety Branch.

I.A. INTRODUCTION

Naled is an organophosphate insecticide that controls pests on raw agricultural commodities, in space treatment, on farm animals premises, on pets, and on ornamentals.

Tolerances have been established for its use on food crops, feeds, and around livestock. As of 1999, 15 products are registered in California for agricultural and non-agricultural uses. From 1991 to 1997, the use of naled increased from 175,000 pounds to more than 600,000 pounds primarily due to increased use of naled on cotton. Human illnesses from naled exposure were due to accidental exposure from spills, contact with residues, and spray drift.

Naled readily degraded in water, under sunlight, in soil under aerobic and anaerobic conditions, in the air, and on plants. Under some environmental conditions, naled may be completely degraded to carbon dioxide. Photolysis of naled occurred in the presence of photosensitizers. Naled was more mobile in soil of low organic content such as sandy loam when compared with other soil types. On plant surfaces, naled was degraded to DDVP. Processing (rinsing, cooking, trimming, and storage) decreased both naled and DDVP residues.

I.B. TOXICOLOGY PROFILE

Pharmacokinetics- Naled was rapidly absorbed by all routes (oral, inhalation, and intraperitoneal) and was distributed to all tissues in the rat, chicken, goat, and cow. In all the species (rat, chicken, goat) studied, the proposed metabolic pathways are similar. Naled was initially metabolized to DDVP which in turn was metabolized to desmethyl DDVP and dichloroacetaldehyde. Subsequent reactions resulted in the incorporation of a carbon into peptides, and the formation of conjugates, urea, and hippuric acid. Metabolites were excreted primarily in the urine, with a moderate amount in the expired air as carbon dioxide. In naled treated hens, goats, and cows, naled metabolites were detected in eggs and goat milk, but not in cow milk. In the rat, the amounts (about 100%) of naled absorbed and distributed to the body compartments (tissues, urine, and expired carbon dioxide) were similar regardless of the routes of exposure (whole body inhalation, head only inhalation, oral, and intraperitoneal).

Acute Toxicity- Cholinergic signs (such as salivation, tremors, convulsions) were observed in experimental animals given naled by the oral, dermal, and inhalation routes. Atropine and 2-PAM decreased the lethality and delayed the onset of signs.

Subchronic Toxicity- Naled inhibited the plasma, erythrocyte, and brain cholinesterase (ChE) activities in rats and dogs after subchronic exposure by the oral, dermal, and inhalation routes. Cholinergic signs (including tremors, salivation, and death) were observed in the oral and inhalation studies. Naled caused skin inflammation and necrosis in rats from dermal exposure.

Chronic Toxicity- Naled caused inhibition of plasma, erythrocyte, and brain ChE activities in rats and dogs. Chronic exposure to naled resulted in mild testicular degeneration, focal mineralization of the spinal cord, and mild splenic siderosis in dogs. At sublethal doses, naled caused decreased body weight gain in mice. Naled was not considered oncogenic in rodents or dogs.

Genotoxicity- Naled was not genotoxic in *in vitro* and *in vivo* genotoxicity studies.

Reproductive Toxicity- In a two-generation rat reproductive toxicity study with naled, the only significant parental effect was a dose-related decrease in body weights of all F₁ males during both pre- and post-mating periods. The effects on the pups included decreased survival, body weight, and number of pups at birth.

Developmental Toxicity- Pregnant rats and rabbits showed cholinergic signs after oral exposure to naled. In the presence of maternal toxicity, the only developmental effect was decreased fetal body weight.

Neurotoxicity- Naled caused acute neurotoxicity in rats as determined by a Functional Observation Battery and motor activity evaluations. In hens, there was significant inhibition of brain ChE activity and axonal degeneration of the spinal cord, but no delayed neurotoxicity.

I.C. RISK ASSESSMENT

Hazard Identification- For acute exposure, the estimated No-Observed-Effect Level (NOEL) was 2.5 mg/kg/day for neurotoxicity observed in Functional Observation Battery testing at 25 mg/kg/day. For subchronic exposure, the critical NOEL was 1 mg/kg/day for brain ChE as well as plasma and erythrocyte ChE inhibition in the rat after dermal exposure (Rausina and Zimmerman, 1986). For chronic exposure, the critical NOEL was 0.2 mg/kg/day for brain cholinesterase inhibition in both rats and dogs, and lesions observed in dogs. Naled was neither genotoxic nor oncogenic.

Exposure Assessment- Occupational exposure to naled was estimated for workers in agricultural and non-agricultural settings. For field workers, exposure to DDVP as a metabolite of naled was also determined.

For occupational exposure, the backpack applicator had the highest exposure; the ADD, SADD, and AADD were 1290.4 $\mu\text{g/kg/day}$, 737.3 $\mu\text{g/kg/day}$, and 141.4 $\mu\text{g/kg/day}$, respectively. For field workers, the ADD ranged from 0.9 $\mu\text{g/kg/day}$ for the grape harvester to 320.1 $\mu\text{g/kg/day}$ for the greenhouse harvester. The SADD ranged from 0.39 $\mu\text{g/kg/day}$ to 137.6 $\mu\text{g/kg/day}$ for these workers. The AADD ranged from 0.15 $\mu\text{g/kg/day}$ for the cotton scout to 65.8 $\mu\text{g/kg/day}$ for the greenhouse harvester. For seasonal dermal exposure, the unabsorbed dose was two-times that for the SADD of each exposure scenario.

For the general population, exposure to naled used in the home as well as when near treatment sites was estimated. Homeowners may be exposed to naled from the use of pet collars, hand-wand or backpack sprayer containing naled. The highest residential exposure to naled was for collar users; the ADD and AADD were 317.5 $\mu\text{g/kg/day}$ and 1.74 $\mu\text{g/kg/day}$,

respectively. Other home uses (hand wand and backpack sprayer) resulted in lower exposures. For the exposures to ambient air concentration of naled, the calculated ADD for naled were 0.01 $\mu\text{g/kg/day}$ and 0.03 $\mu\text{g/kg/day}$, for adult and children, respectively. The ADD for DDVP were 0.007 $\mu\text{g/kg/day}$ and 0.02 $\mu\text{g/kg/day}$ for adults and children, respectively.

The dietary exposure estimates were based on naled residues as well as DDVP residues, from the degradation of naled. They were calculated by a toxicity equivalency factor approach with equivalency factors of 5 and 4 for acute and chronic exposures, respectively. The acute 95th percentile of exposure ranged from 1.069 $\mu\text{g/kg/day}$ (seniors 55+ years old) to 2.635 $\mu\text{g/kg/day}$ (children 1-6 years old). The annualized average chronic exposure ranged from 0.027 $\mu\text{g/kg/day}$ (nursing infants < 1 year old) to 0.251 $\mu\text{g/kg/day}$ (children 1-6 years old).

For combined exposure, the dietary exposure was added to either the occupational or residential exposures. The total exposure was essentially those for the non-dietary exposures.

I.D. RISK CHARACTERIZATION AND RISK APPRAISAL

The critical NOELs for risk characterization were derived from experimental animal studies because of a lack of toxicology and pharmacokinetic data for humans. Risks were calculated as the margin of exposure, a quotient of the NOEL and exposure level. A MOE of at least 100 is generally considered to be health protective when the NOEL is derived from experimental animal studies.

Only the MOEs of grape harvesters were above the benchmark for all exposure durations. For other workers, the MOEs were less than 100 for most exposure scenarios.

The MOEs for ambient air exposures by adults and children to naled or DDVP were $\geq 16,250$. The MOEs for bystanders and residents near naled treatment sites were greater than 100. While the MOEs for homeowner use of low pressure hand wand were greater than 100, those exposed to naled from flea collars or backpack sprayers had MOEs of less than 100 only for acute exposure.

The MOEs for acute and chronic dietary exposures to naled and DDVP were ≥ 800 for all population subgroups. The lifetime risks for dietary exposure to DDVP were 6.9×10^{-7} and 1.2×10^{-6} for q1 and q1*, respectively. The combined acute and chronic MOEs were similar in magnitude as those for non-dietary exposure alone.

There were uncertainties in the assumptions used in the determination of the estimated NOEL for acute exposure; worker, residential, and dietary levels; as well as interspecies and intraspecies extrapolation of the data.

The risks were also evaluated under the mandates in the Food Quality Protection Act of 1996. An additional uncertainty factor was considered not necessary since there was no evidence of increased pre-and post-natal sensitivity to developmental or reproductive toxicity. Aggregate exposure was evaluated as combined dietary and occupational or residential exposure. While there is a potential for cumulative toxicity between naled and other organophosphates, the methodology for such determination is currently being developed. There is no known naled-induced endocrine disruption effect.

I.E. TOLERANCE ASSESSMENT

The MOEs for residues at tolerances were greater than the benchmark except for 3 commodities: orange (infants and children 1-6 years), grapefruit (Non-Hispanic blacks, and children 7-12 years), and spinach (children 1-6 years).

I.F. CONCLUSIONS

The risk of potential exposure to naled was evaluated for occupational, residential, dietary, and combined uses. It was based on toxicity observed in experimental animal studies and was expressed as the margin of exposure. The benchmark MOE traditionally considered as adequate for the protection of human health is a MOE of 100 when based on no-effect levels from experimental animal toxicity studies. It is essential that the significance of the MOEs be viewed in the context of the limitations and uncertainties discussed.

Based on the currently available toxicity and exposure information, DPR concluded that the MOEs for skin effects for all workers from seasonal exposure were less than the benchmark. For systemic effects, scenarios and workers or residents with MOEs of less than the benchmark were:

- (1) acute exposure only: homeowners using flea collars or backpack sprayers;
- (2) seasonal exposure only: aerial spray applicators and groundboom applicators; grape girdler/thinners, cotton scouts, hand-wand sprayer workers; aerial mosquito control workers;
- (3) acute and seasonal exposures: aerial spray and groundboom mixer/loaders, aerial spray flaggers, airblast and backpack applicators, veterinarians, backpack sprayer (non-agricultural use), and sewage system injection workers;
- (4) seasonal and chronic exposures: vegetable crop harvesters; and
- (5) acute, seasonal, and chronic exposures: greenhouse harvesters.

For dietary exposure, the MOEs for acute and chronic dietary exposures to naled and DDVP residues were greater than the benchmark of 100. The oncogenic risk for lifetime exposure to DDVP derived from naled and direct DDVP uses was $\leq 1.2 \times 10^{-6}$. In combined exposures, MOEs were essentially those from non-dietary routes since the dietary exposure was relatively low and had minimal impact on the total combined exposure.

The MOEs for residues at tolerances were greater than the benchmark for most commodities with the exceptions of oranges (infants and children 1-6 years), grapefruit (Non-Hispanic blacks, and children 7-12 years), and spinach (children 1-6 years).

II. INTRODUCTION

The human health risk assessment for naled was conducted because of possible adverse effects identified in chronic, oncogenicity, and reproductive studies. Naled is a high priority active ingredient under The Birth Defect Prevention Act of 1984 (SB 950) and is a candidate for evaluation under The Toxic Air Contaminant Identification and Control Act of 1983 (AB1807). In Volume I, the environmental fate, toxicology profile, dietary exposure, and risk assessment of naled are discussed. The potential risk of human exposure to DDVP, an active metabolite of naled, is also addressed. Dichlorvos (DDVP) is listed under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the State of California to cause cancer. A risk characterization document of DDVP as the active ingredient has been completed (Lim *et al.*, 1996; Lim, 1997 and 1998) and a summary of the document is provided in Appendix A. Worker and residential exposure to naled are presented in Volume II.

II.A. CHEMICAL IDENTIFICATION

Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) is a non-systemic organophosphate insecticide with both agricultural and non-agricultural uses. A list of the U.S. Environmental Protection Agency (U.S. EPA) established tolerances for its use on fruits and vegetables is in Appendix B. Non-agricultural uses include the following sites: aquatic area (e.g., marina, swamp), greenhouse (ornamental), forest, dwelling (e.g., hotel, patio), indoor environment (e.g., animal building, hospital, factory, feedlot, restaurant, warehouse), and home.

The primary biological activity of naled is the inhibition of cholinesterase (ChE). Since naled is rapidly degraded to DDVP under biological and environmental conditions (**II.G. ENVIRONMENTAL FATE**), DDVP is likely the active metabolite involved in cholinesterase inhibition. Cholinesterases consist of a family of enzymes found throughout the body that hydrolyze choline esters. In the nervous system, acetylcholinesterase (AChE) is involved in the termination of impulses across nerve synapses including neuromuscular junctions by rapidly hydrolyzing the neural transmitter, acetylcholine. Inhibition of AChE leads to accumulation of acetylcholine in the synaptic cleft which results in the overstimulation of the nerves followed by depression or paralysis of the cholinergic nerves throughout the central and peripheral nervous system. AChE is highly selective, although not exclusively, for acetyl esters as substrates (Brimijoin, 1992). Another form of cholinesterase, butyrylcholinesterase (BuChE), preferentially hydrolyzes butyryl and propionyl esters, depending on the species; however, it will hydrolyze a wider range of esters, including acetylcholine (Brimijoin, 1992). Unlike AChE, the physiological function of BuChE is not known. Although AChE and BuChE are found in most tissues, the ratio varies from one tissue to another and from one species to another. In rats, AChE is the predominant form of ChE in the central nervous system and in the neuromuscular junctions of peripheral tissues such as the diaphragm, skeletal muscle, heart, and spleen (Gupta *et al.*, 1991; Mendoza, 1976). AChE and BuChE are present in roughly equal proportions in the liver and kidney. Non-synaptic AChE is also present to a lesser extent in peripheral tissues, however, its function is not known (Brimijoin, 1992). Non-synaptic AChE is essentially the only ChE present in erythrocytes of higher animals. BuChE is the predominant form of ChE in the plasma of human, however, the ratio of AChE to BuChE varies greatly from species to species.

and between sexes. For example, the AChE:BuChE ratio in human plasma is approximately 1:1000, but closer to 1:2 in female rats and 3:1 in male rats.

In acutely toxic episodes, muscarinic and nicotinic receptors are stimulated by acetylcholine with characteristic signs and symptoms in the peripheral and central nervous systems (Murphy, 1986). Peripheral muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Peripheral nicotinic effects include muscle weakness, cramps, twitching, and general fasciculation. Stimulation of muscarinic and nicotinic receptors in the central nervous system can cause headache, restlessness, insomnia, anxiety, slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers, and coma. Death is usually due to respiratory failure from peripheral and central effects.

The effect of naled on the brain has been hypothesized to involve primarily cholinergic mechanisms (Soininen *et al.*, 1990). At doses which caused brain ChE inhibition, naled, DDVP, and metrifonate did not affect the brain monoamines. In comparison, physostigmine and tetrahydroaminoacridine altered the rat forebrain monoamines and metabolite levels.

II.B. REGULATORY HISTORY

Naled was introduced in 1956 by Chevron Chemical Company (Gallo and Lawryk, 1991). Amvac Chemical Company is the current registrant for technical naled in the U.S.

The U.S. EPA determined that naled did not meet or exceed the Special Review risk criteria. The chronic reference dose (RfD) is 0.002 mg/kg/day based on a No-Observed-Effect Level (NOEL) of 0.2 mg/kg/day for brain ChE inhibition in rats from a 2-year chronic dietary study (U.S. EPA, 1992; Batham *et al.*, 1984). The Permissible Exposure Limit (PEL) of naled in the work place is 3 mg/m³ (0.19 ppm) at 25°C and 760 mm Hg (California Code of Regulations, 1991). In January 1989, DDVP was listed under Proposition 65 as a chemical known to the state to cause cancer.

Recently, U.S. EPA revoked the tolerances for naled on mushroom and rice as part of the reregistration program to revoke tolerances no longer necessary to cover residues of the relevant pesticides (U.S. EPA, 1998).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

In 1999, 15 products were registered in California. The products included flea collars for cats and dogs as well as ready-to-use solution and emulsifiable concentrates for agricultural and non-agricultural uses. The percentages of naled in the formulations are: 7-15% for flea collars, 58-62% for use on fruits and vegetables, and 1 (ready-to-use) -87.4% for all other uses.

II.D. USAGE

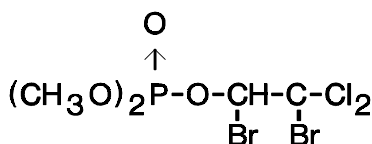
From 1991 to 1993, about 170,000 pounds of naled were used in California. However, the use has increased to more than 600,000 pounds from 1995 to 1997 because of increased use on cotton (DPR, 1991-1999). In 1997, the use on cotton was 70% of the total use, and 1-5% in each of the following uses: almond, broccoli, cauliflower, grape, orange, safflower, strawberry, and sugar beets. Other uses accounted for less than 1%.

II.E. ILLNESS REPORTS

From 1982 to 1996, 145 illness cases associated with naled, alone or with other pesticides, were reported in California (discussed in **Volume II. VII. WORKER ILLNESSES AND INJURIES**). The majority of the cases were due to contacts from accidental spills, treated foliage, and spray drifts resulting in eye and skin irritations. Naled may be a skin sensitizer and caused dermatitis in some workers (Edmundson and Davies, 1967; Mick *et al.*, 1970).

II.F. PHYSICAL AND CHEMICAL PROPERTIES^a

Chemical name:	1,2-dibromo-2,2-dichloroethyl dimethyl phosphate, an organophosphate
CAS Registry number:	300-76-5
Common name:	naled
Trade names:	Bansect, Clean Crop, Dibrom, Hopkins, Legion, Sergeant's, Trumpet, Valent.
Molecular formula:	C ₄ H ₇ Br ₂ Cl ₂ O ₄ P
Molecular weight:	380.79 g/mole
Chemical structure:	



Physical appearance:	yellow liquid with a pungent odor
Solubility:	0.2 g/100 ml water at 22°C (completely hydrolyzed in water within 48 hours). Freely soluble in aromatic and chlorinated hydrocarbons, ketones, alcohols. Solubility in heptane is 8.2 g/100 ml at 20°C. Sparingly soluble in petroleum solvents and mineral oils.
Boiling point:	110°C at 0.5 mm Hg
Melting point:	26.5-27.5°C
Vapor pressure:	2 x 10 ⁻³ mm Hg at 20°C
Octanol-water coefficient:	log P= 2.18 for naled at 500 ppm
Henry's Law constant:	5.014 x 10 ⁻⁸ atm m ³ g.mol ⁻¹
Specific gravity	1.9711

^{a/} Farm Chemicals Handbook, 1992; Merck Index, 1989; Chevron Chemical Company, 1980; Chevron Chemical Company, 1983a; Chevron Chemical Company, 1983b; Chevron Chemical Company, 1983c; Chevron Chemical Company, 1983d; Chevron Chemical Company, 1983e; Chevron Chemical Company, 1983f; Thornberry, 1987.

II.G. ENVIRONMENTAL FATE

Summary: Naled readily degraded in water, under sunlight, in soil under aerobic and anaerobic conditions, in the air, and on plants. Depending on the environmental conditions, naled may be completely degraded to carbon dioxide. Photolysis of naled occurred in the presence of photosensitizers. Naled was more mobile in soil of low organic content such as sandy loam when compared with other soil types. On plant surfaces, naled was degraded to DDVP. Processing (rinsing, cooking, trimming, and storage) decreased both naled and DDVP residues.

II.G.1. Hydrolysis

The hydrolysis of naled (ethyl-1-¹⁴C) in sterilized buffer solutions followed first-order kinetics and the half-lives were 96 hours, 15.4-17 hours, and 1.6-1.7 hours for pH 5, 7, and 9 buffers, respectively (Fujie, 1984a; Chen, 1986a). The major metabolites were bromodichloroacetaldehyde (BDCA) and 1,2-dibromo-2,2-dichloroethyl methyl phosphate (desmethyl naled).

II.G.2. Photolysis or Photodegradation

Naled (ethyl-2-¹⁴C) was degraded on dried cotton leaves under natural sunlight (Chen, 1987). The estimated half-life of naled photolysis was less than 5 days. DDVP was the only product detected after 0.5 to 4 hours of exposure. Dichloroacetic acid (DCAA) and dichloroethanol (DCE) were not detected. Naled was not degraded in samples stored in the dark.

Under natural sunlight, naled (1-ethyl-¹⁴C) in water hydrolyzed with a half-life of 4.4 days (Chen, 1989). Photolysis occurred only when acetone, a photosensitizer, was added and the effective half-life was 1.26 days. The initial photolysis product was DDVP which was then degraded to glyoxylic acid, formic acid, and carbon dioxide.

Under artificial sunlight, the calculated half-lives for hydrolysis, photodegradation, and both reactions of naled (ethyl-2-¹⁴C) in water were 78 hours, 91 hours, and 42 hours, respectively (Chen, 1986b). The hydrolysis products were BDCA and desmethyl naled, while the photolysis products were DDVP, dichloroacetaldehyde (DCA), DCAA, and carbon dioxide. Further study showed that under sunlight, BDCA was converted to DCA; while DCAA was converted to chloroacetic acid (CAA) and acetic acid (AA).

When naled (ethyl-1-¹⁴C) was exposed to water-saturated air at 30°C, it was not photolyzed by an artificial sunlight source (Teeter, 1986). The half-lives, 10.4 and 10.3 days were similar for naled with or without exposure to sunlight, respectively. Possible metabolites were DCAA, AA, and CAA.

In the vapor phase, ¹⁴C-naled was degraded with first-order half-lives of 57.8 hours in natural sunlight and 99.0 hours in the dark (McGovern *et al.*, 1989a). The effective half-life for photolysis was 139 hours. Under both light and dark conditions, only hydrolysis products, DDVP and BDCA, were detected.

No photolysis was detected when ¹⁴C-naled was applied to air dried non-sterile sandy loam soil surface (McGovern *et al.*, 1989b). The first order half-life of naled degradation in

natural sunlight (0.54 hours) was similar to that in the dark (0.58 hours). The metabolites detected, DDVP, BDCA, and DCA, were likely products of microbial degradation.

II.G.3. Microbial Degradation

The metabolism of naled (ethyl-1-¹⁴C) in Oakly sandy loam soil (1.4% organic matter) was studied under aerobic and anaerobic conditions (Pack, 1980). The degradation of naled to ¹⁴C-carbon dioxide was rapid with half-lives of 3 days and 6 days for aerobic and anaerobic conditions, respectively. Intermediate metabolites were DDVP, DCAA, and DCE.

In a cranberry bog, the half-life for the aerobic metabolism of naled (ethyl-1-¹⁴C) was about 6 hours (Pack and Abell, 1986). Most of the naled were metabolized to carbon dioxide (71% in 30 days) and lesser amounts as DDVP, DCAA, and DCE. Similar results were obtained with the bog under an anaerobic environment in the dark (Pack and Fry, 1988). Desmethyl DDVP was tentatively identified as a metabolite.

The metabolism of naled in unsterile sandy loam was 3 times faster than in sterile sandy loam, and was 2-3 times faster than in sand, loam, and silt soils (Leary, 1970). The half-lives were 1.4 and 4 hours, respectively, for unsterile and sterile sandy loams. The half-lives for naled ranged from 2.6 to 4.0 hours for other soil types. DDVP was detected in all soil samples.

II.G.4. Mobility (Soil, Air, Water)

II.G.4.a. Soil

The mobility of naled depended on the amount of organic matter (Chevron Chemical Company, 1980; Pack, 1987). Naled was more mobile in sandy loam (1.4% organic matter), adobe clay (2.4%), and loamy sand (1.4%) than in clay loam (6.7%). The estimated adsorption coefficient (K_{ps}) for sandy loam, clay loam, loamy sand, and adobe clay were 1.3, 3.6, 1.8, and 3.6, respectively.

In soil columns (sandy loam, clay loam, sand, and loam), naled (ethyl-1-¹⁴C) rapidly degraded with half-lives of 0.4 to 3.0 hours (Pack, 1986). DDVP, DCAA, and DCE, not naled, were detected in the leachate. The total recovery ranged from 34-83% with 3-14% in the soil and the rest presumably in the air as carbon dioxide.

The volatilization of ¹⁴C-naled from wet and unsterile loamy sand soil was studied in Erlenmeyer flasks under laboratory conditions (Kesterson *et al.*, 1989). A majority (56%) of the radioactivity was volatilized with 48% in form of carbon dioxide. Of the radioactivity remaining in the soil, desmethyl DDVP (16.5% of applied), DDVP (8%), and naled (1%) were detected.

II.G.4.b. Ambient Air

Ambient naled air levels were measured in central Tulare County during May and June of 1991 (Royce *et al.*, 1993). Sampling periods were nominally 24 hours and varied from 23 to 25 hours over the 4-week period. Naled and DDVP were detected at four of the five monitoring sites which included a background site. The highest naled and DDVP levels measured over a

24-hour period were 0.077 and 0.059 $\mu\text{g}/\text{m}^3$, respectively. The results of this study were used to estimate the ambient air exposure assessment (Volume II).

Another air monitoring in Tulare County was conducted after a ground application of naled at a selected orange grove (ARB, 1995). Samples were collected before, during and for 72 hours after the start of the application. The highest 24-hour time-weighted average levels were 2.3 $\mu\text{g}/\text{m}^3$ (first day) and 0.91 $\mu\text{g}/\text{m}^3$ (first night to second day) for naled and DDVP, respectively.

In a 3-phase study, naled and DDVP were monitored in the air after a routine application to a bait station in the first phase (Turner *et al.*, 1989). Air samplers were placed 1 and 25 meters from the station and samples were collected for 4, 8, and 24 hours on day 0, 1, and 7 after treatment. While naled was not detected, DDVP was found on all sampling days with the highest level at 29 ng/m^3 (3 ppt) at 1 meter on day 0 and 16 ng/m^3 at 25 meters on day 1. By day 7, the levels for both distances decreased to $<1 \text{ ng}/\text{m}^3$. The second phase was done for oriental fruit fly eradication. Four-hour ambient air samples were collected during the first and fourth applications of bait. No naled was detected. After the fourth application, the mean level of DDVP was 10 ng/m^3 and this level decreased to less than 2 ng/m^3 at 4 days after application. The third phase determined the residue levels in citrus fruits. DDVP residues were found only in samples from sites re-baited in the morning of the study. At 1 and 4 meters from the trap, the DDVP levels in the fruits were 1.2 ppb and 0.73 ppb, respectively.

II.G.4.c. Water

After aerial application to ponds, naled and DDVP levels in the pond water were <0.1 ppm and were too low for the determination of a decay curve (Lee, 1988). Naled and DDVP were not detected (minimum detection limit, MDL = 0.01 ppm) in the sediment samples.

II.G.5. Plant Residues/Metabolism

^{82}Br -Naled was degraded to bromide ions after application to potato foliage, potato tuber, spinach, alfalfa, and strawberries (Chevron Chemical Company, 1966a). At 48 hours, less than 0.4 % of the radioactivity was naled.

Naled residues were detected in lettuce, wheat, and carrots grown on naled (ethyl- ^{14}C)-treated soil (Cheng, 1986). Radioactivity in the soil on days 0, 30 days of aging, and at harvest were 0.52 ppm, 0.03 ppm, and 0.01 ppm, respectively. Residues detected were: lettuce top (<0.01 ppm), lettuce roots (0.02 ppm), wheat grain (0.01 ppm), wheat bran (0.02 ppm), wheat straw (0.03 ppm), wheat roots (0.07 ppm), carrot tops (<0.01 ppm), and carrot roots (<0.01 ppm).

Three field trials were conducted to study the magnitude of the naled residues on sugar beets (Chevron Chemical Company, 1971). One day after the fifth application, residues in the roots were below the MDL (0.02 ppm) for naled and 0.01 ppm for DDVP. The mean residue levels in the whole plants were 0.02 ppm as naled and 0.15 ppm as DDVP.

The reaction involved in the rapid conversion of naled to DDVP and metabolites in plants was studied in a series of short experiments (Chevron Chemical Company, 1966c). Less than 50% of added naled was recovered 1 hour after addition to grounded apples, cabbage,

tomatoes, cantaloupe, grapes, and alfalfa. The reaction with the plant material was inhibited, but not reversed, by mineral acid suggesting that naled interacted with components of the plant material. Further studies showed that naled reacted with sulfhydryl compounds (cysteine, thioglycolic acid) with the release of bromine and the formation of DDVP. DDVP was then hydrolyzed to DCA by plant juices, with DCA in turn degraded by sulfhydryl compounds.

The degradation of naled on tomato and orange after processing was studied by the addition of naled (ethyl-1-¹⁴C) topically at 2 mg per fruit surface (Chen, 1981). When the fruits were processed on 1, 3, and 7 days after treatment, most of the radioactivity was found in the tomato juice and in the orange peel. In the orange peel, DDVP, DCE, and DCE conjugates, each accounted for 20-30% of added radioactivity. DDVP was the primary metabolite in the tomato juice with 62% and 30% of added radioactivity found 1 and 7 days, after treatment. The levels in the tomato wet pomace and orange wet pulp were 8 and <1%, respectively. There was a 60-70% loss of radioactivity when the tomato wet pomace was dried.

No naled residues were detected on leaf, cane, and soil samples taken 28 days after the application of naled (Dibrom) on grape vines (Serat and Bailey, 1974; Winterlin *et al.*, 1974). Naled residues (8.2 ppm) were detected on the bark.

More recent studies on grapes showed no naled and low levels of DDVP residues in the grapes and processed commodities (Erhardt-Zabik *et al.*, 1994; Erhardt-Zabik and Ruzo, 1994; Curry and Brookman, 1994). Field trials were conducted with Dibrom 8 Emulsive at 1 or 5 times the maximum label rate with preharvest intervals at 3, 7, and 10 days. In grapes at 3-day PHI, naled and DDVP residues were 0.05 ppm and 0.04 ppm, respectively. By 10-day PHI, both residue levels declined to ≤ 0.01 ppm. Naled and DDVP residues were at the detection limit (≤ 0.005 ppm) for grape juice, wet pomace, dry pomace, raisins, and raisin waste from grapes treated at both rates (Curry and Brookman, 1994). The maximum concentration factor was 0.88 for the processed commodities.

The decline of naled residues from harvest to the consumer level was studied in collards, oranges, strawberries, and celery treated with Dibrom 8 Emulsive (Pensyl, 1992a, b, c, and d). Application rates were higher than the maximum label rate to insure detectable residues for the studies. For the effects of processing on the residues, samples were collected and processed according to common practices before residue analysis. For the dissipation of residues in the field, samples were collected at specified days after the application and analyzed without processing. A summary of the results is presented in Table 1. In fresh commodities, both naled and DDVP were detected. However, commercial processing procedures (rinsing, trimming, peeling, cooking, canning, and storage) reduced both naled and DDVP residues. Highest DDVP residue levels were detected on the day of application. Naled dissipated faster than DDVP as the half-lives were 50% lower than those for DDVP.

In other field trials, snap beans and spinach were treated with Dibrom 8 Emulsive (1 or 5x maximum label rate) (Pensyl, 1993 and 1994a). For snap beans collected one day after the last application, naled and DDVP residues were found primarily in the vines, not the whole pods (Pensyl, 1993; Table 1). Canning of beans on the same day as the last application removed the residues from the beans to the waste, a concentration factor of 3-fold in the waste. For spinach collected one day after the last application, the highest naled and DDVP residues from 4 trials were 0.04 ppm, and 2.0 ppm, respectively (Pensyl, 1994a).

The dissipation of naled from range/pasture grass and hay was studied using Dibrom 8 Emulsive and Dibrom concentrate (Pensyl, 1994b). The result for the concentrate was questioned since it was mixed in water in error; it was not an emulsifiable formulation. Grass forage was harvested one day after the last application while the grass hay was allowed to field dry for three days before sampling. For Dibrom 8 Emulsive, the maximum naled and DDVP levels in the grass were 0.04 ppm and 0.14 ppm, respectively. There was a decline in the residues in the hay; the maximum levels were <0.01 ppm naled and 0.04 ppm DDVP.

Cotton and cucumber seedling leaves were treated with naled (ethyl-1-¹⁴C) at a rate of 250 to 350 $\mu\text{g}/\text{cm}^2$ and harvested 1, 3, or 7 days after application (Chen, 1980). At all sampling periods, the radioactivity was confined to the leaves and was approximately 10 to 25% of the initially applied radioactivity. Less than 1 % of the applied radioactivity was found on the petiole and stem. DDVP and BDCA were found only in samples collected 1 day after application. Most of the radioactivity was identified as conjugates of DCE (DCE glucoside, DCE disaccharide, and DCE oligosaccharide). The proposed pathway for the metabolism of naled in plants was:

naled \rightarrow DDVP and BDCA \rightarrow DCE glucoside \rightarrow DCE disaccharide \rightarrow
DCE oligosaccharide \rightarrow cellulose tissue and lignin

The fate of the naled residues was further studied in cotton as well as in cotton processed commodities (Pensyl, 1994c). Cotton was treated with Dibrom 8 Emulsive at 1 and 5 times the maximum label rate and harvested 4 days after the last application. For both rates, no naled or DDVP residues (detection limits at 0.01 and 0.02 ppm depending on the form) were detected in the cotton fuzzy seed (the raw agricultural commodity) and lint. Residues were also not detected in cotton treated with a 5x rate and processed into fuzzy cotton seed, lint, solvent extracted meal, hulls, crude oil, refined oil, bleached oil, deodorized oil, and soapstock.

Neither naled nor DDVP residues were found in almond nutmeat and hulls from trees that received a dormant spray of naled 7 to 8 months earlier (Chevron Chemical Company, 1994; Sakamoto, 1971). The detection limits were 0.02 ppm for naled and 0.01 ppm for DDVP. While no residues were found in the nutmeat, the total (naled and DDVP) residues in the hulls were 0.08 to 3.8 ppm, and <0.01 to 0.72 ppm for samples collected 2 and 4 weeks after the last applications, respectively, from 5 field trials.

Freezer stability studies showed that both naled and DDVP were stable in some commodities after freezer storage (Pensyl, 1994d). Almond nutmeat, almond hull, walnut nutmeat, and safflower seed were fortified with either 0.1 ppm of naled or DDVP and stored in the freezer for up to 43 days. In the naled fortified samples, most of the naled were converted to DDVP in almond nuts (<0.01 ppm naled and 0.034 ppm DDVP) and safflower seeds (0.016 ppm naled and 0.038 ppm DDVP) after 43 and 7 days, respectively. In almond hulls and walnuts, the naled levels were 0.056 ppm and 0.058 ppm, respectively. On other hand, DDVP was recovered (77 to 107% recovery) in all DDVP-fortified commodities.

Safflower plants were sprayed with Dibrom 8 and sampled 16 days after application (Kohn, 1963). No naled residues were detected in the meal and the oil.

Table 1. Mean residues of naled and DDVP in commodities ^a.

Processing study ^b	Naled	DDVP	Dissipation study ^c	Naled	DDVP	Ref.
Collard						1
Fresh	<0.01	0.05	Day 0	0.05	0.13	
Rinsed	<0.01	0.02	Day 1	<0.01	0.03	
Cooked (10 min)	<0.01	< 0.01	Day 8	<0.01	<0.01	
Stored- 1 day	<0.01	0.12	Half-life	NA	0.85 days	
4 days	<0.01	0.05				
Oranges						2
Fresh	0.04	0.09	Day 0	0.13	0.23	
Rinsed	<0.01	<0.01	Day 1	0.16	0.61	
Rinsed and Waxed	<0.01	0.02	Day 8	0.03	0.35	
Peeled	<0.01	<0.01	Day 15	<0.01	<0.01	
Stored- 0 day	<0.01	0.01	Half-life	1.85 days	2.97 days	
5 days	<0.01	0.01				
10 days	<0.01	<0.01				
Celery						3
Fresh	0.21	1.3	Day 0	0.89	5.1	
Trimmed	0.15	1.7	Day 1	0.06	1.6	
Trimmed + Rinsed	0.05	1.5	Day 6	<0.01	0.06	
Cooked- 2 min	0.01	0.2	Day 8	<0.01	<0.01	
30 min	<0.01	0.05	Half-life	0.49 days	0.99 days	
Stored- 1 day	0.05	1.4				
5 days	0.06	1.0				
10 days	<0.01	0.51				
Strawberry						4
Fresh	0.07	2.7	Day 0	0.24	4.6	
Capped	0.01	1.5	Day 1	0.09	1.9	
Stored- 0 day	0.01	1.2	Day 6	0.04	0.09	
1 day	<0.01	1.5	Day 8	0.04	0.04	
4 days	<0.01	1.5	Half-life	3.49 days	1.18 days	
Snap beans^c						5
<u>1x rate day 1 PHI</u>						
Whole pod	<0.01	0.019				
Vine	0.18	1.4				
<u>5x rate day 0 PHI</u>						
Whole pod	0.33	3.5				
Canned beans	<0.01	<0.01				
Canned waste	2.6	9.2				

a/ Selected results are presented in this table. References: 1. Pensyl, 1992a; 2. Pensyl, 1992b; 3. Pensyl, 1992c; 4. Pensyl, 1992d; 5. Pensyl, 1993.

b/ Processing Study : samples collected one day after application (except snap beans). Fresh =samples collected (no washing) and shipped frozen to the laboratory. Rinsed =field rinsed (and waxed for oranges) after collection and shipped frozen to the laboratory. Cooked=field rinsed after collection, shipped cold (not frozen), and then cooked in boiling water (collard) or peeled (oranges) before residue analysis. Trimmed/rinsed=rinsed and crowns removed. Stored= field rinsed after collection, shipped cold, and then stored in the refrigerator for specified days before residue analysis. Capped=stem and leaves removed.

c/ Dissipation Study- Decline of naled residues and the rates of formation and decline of DDVP residues in the field. Samples (not rinsed, trimmed, or peeled) were collected at specified days after application.

III. TOXICOLOGY PROFILE

Pharmacokinetics and toxicity studies of naled are summarized in this section. Acceptability of the studies (except genotoxicity studies) where noted, is determined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). The toxicology summary for studies required under Senate Bill 950, The Birth Defect Prevention Act of 1984, is included in Appendix C.

The inhalation studies with naled were conducted with whole-body or head-only exposure as noted. The absorbed dose from whole-body exposure was assumed to be only due to inhalation. Berteau and Chiles (1977) showed that the total absorbed doses were similar from the 2 methods of inhalation exposure. Potential exposure due to grooming, resulting in oral ingestion and dermal absorption of naled from the fur during whole-body exposure, did not increase the dose compared with that obtained from head-only exposure. Equations in Appendix D were used to calculate the absorbed dose from the nominal air concentrations.

III.A. PHARMACOKINETICS

Summary: Naled was rapidly absorbed by all routes (oral, inhalation, and intraperitoneal) and was distributed to all tissues in the rat, chicken, goat, and cow. Of the species (rat, chicken, goat) studied, the proposed metabolic pathways were similar. Naled was initially metabolized to DDVP which in turn was metabolized to desmethyl DDVP and dichloroacetaldehyde. Subsequent reactions resulted in the incorporation of a carbon into peptides, and the formation of conjugates, urea, and hippuric acid. Metabolites were excreted primarily in the urine, with a moderate amount in the expired air as carbon dioxide. In naled treated hens, goats, and cows, naled metabolites were detected in eggs and goat milk, but not in cow milk. In the rat, the amount (>90%) of naled absorbed and distributed to the body compartments (tissues, urine, and expired carbon dioxide) were similar regardless of the routes of exposure (whole body inhalation, head only inhalation, oral, and intraperitoneal).

III.A.1. Oral - Rat

III.A.1.a. Absorption

Naled (ethyl-1-¹⁴C, > 99.0% pure) was given to 2 Sprague-Dawley rats (28 mg/kg for the male and 50 mg/kg for the female) by gavage (Cheng, 1981a). Forty-eight hours after dosing, the percentages (female/male) of total radioactivity in the urine, feces, expired air, cage wash, and carcass were 38.7%/37.1%, 6.6%/8.1%, 16.1%/27.0%, 3.1%/2.7%, and 30.7%/23.4%, respectively. Radioactivity was found in all the tissues examined with the highest amounts (% of total radioactivity) in the liver (4.3-7.6%) and gut (6.0-2.5%). Radioactivity in the urine, air, carcass, and liver showed that the oral absorption of naled in rats was at least 90% for both sexes.

III.A.1.b. Distribution

The distribution of naled in the tissues was examined with male Sprague-Dawley rats (1/group) given naled (ethyl-1-¹⁴C, > 99.0% pure, 25 mg/kg) by gavage and sacrificed at 2, 6, 24, and 96 hours (Cheng, 1981b). By 2 hours, the gut, liver, and blood had higher radioactivity than the other tissues (kidney, testicles, heart, muscle, fat, and brain). At 24 hours and 96 hours, the radioactivity declined in the gut but increased in other tissues.

Following a similar protocol, a single dose of naled (ethyl-1-¹⁴C, > 99.0% pure, 5 mg/kg) was given orally to White Leghorn hens (1/control, and 4/treated) (Cheng, 1983a). The peak levels of radioactivity (equivalent to 0.2 to 14.0 ppm) were found 2 hours after dosing, with the highest amount in the kidneys. At 96 hours, the amounts of radioactivity, calculated as naled, in the liver and kidneys, were 1.5 ppm and 0.8 ppm, respectively.

The distribution of naled and its metabolites was studied in hens given naled (¹⁴C, > 99.0% pure, 2.5 mg/kg) twice a day for 10 consecutive days (Cheng, 1983b). The highest radioactivity level was in the kidneys (42.7 ppm) and lower levels in other tissues (liver, gizzard, heart, muscle, blood, skin, and fat) and eggs. The radioactivity in eggs was equivalent to 0.1 ppm, 1.3 ppm, and 2.5 ppm naled for days 1, 3, and 4, respectively. There was no result reported for metabolites in eggs after 4 days.

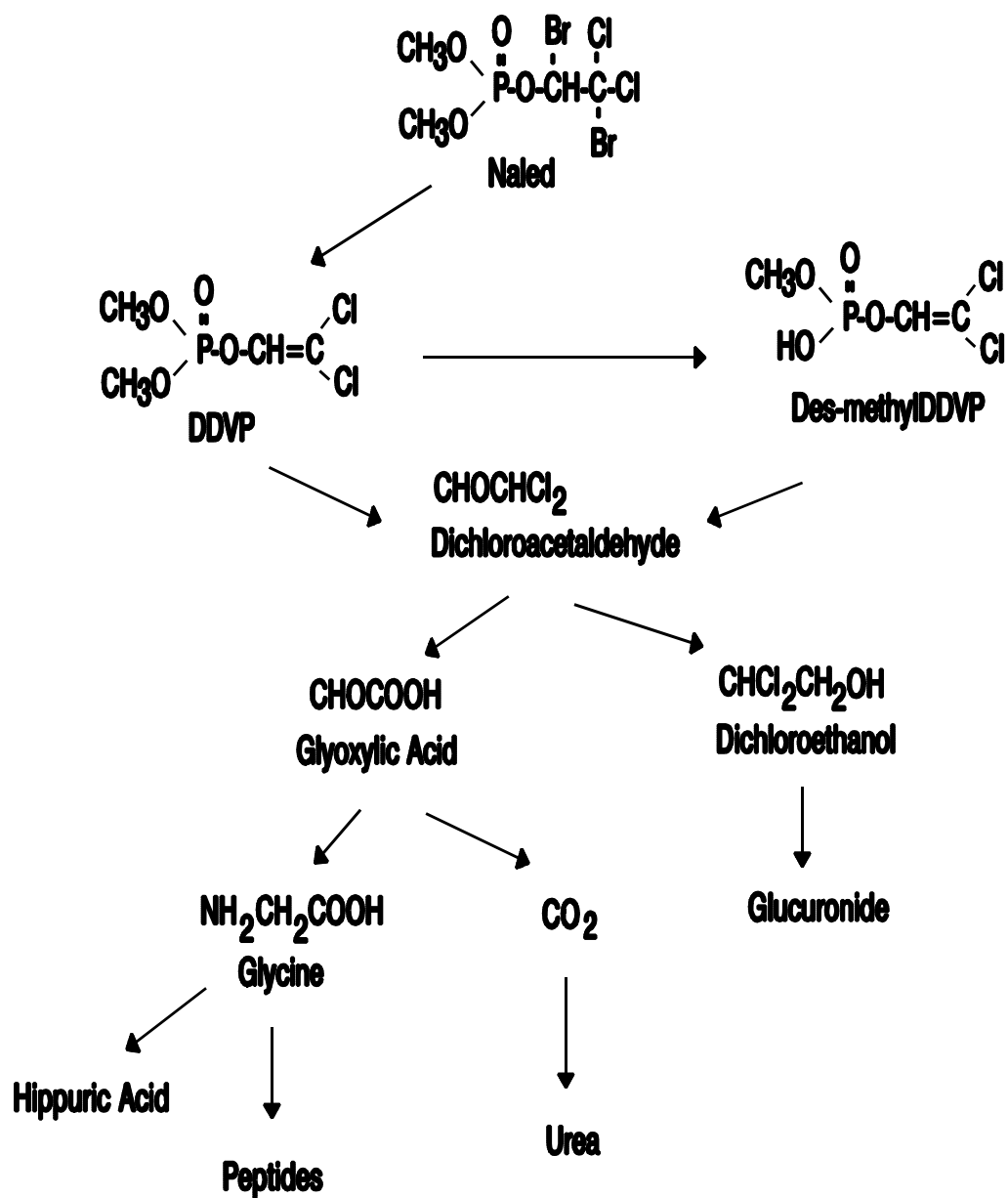
Naled (ethyl-1-¹⁴C, > 99.5% pure, 25 mg/dose) in gelatin capsules was given to a lactating goat 3 times a day for 10 doses (Chen, 1982). At sacrifice, the distribution of the radioactivity (as % of the dose) was: 18.9% in urine, 4.0% in feces, 3.9% in milk, 4.6% in liver, 1.3% in blood, 0.4% in kidney, 0.1% in heart, 0.1% in brain, and the remainder in expired air, muscle, fat, and carcass. Neither naled nor DDVP was detected. The radioactivity was associated with proteins, lipids and carbohydrates.

III.A.1.c. Biotransformation

Naled (ethyl-1-¹⁴C, > 99.0% pure) was given to 2 Sprague-Dawley rats (28 mg/kg for the male and 50 mg/kg for the female) by gavage (Cheng, 1981a). Forty-eight hours after dosing, more than 90% of the radioactivity in the urine was identified as dichloroethanol (DCE) and its conjugates (Figure 1). The minor metabolites were hippuric acid, urea, and desmethyl DDVP. These metabolites were also found in the feces.

In the previously described study, DDVP was detected only in the gut and was the major metabolite constituting 80% and 50% of total tissue radioactivity at 2 hours and 6 hours, respectively, after dosing (Cheng, 1981b). The minor metabolites were desmethyl DDVP, glucuronide conjugates of DCE, hippuric acid, and urea. In the kidney, desmethyl DDVP, hippuric acid, and DCE glucuronide conjugates were detected. In the blood, liver, muscle, and carcass, only desmethyl DDVP and the DCE glucuronide conjugate were detected. The "bound" radioactivity in the liver was associated with glycine, serine, and alanine. Analysis of the urine showed a similar biotransformation pattern as in the previous study (Cheng, 1981a).

Figure 1. Biotransformation pathways of naled in rats.



Shay rats were fed 1 milliliter of lettuce mulch containing one gram of lettuce and 20 mg of naled (92-96% pure) (Chevron Chemical Company, 1966b). The DDVP level in the stomach was 0.05 mg at 5 minutes after dosing. At 120 minutes, DDVP, naled, DCA, and BDCA levels in the stomach were 5.0 mg, 8.4 mg, 0.06 mg, and 0.08 mg, respectively.

In White Leghorn hens, DDVP and desmethyl DDVP were found only in the gizzard (Cheng, 1983a). Most of the radioactivity in the tissues was DCE conjugate and those incorporated in amino acids, particularly glycine. The proposed biotransformation pathways for naled in chicken were similar to those for the rat (Fig. 1).

In goats, most of the radioactivity in the tissues was associated with DCE glucuronide, amino acids, fatty acids, and urea (Chen, 1982). Trace amounts of desmethyl DDVP and DCE glucuronide were detected in the milk. The proposed pathways for the biotransformation of naled in the goat were similar to that for the rat.

In dairy cows(5/group) fed naled (purity not stated, 1 or 10 ppm) in the diet for 21 days, naled, DDVP, DCA, and BDCA were not detected in any of the milk and tissue samples (kidney, liver, muscle, and fat) (Chevron Chemical Company, 1966b). The limit of detection of the analytical method was 0.02 ppm with "good" recoveries at 0.05 ppm.

III.A.1.d. Excretion

In rats given naled by gavage, the percentages (female/male) of total radioactivity in the urine, feces, and expired air were 38.7%/37.1%, 6.6%/8.1%, and 16.1%/27.0%, respectively (Cheng, 1981a).

III.A.2. Dermal

There were no dermal absorption studies conducted with naled.

III.A.3. Inhalation, Oral, and Intraperitoneal - Rat

Female Sprague-Dawley rats (2/group) were exposed to naled ($1\text{-}^{14}\text{C}$ -ethyl, > 99% pure, aerosols of mass median diameter 1.8-2.0 μm for inhalation exposure) by either whole body or head only inhalation, oral or intraperitoneal exposures (Berteau and Chiles, 1977). With all routes of administration, radioactivity was detected in all major tissues (kidney, liver, lung, muscle, small intestine and stomach) at 48 hours after exposure. The tissues with the highest amounts of radioactivity, in decreasing order, for the 4 routes of exposure were liver, muscle, and small intestines. There was a difference among routes in percentage of total recovered radioactivity in urine. There were no major differences in the tissue distribution and excretion patterns between whole body and nose only inhalation exposures, although only one rat was used for each method of exposure. Percentage of total recovered radioactivity in each compartment is summarized below (Table 2). Results showed that the absorbed dose was almost 100% and was similar for the 4 routes of administration. About 3% of the total recovered radioactivity was found in the feces.

Table 2. The distribution of naled radioactivity in the rat^a.

Route of exposure	Number of animals	Percent of total recovered radioactivity			total
		tissues/organs	urine	expired carbon dioxide	
whole body	1	23.08	29.76	44.53	97.37
head only	1	35.96	24.54	36.58	97.08
oral	2	33.38	17.90	46.18	97.46
intraperitoneal	2	37.47	16.19	43.48	97.14

a/ Data from Berteau and Chiles, 1977.

III.A.4. All Routes - Human

Residents (age 4 to 68 years old) in the vicinity of an aerial application of naled (0.05 pounds/acre; with a trace amount of temephos) for mosquito control were monitored (Kutz and Strassman, 1977). There were 107 residents in the actual spray target area and 100 residents in the 1 mile margin outside the treated area. From each individual, two urine specimens were collected at several hours before the beginning of the application and within 3 hours after the application. The air concentration was not monitored. Of the six metabolites detected, dimethyl phosphate (DMP) and dimethyl phosphorothionate (DMTP) were considered to be indicators of exposure to naled (DMP) and temephos [o,o'-(thiodi-4,4-phenylene) phosphorothioic acid o,o,o',o'-tetramethyl ester] (DMP and DMTP). There was a significant ($p \leq 0.05$) increase in the urinary DMP levels of individuals inside the treated area after application. The mean levels were 0.004 ppm and 0.009 ppm before and after applications, respectively. Of those inside the treated area, only those who were outdoors during the application had significantly increased DMP levels (from 0.005 ppm to 0.014 ppm) after application. The DMP and DMTP levels of those who stayed inside during the application were similar for before and after spraying and suggested previous exposure to organophosphates.

III.A.5. In vitro Studies

Rat liver homogenate was fortified with 100 ppm naled (Chevron Chemical Company, 1966b). Naled was rapidly converted to DDVP; there were 10.6 ppm naled and 14.0 ppm DDVP in the homogenate after 5 minutes of incubation. At the longer times, naled was further degraded while DDVP increased in low levels (0.11 ppm or less) as DDVP was further degraded. Both DCA and BDCA were detected in low amounts (≤ 0.10 ppm).

III.B. ACUTE TOXICITY

Summary: Cholinergic signs (such as salivation, tremors, convulsions) were observed in experimental animals given naled by the oral, dermal, and inhalation routes. Atropine and 2-PAM decreased the lethality and delayed the onset of signs.

Acute lethality and irritation potential studies are summarized in Table 3. NOELs and Lowest-Observed-Effects Levels (LOELs) for non-lethal effects are summarized in Table 4. NOELs and LOELs were determined only for those studies with adequate information on the experimental protocol and results.

III.B.1. Oral - Rat

Sprague-Dawley rats (5/sex/group) were given a single dose of Dibrom 8E (containing 58% naled; 77 to 585 mg/kg) by gavage to determine acute lethality (Rittenhouse and Narcisse, 1974). The protocol did not state whether the dosage was corrected for 100% naled. For clinical signs, the times of onset of signs were less than 10 minutes for tremors, less than 1 hour for ataxia or convulsions, and 8 minutes to 240 minutes for salivation. Recovery from nonlethal effects of the single dose ranged from 2.5 hours to overnight. Mortality occurred at 173 mg/kg and higher concentrations for females, and 390 mg/kg for males. The mean oral LD₅₀ levels were 345 and 180 mg/kg for male and female rats, respectively. Tissues from survivors showed no gross pathology.

Sprague-Dawley rats (5/sex/group) were exposed to a single dose of naled (purity not stated; 0, 50, 62.5, 78.0, or 97.5 mg/kg) by gavage to determine the acute LD₅₀ level (EG&G Mason Research Institute, 1983). The mean oral acute LD₅₀ levels were 85.1 mg/kg for males and 81.2 mg/kg for females. All deaths occurred on the first day. Dyspnea, inactivity, and clear exudate from the mouth were observed in all treated groups. Trembling, convulsions, and red exudate from the eyes (males only) were observed in the 62.5 mg/kg and higher dose groups. Time to onset of the clinical signs was not stated in the report. The NOEL for cholinergic signs was <50 mg/kg.

Sprague-Dawley rats (5/sex/group) were gavaged with a single dose of naled (purity not stated) either in corn oil or 0.5% carboxymethyl cellulose (Cerknowicz, 1984). The dose levels were: 100- 560 mg/kg for naled in corn oil, and 70-400 mg/kg for naled in carboxymethyl cellulose. The LD₅₀ were: 325 mg/kg (males, corn oil), 230 mg/kg (females, corn oil), 191 mg/kg (males, carboxymethyl cellulose), and 92 mg/kg (females, carboxymethyl cellulose). Clinical signs were observed in all treated animals in both groups; they included: decreased motor activity, weakness, tremors, gasping, salivation, ocular discharge, piloerection, and collapse. Additional signs such as nasal discharge, ptosis, and excessive urination were noted in the corn oil group. Fasciculation, convulsions, ataxia and pale eyes were observed only in the carboxymethyl cellulose group. The NOELs for cholinergic signs were <100 mg/kg for the corn oil group and <70 mg/kg for the carboxymethyl cellulose group.

Table 3. The acute toxicity of naled.

Routes/ Species	Gender	Dose/Results	References ^a
TECHNICAL GRADE			
<u>Oral LD₅₀</u>			
Rat	M/F	81-85 mg/kg	1
Rat	F	160 mg/kg	2
Rat	M	250 mg/kg	3
Mouse	M/F	257-336 mg/kg	4
Mouse	F	222 mg/kg	2
<u>Dermal LD₅₀</u>			
Rat	M	800 mg/kg	3
Rabbit	M	354 mg/kg	5
Rabbit	M	702 mg/kg	6
Rabbit	M	390 mg/kg	7
Rabbit	F	360 mg/kg	7
<u>Inhalation LC₅₀</u>			
Rat	M/F	0.19-0.20 mg/L (32 mg/kg) ^b for 4 hours	8
Rat	F	3.1 mg/kg for 1 hour	2
Mouse	F	156 mg/kg for 1-2 hours	2
<u>Dermal Sensitization</u>			
Guinea pig	M	0.5 ml of a 3.0% solution (positive skin sensitization)	9
<u>Aquatic and Wildlife Toxicity</u>			
Mallard LD ₅₀		52 mg/kg	10
Honey bee LD ₅₀		0.48 ug/bee	10
Blue gill LC ₅₀		0.33 ppm	10
Rainbow trout LC ₅₀		0.08 ppm	10
Mullet LC ₅₀		0.55 ppm	10
Sheephead minnow LC ₅₀		1.2 ppm	11
<i>Daphnia</i> LC ₅₀		0.00035 ppm	10
Pink shrimp EC ₅₀		0.0055 ppm	10
Grass shrimp LC ₅₀		8.9 ppm	12
Eastern Oyster EC ₅₀		0.19 ppm	13

^{a/} References: 1. EG&G Mason Research Institute, 1983. 2. Berteau and Deen, 1978; Berteau *et al.*, 1976; 3. Gaines, 1969; 4. Thompson, 1984; 5. Narcisse and Cavalli, 1971; 6. Bullock and Narcisse, 1975; 7. Brorby, 1985; 8. Rittenhouse, 1985a; 9. Rittenhouse, 1978; 10. Kenaga, 1979; 11. Springborn Bionomics, Inc., 1986a; 12. Springborn Bionomics, Inc., 1986b; 13. Springborn Bionomics, Inc., 1986c.

^{b/} Based on respiration rate of 0.96 m³/kg/day (Appendix D). The air also contained 1.6% DDVP and 0.29% BDCA.

Table 3. The acute toxicity of naled (continued).

Route/ Species	Sex	Dose/Results	References ^a
FORMULATIONS			
Dibrom 8E, 58% Naled			
<u>Oral LD₅₀</u>			
Rat	M/F	180-345 mg/kg	1
<u>Dermal LD₅₀</u>			
Rabbit	M	315 mg/kg	2
<u>Ocular Irritation</u>			
Rabbit	M	conjunctivitis with frank bleeding, corneal opacity, severe chemosis	3
<u>Dermal Irritation</u>			
Rabbit	M/F	severe erythema, necrosis, and severe edema	4
<u>Aquatic and Wildlife Toxicity (96 hours)</u>			
Rainbow trout LC ₅₀		0.13 ppm	5
Blue gill LC ₅₀		0.24 ppm	6
<i>Daphnia</i> LC ₅₀		1.5 µg/L	7

^{a/} References: 1. Rittenhouse and Narcisse, 1974; 2. Narcisse and Cavalli, 1971; 3. Cavalli, 1971; 4. Gregory and Narcisse, 1974; 5. Springborn Bionomics, Inc., 1986d; 6. Springborn Bionomics, Inc., 1986e; 7. Springborn Bionomics, Inc., 1986f.

The effects of atropine sulfate and pralidoxime chloride (2-PAM) as antidotes for the acute oral toxicity of naled were investigated (Duke, 1982 and 1983). Sprague-Dawley rats (5/sex/group) were gavaged with naled (purity not stated; dose levels ranged from 135 mg/kg to 900 mg/kg) and then given saline alone, atropine (10 or 20 mg/kg) alone, or atropine and 2-PAM (50 mg/kg) by intramuscular injection. Atropine (20 mg/kg) increased the LD50s of naled by 1.4 to 1.8 times (from 371 mg/kg for males and 207 mg/kg for females to 533 mg/kg for males and 376 mg/kg for females). Atropine and 2-PAM increased the levels by 1.3 to 1.9 times (479 mg/kg for males and 400 mg/kg for females). While clinical signs were observed in all groups, there was a delay in the onset on some effects in the antidote treated groups.

III.B.2. Inhalation - Rat

Sprague-Dawley rats (5/sex/group) were exposed to naled vapor (91.5% pure; 1.14 µg/L naled and 2.3 µg/L DDVP) by whole-body inhalation exposure for 4.3 hours (Rittenhouse, 1983). The calculated dosages^a were 0.2 mg/kg/day of naled and 0.4 mg/kg/day of DDVP.

^a Equivalent dosages were calculated based on Equation 1 in Appendix D.

Clinical signs of toxicity (ocular discharge, nasal discharge, salivation, shaking, squinted eyes, and labored breathing) were observed in the first 30 minutes of exposure and the animals appeared normal on the following day. Only the mean body weight of the treated females (specific group not identified) was significantly ($p \leq 0.05$) different (97% of controls) than the controls. No gross pathological changes were noted in the tissues examined. The NOEL for cholinergic signs was $< 1.4 \mu\text{g/L}$ ($< 0.2 \text{ mg/kg/day}$) of naled. This was considered a supplemental study to DPR and was not considered for risk assessment because of the high levels of DDVP.

Sprague-Dawley rats (5/sex/group) were exposed to naled (90% pure with 1.6% DDVP and 0.29% BDCA; nominal concentrations of 0.1, 0.15, 0.2, or 0.4 mg/L) by whole-body inhalation exposure for 240 minutes (Rittenhouse, 1985a). The calculated dosages^a were 16, 24, 32, and 64 mg/kg/day. In the 0.1 mg/L group, cholinergic signs were observed within 2 hours post dosing, and included squinted eyes, salivation, labored breathing, abnormal respiratory sounds, decreased motor activity, and weakness. Tremors and fasciculation, and death were also observed in rats treated at higher concentrations. At necropsy, corneal opacity, dark red livers, and congestion in the lungs were observed in most of these treated animals. The NOEL for cholinergic signs was $< 0.1 \text{ mg/L}$ ($< 16 \text{ mg/kg/day}$).

Crl:CD(SD) BF rats (5/sex/group) were exposed to Dibrom 235 spray (27.9% naled) diluted to 8.75% in distilled water (gravimetric concentration 0 or 5.9 mg naled/L) by whole-body exposure for 4 hours (Bruce, 1984; Fujie, 1984b). In the treated group, one death, clinical signs (salivation, nasal discharge, tremors, weakness, labored breathing, miosis, wheezing, decreased motor activity), corneal opacity, and reduced weight gain were observed. No treatment related histopathology was reported. This study was considered unacceptable to DPR and cannot be upgraded because the test article was highly diluted before testing.

Female Sprague-Dawley rats were exposed to naled (87% pure; 1.3 mg/L) in a head-only exposure with two aerosol sizes (mass median diameter, 2 μm and 13-20 μm) (Berteau *et al.*, 1976). Exposure was continued until animals died and the time to death was used to calculate the dosage for lethality. The LC_{50} value was 3.1 mg/kg for the 2 μm aerosol but no LC_{50} value was determined for the 13-20 μm aerosol since only 25% mortality was observed after 60 minutes at the highest concentration tested (12.4 mg/kg).

Rats (species and sex not specified, 10/group) were exposed to an aerosol of Dibrom 8 Emulsive (purity not stated, theoretical concentration of 1.52 mg/L) for 6 hours (Hazleton Laboratories, 1959). At the end of the first hour, all showed slow and deep (labored) respiration. All animals appeared normal during the 12-hour post-exposure observation. The lungs were dark red and had multiple darker areas that may be atelectasis. The study was considered unacceptable to DPR and cannot be upgraded because the exposure atmosphere was not characterized and the observation period was too short.

III.B.3. Oral - Mouse

Swiss-Webster mice (5/sex/group) were given a single dose of naled (technical, purity not stated; 0, 178, 215, 261, 316, 383, or 464 mg/kg) by gavage to determine the LD_{50} (Thompson, 1984). Cholinergic signs (tremors, decreased motor activity) were observed in all

treatment groups and were more severe (included convulsions) in the high dose groups. The onset of the signs was within 35 minutes after dosing. The average LD₅₀ levels were 257 and 336 mg/kg for males and females, respectively.

III.B.4. Inhalation - Mouse

Mice (species and sex not specified, 10/group) were exposed to an aerosol of Dibrom 8 Emulsive (purity not stated, theoretical concentration of 1.52 mg/L) for 6 hours (Hazleton Laboratories, 1959). At the end of the first hour, all showed slow and deep (labored) respiration. All animals appeared normal during the 12-hour observation post exposure. The lungs were dark red and had multiple darker areas that may be atelectasis. The study was considered unacceptable to DPR and cannot be upgraded because the exposure atmosphere was not characterized and the observation period was too short.

III.B.5. Dermal - Rabbit

Naled technical (88% pure) was applied to the shaved trunks of male New Zealand white rabbits (6/group) for 24 hours (Narcisse and Cavalli, 1971). The dose levels, based on naled, ranged from 125 to 1000 mg/kg. The dermal LD₅₀ level was 354 mg/kg and death occurred within 2 days. Clinical signs (tremors, salivation, and generalized muscular weakness) were observed, but the times of onset and treatment levels were not specified. At the end of the observation period, the applied areas of the skin were necrotic with eschar formation. Mottled kidneys were found in one animal of the 125 mg/kg group. At 250 mg/kg, pathological changes included congested lungs, pale kidneys, and enlarged kidneys (one rabbit). At 500 mg/kg, fibrotic areas in the liver, slightly pale kidneys, and small spleen (one rabbit) were observed.

Naled technical (purity not stated; 445, 667, 1000 or 1500 mg/kg) was applied to the shaved trunks of male New Zealand white rabbits (6/group) for 24 hours (Bullock and Narcisse, 1975). Clinical signs (ataxia, tremors, miosis, salivation, and collapse) were observed in several animals in each treated group within 2 hours of dosing. Deaths occurred in all treated groups 2 to 7 days after dosing. The acute dermal LD₅₀ level was 702 mg/kg. The NOEL for cholinergic signs was < 445 mg/kg.

Naled technical (92% pure; 0, 125, 210, 360, or 615 mg/kg) was applied to the unabraded skin of the trunks of New Zealand white rabbits (5-6/sex/group) for 24 hours (Brorby, 1985). Cholinergic signs were observed in all treated rabbits. At 125 mg/kg, the clinical signs were noted on the first day; and included: diarrhea (2/5), ocular (2/5) and nasal discharges (1/5), and decreased motor activity (1/5). At the higher concentrations, more severe signs were observed and included: ataxia, salivation, tremors, collapse, and difficulty in breathing. Death occurred at \geq 360 mg/kg and the LD₅₀ was 390 mg/kg. The skin of all treated rabbits were observed as brown and thickened with necrosis, fibrosis, hyperkeratosis, acanthosis, ulceration, and inflammation. The NOEL for local effects to the skin and cholinergic signs was < 125 mg/kg.

III.B.6. Dermal Sensitization - Guinea Pig

Naled (0.2 and 2%; purity not stated) was applied onto the skin of Harley female guinea pigs in the guinea pig maximization test for allergenicity (Matsushita *et al.*, 1985). At 0.2% naled, the response was considered to be weak (grade I). At 2% naled, 80% and 90% of the animals showed a grade IV response at 24 hours and a grade V (extreme) response at 48 hours, respectively.

III.B.7. Inhalation - Guinea Pig

Guinea pigs (species and sex not specified, 10/group) were exposed to an aerosol of Dibrom 8 Emulsive (purity not stated, theoretical concentration of 1.52 mg/L) for 6 hours (Hazleton Laboratories, 1959). At the end of the first hour, all showed slow and deep (labored) respiration. All animals appeared normal during the 12-hour post-exposure observation. The lungs were dark red and had multiple darker areas that may be atelectasis. The study was considered unacceptable to DPR and cannot be upgraded because the exposure atmosphere was not characterized and the observation period was too short.

III.B.8. Additional Acute Studies

The toxicity of naled to aquatic and wildlife has been extensively studied (Chevron Chemical Company, 1984; Kenaga, 1979; Springborn Bionomics, Inc., 1986a, b, and c; Bettencourt, 1992; Putt, 1993). A partial listing of the results is included in Table 3.

Acute effects were also observed in studies described (in detail) in the **III.C. SUBCHRONIC TOXICITY**, **III.E. GENOTOXICITY**, **III.G. DEVELOPMENTAL TOXICITY**, **III.H. NEUROTOXICITY**, and **III.I. OTHER STUDIES**. These studies are summarized in Table 4.

Table 4. Selected No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) for acute effects of naled.

Species	Route	Exposure Duration	NOEL mg/kg/day	LOEL	Effects	Ref. ^b
Rat^c	gavage	1 dose	<25	25	cholinergic signs (convulsions, tremors)	1*
Rat ^d	gavage	1 dose	<50	50	dyspnea, inactivity, oral exudate, death	2
Rat ^e	gavage	gestation d6 to 19	10	40	tremors, salivation	3*
Rat ^d	inhalation	4.0 h	<16	16	squinted eyes, salivation, labored breathing, and other cholinergic signs	4
Rat ^{d,g}	inhalation	6 h/d for 5d	<0.58	0.58	plasma and erythrocyte ChE inhibition	5
Rat ^g	inhalation	6h/d for 13w	0.22	1.0	salivation, respiratory sounds (2 doses)	6
Mouse ^h	gavage	1 dose	55	110	cholinergic signs (tremor, death)	7*
Rabbit ^f	gavage	gestation d7 to 19	10	40	death after 1 day	8
			10	20	cholinergic signs and death, sacrificed after 3 days	8
Rabbit ^d	dermal	24 h	<445	445	cholinergic signs (salivation, ataxia, tremor, death)	9
Rabbit ^d	dermal	24 h	<125	125	cholinergic signs (diarrhea, ocular and nasal discharges); skin effects	10
Dog ^g	gavage	4 weeks	1.0	5.0	emesis after each dose	11

a/ The abbreviations are: h=hours and d=days. The study selected for risk characterization is indicated in bolded-type.

b/ * after the reference indicates the study was considered acceptable by DPR according to FIFRA guidelines. References: 1. Lamb, 1993a; 2. EG&G Mason Research Institute, 1983; 3. Science Applications, Inc., 1984; 4. Rittenhouse, 1985a; 5. Rittenhouse, 1985b and Wong, 1986; 6. Griffis, 1986; 7. Machado, 1984; 8. Hardy, 1985; 9. Bullock and Narcisse, 1975; 10. Brorby, 1985; and 11. Batham *et al.*, 1983.

c/ The study is described in III.H. NEUROTOXICITY.

d/ Lowest dose tested.

e/ The study is described in III.G. DEVELOPMENTAL TOXICITY.

f/ The only concentration tested, not necessarily the LOEL. Also contained 0.4 mg/kg (2.3 ug/L) DDVP.

g/ The study is described in III.C. SUBCHRONIC TOXICITY.

h/ The study is described in III.E. GENOTOXICITY.

III.C. SUBCHRONIC TOXICITY

Summary: Naled inhibited plasma, erythrocyte, and brain ChE activities in rats and dogs after subchronic exposure by the oral, dermal, and inhalation routes. Cholinergic signs (including tremors, salivation, and death) were observed in the oral and inhalation studies. Naled caused skin inflammation and necrosis in rats from dermal exposure. A summary of selected studies is presented in Table 7.

III.C.1. Gavage - Rat

Sprague-Dawley rats (10/sex/group) were given naled (91% pure; 0, 0.25, 1.0, 10, or 100 mg/kg/day) by gavage daily for 4 weeks (Lough *et al.*, 1981). Cholinergic signs were observed in animals treated with 10 and 100 mg/kg/day of naled. After the sixth dose, one male (10 mg/kg/day) showed muscular tremors 30 minutes after the dosing, and 5 rats showed slight lethargy. At 100 mg/kg/day, all females and 3 males showed muscular tremors within 10 to 30 minutes after almost every dose. General weakness, pallor, lethargy, respiratory distress, salivation, ocular discharge, increased urination and diarrhea were also observed in most of the rats after dosing. Twelve of 20 rats in this group died during the study. Body weight gain and food consumption were transiently affected. Erythrocyte, plasma, and brain ChE activities determined at the end of the experiment showed significant ($p \leq 0.05$) inhibition from exposure to naled. The plasma, erythrocyte, and brain ChE activities (male/female) of the 10 mg/kg/day group were 63%/52%, 74%/72%, and 47%/48% of control activity, respectively. At 100 mg/kg/day, the plasma, erythrocyte, and brain ChE activities (male/female) were 48%/26%, 76%/70%, and 26%/27% of control activity, respectively. Macroscopic examination of the tissues of animals that died during the study and at sacrifice did not show any treatment related lesions. Cited appendices with individual data were not included in the report on file at DPR. The NOEL was 1.0 mg/kg/day for both ChE inhibition and cholinergic signs.

Sprague-Dawley rats (10/sex/group) were given naled (92.7% pure with 1.2% DDVP; 0, 0.4, 2.0, or 10.0 mg/kg/day) by gavage daily for 13 weeks (Lamb, 1994a). No treatment-related effects were observed in viability, mean body weight, body weight gain, mean food consumption, Functional Observational Battery and locomotor activity evaluations, brain weight or dimensions, and microscopic examination of tissues. The only significant finding was tremor in 3 of the 10 mg/kg/day females with the first observation noted on day 19. At 10 mg/kg/day (males) and at ≥ 2.0 mg/kg (females), there was an increased incidence of hair loss. The NOEL for neurotoxicity was 2.0 mg/kg/day for females and 10.0 mg/kg/day for males. This study was considered acceptable by DPR.

III.C.2. Inhalation - Rat

Fischer 344 rats (10/sex/group) were exposed to naled aerosol (89.3% pure; actual air concentrations were 0, 3.4, 7.2, or 12.1 $\mu\text{g/L}$) by whole-body exposure for 6 hours/day, 5 days/week, for 15 exposures in a 3-week period (Rittenhouse, 1985b; Wong, 1986). The equivalent dosages^a were 0.58, 1.23, and 2.07 mg/kg/day. Plasma and erythrocyte ChE activities after 5 and 15 exposures, as well as the brain ChE activities after 15 exposures were

^a Equivalent dosages were calculated based on Equation 1 in Appendix D.

significantly decreased in all dose groups in a dose-related manner. There was little difference in the plasma and erythrocyte ChE inhibition between the two sampling period. For the 15 exposure groups, the brain ChE activity (male/female) was 78%/72%, 59%/56%, and 38%/38% of controls for 3.4, 7.2, and 12.1 $\mu\text{g/L}$, respectively.

Treatment-related clinical signs in the 7.2 and 12.1 $\mu\text{g/L}$ groups included colorless and red discharge from the eyes, unkempt appearance, reduced food intake, loss of weight, salivation, colorless and red discharge from the nose, abnormal sounds and labored respiration, weakness, reduced stools, and corneal opacity (females only). The time of onset of these signs was not specified in the report. The 3.4 $\mu\text{g/L}$ group showed primarily salivation and abnormal sounds in respiration. Ophthalmological examinations showed exposure-related increases in the incidences of corneal edema, iris hyperemia, and keratitis in the eyes of the 12.1 $\mu\text{g/L}$ group. The mean body weights of the males of 12.1 $\mu\text{g/L}$ and both sexes of the 7.2 $\mu\text{g/L}$ groups were significantly reduced ($p \leq 0.05$) on 7, 14, and 21 days following the first exposure. The body weight reductions for those 3 days were in the ranges of 78-85% of control values for the males, and were 92-93% and 77-81%, respectively, for the 7.2 $\mu\text{g/L}$ and 12.1 $\mu\text{g/L}$ females. The decrease in body weights was likely to be related to the reduced food consumption (58-89% of control rate in the 12.1 $\mu\text{g/L}$ group). There was an increased organ/body weight ratio for the brain, lung, kidneys, adrenal glands, and testes.

Significant microscopic lesions (trace-mild squamous metaplasia and acute rhinitis) were found in the nasal tissues primarily of the high dose group. The incidences for squamous metaplasia with increased doses were 0%, 0%, 40%, and 100% for the males and 0%, 0%, 22%, and 80% for the females. Elevated incidence of acute rhinitis was observed only in the high dose group with incidences of 70% and 20% for the males and females, respectively. The NOEL was $< 3.4 \mu\text{g/L}$ ($< 0.58 \text{ mg/kg/day}$) for ChE inhibition and cholinergic signs. The NOEL for nasal damage was 3.4 $\mu\text{g/L}$ (0.58 mg/kg/day).

In a longer-term study, Fischer 344 rats (12/sex/group) were exposed to naled (92.1% pure; average measured concentrations of 0, 0.23, 1.29, and 5.8 $\mu\text{g/L}$) 6 hours per day and 5 days per week by inhalation for 13 weeks (Griffis, 1986). Additional control and high concentration groups (10/sex/group, satellite groups) were held for a 6-week recovery period. The equivalent dosages^a were 0.039, 0.22, and 1.0 mg/kg/day . There was an increased incidence of clinical signs (salivation, nasal and anogenital discharge, and abnormal respiratory sounds) in the 5.8 $\mu\text{g/L}$ group. Salivation and respiratory sounds were observed in some treated rats within the first two exposures and frequently for the rest of the experiment.

The magnitude of brain, erythrocyte, and plasma ChE inhibition was not time-dependent and was similar for each of the testing period (Table 5). At 1.29 $\mu\text{g/L}$, only plasma and erythrocyte ChE activities were inhibited at some time points. At 5.8 $\mu\text{g/L}$, all ChE activities were inhibited and were statistically significant ($p \leq 0.05$). Plasma and erythrocyte ChE activities were inhibited to a greater extent (26.9-46.0% of control) compared with that for brain ChE (53.9-61.9% of control). The inhibition of ChE activity was apparently reversible. Three weeks after exposure, both plasma and erythrocyte ChE activities were greater than 60% of control. At 6 weeks after exposure, ChE activities were $\geq 79\%$ of control levels (Table 5).

^a

Equivalent dosages were calculated based on Equation 1 in Appendix D.

Table 5. The inhibition of plasma, erythrocyte, and brain cholinesterase activity in rats after 13-week subchronic inhalation exposure to naled and during recovery ^a.

Dosage mg/kg/day	Cholinesterase Activity as % of Control Activity ^a					
	MALES Main Group			Satellite Group		
	wk 2	wk 7	wk 13	wk 12	wk 3 recovery	wk 6 recovery
	Plasma Cholinesterase Activity					
0.039	103.7	93.7	87.0	-	-	-
0.22	88.2	78.2	81.1	-	-	-
1.0	52.0**	58.7*	46.0**	36.1**	75.4*	79.0*
	Erythrocyte Cholinesterase Activity					
0.039	95.6	83.1	97.7	-	-	-
0.22	62.0*	52.7*	85.8	-	-	-
1.0	28.1**	7.7**	32.6**	24.7**	70.7**	114.0*
	Brain Cholinesterase Activity					
0.039	-	-	103.6	-	-	-
0.22	-	-	100.3	-	-	-
1.0	-	-	61.9**	-	-	94.4
	FEMALES Main Group			Satellite Group		
	wk 2	wk 7	wk 13	wk 12	wk 3 recovery	wk 6 recovery
	Plasma Cholinesterase Activity					
0.039	91.7	87.7	97.4	-	-	-
0.22	86.7	73.5**	92.8	-	-	-
1.0	41.1**	29.1**	38.7**	28.6**	103.5	105.2
	Erythrocyte Cholinesterase Activity					
0.039	83.0	89.3	97.7	-	-	-
0.22	71.6	71.2	82.5	-	-	-
1.0	23.9**	6.8**	26.9**	11.4**	60.8**	117.6
	Brain Cholinesterase Activity					
0.039	-	-	105.7	-	-	-
0.22	-	-	96.5	-	-	-
1.0	-	-	53.9**	-	-	94.8*

a/ Data from Griffis (1986). Cholinesterase activity data are presented for the main groups determined on weeks 2, 7, and 13; and for satellite groups determined on week 12 of treatment, and weeks 3 and 6 of recovery period. Statistically significant difference from controls, * $p \leq 0.05$, and ** at $p \leq 0.01$ was based on ANOVA and Dunnett's t tests.

b/ Dosages were calculated based on nominal air concentrations of 0.23, 1.29, and 5.8 $\mu\text{g/L}$.

There was also increased food consumption (5.8 $\mu\text{g/L}$ females), increased MCH (≥ 1.2 $\mu\text{g/L}$), increased MCV (≥ 5.8 $\mu\text{g/L}$), and increased albumin/globulin ratio (5.8 $\mu\text{g/L}$ females). Absolute and relative kidney weights were increased in females at 5.8 $\mu\text{g/L}$. Histopathological examination showed nasal effects (epithelial dysplasia, chronic rhinitis, and hemorrhage) almost exclusively in treated rats. The incidences for all effects combined in males were 0, 13, 8, and 5 for 0, 0.23, 1.29, and 5.8 $\mu\text{g/L}$, respectively. The incidences for all effects combined in females were 2, 6, 11, and 10 for 0, 0.23, 1.29, and 5.8 $\mu\text{g/L}$, respectively. The NOEL was < 0.23 $\mu\text{g/L}$ (< 0.039 mg/kg/day) for increased incidences of nasal pathology in all treated groups; and higher NOELs for increased food consumption, hematological parameters, absolute and relative kidney weights at higher doses. The NOELs were 0.23 $\mu\text{g/L}$ (0.039 mg/kg/day) for plasma and erythrocyte ChE inhibition, and 1.29 $\mu\text{g/L}$ (0.22 mg/kg/day) for brain ChE inhibitions and cholinergic signs. This study was considered supplemental data to DPR.

III.C.3. Dermal - Rat

Sprague-Dawley rats (12/sex/group) were exposed to naled (90% pure; 0, 1, 20, or 80 mg/kg/day) dermally for 6 hours per day, 5 days per week for 20 or 21 days (Rausina and Zimmerman, 1986). Naled was suspended in 0.5% (w/v) carboxymethylcellulose, and applied to clipped skin (skin surface area not given). The region was then covered with a non-absorbent binder and wrapped with Elastoplast™ tape. After 6 hours, the tape was removed and the region was cleaned. Application regions were alternated every day between the shoulder area and an area caudal to the shoulders. Increased incidences of acute inflammation, acute ulcerative inflammation, and necrosis were observed in the treated regions of all dose groups (Table 6). The effects for the 1 mg/kg/day female group were described as minimal to mild inflammatory response.

Only the body weights of the males (20 and 80 mg/kg/day) were decreased in a dose-related manner from day 7 onward and were in the ranges of 92-96% and 82-87% of control, respectively, for the two dose groups. Food consumption was slightly increased (108% of control at the low dose to 119% of control at the high dose) and was statistically significant ($p \leq 0.05$). Some serum chemistry parameters (BUN, creatinine, glucose, cholesterol, total serum protein, and albumin levels) were altered, though none of the deviations were markedly different from controls. Clinical signs included coarse or fine tremors, soft stool, and anogenital staining in 1 or 2 animals of the treated groups on days 2, 5 or/and 9. They were considered minor by the investigators because of the low incidence rate and transient nature. There was statistically significant ($p \leq 0.05$) inhibition of plasma, erythrocyte, and brain ChE activities at the end of the study for both the 20 and 80 mg/kg/day groups (Table 6). The NOEL for plasma, erythrocyte, and brain ChE inhibition was 1 mg/kg/day . The NOEL for the localized irritation response was < 1 mg/kg/day .

Table 6. Skin lesions and the inhibition of plasma, erythrocyte, and brain cholinesterase activity in rats after 3 weeks subchronic dermal exposure to naled ^a.

Effects	Dosage (mg/kg/day)							
	MALES				FEMALES			
	0	1	20	80	0	1	20	80
Skin Lesions Incidences (12 animals examined)								
Acute inflammation	0	0	4	1	0	2	8	0
Acute ulcerative inflammation	0	0	8	11	0	1	3	12
Necrosis	0	0	4	9	0	0	1	12
Epidermal hyperplasia	0	0	8	11	0	0	6	11
hyperkeratosis/ parakeratosis	0	0	3	1	0	0	4	3
Cholinesterase Inhibition % control activity								
Plasma	100	89	54**	36**	100	143	47*	17**
Erythrocyte	100	100	79*	83	100	92	75**	71**
Brain	100	100	40**	30**	100	98	40**	31**

a/ Data from Rausina and Zimmerman (1986). Statistically significant difference from controls, * $p \leq 0.05$, and ** at $p \leq 0.01$ was based on results in the report.

III.C.4. Gavage - Dog

Beagle dogs (2/sex/group) were given naled (92.3% pure; 0, 0.2, 1.0, 5.0, or 25.0 mg/kg/day) by gavage daily for 4 weeks (Batham *et al.*, 1983). The only clinical signs were emesis observed immediately after dosing for the 5 and 25 mg/kg/day groups, and soft feces for both males of the 25 mg/kg/day group. Lowered body weight gain, food consumption, and parameters in blood biochemistry (total protein, albumin, calcium and inorganic phosphorus) were noted. No pathological changes were observed in the organs examined histologically. Erythrocyte and plasma ChE activities were determined each week, and brain ChE activity was determined after 4 weeks of exposure. Significant levels of inhibition (based on greater than 20% of inhibition, statistical analysis was not reported) of plasma and erythrocyte ChE occurred on week 2 and inhibition remained constant to the end of the study. After 4 weeks, the inhibition of plasma ChE activity (male/female) was 73%/81%, 57%/61%, and 56%/58% of controls for 1.0, 5.0, and 25.0 mg/kg/day, respectively. The inhibition of erythrocyte ChE activities (male/female, unless indicated) was 70% (male only), 59%/82%, 51%/74% of controls for the 3 dose groups, respectively. The NOEL for plasma and erythrocyte ChE inhibition was 0.2 mg/kg/day. For brain ChE inhibition, the NOEL was 1.0 mg/kg/day based on an inhibition of 86%/52% (male/female) of control activity for the 5 mg/kg/day group, and 33-56% inhibition for the 25.0 mg/kg/day group.

III.C.5. Additional Studies

Additional studies for the consideration of subchronic toxicity are described in the **III. F. REPRODUCTION TOXICITY** and **III. G. DEVELOPMENTAL TOXICITY**. The results of these studies are summarized in Table 7.

Table 7. Selected No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of naled from subchronic toxicity studies.

Species/route/duration	Plasma ChE ^a			RBC ChE ^a			Brain ChE ^a			Other Effects			Ref ^b
	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects	
Rat gavage 1/dx4w	1.0	10	63-52	1.0	10	72-74	1.0	10	47-48	1.0	10	Cholinergic signs (tremors and others after the 6 th dose)	1
Rat gavage 1/dx13w	-			-			-			2.0	10	Tremors (females)	2
Rat ^c gavage 102d	-			-			-			<2 2	2 6	Parental-↓ body weight Pup-↓ survival, body weight, litter size	3*
Rat ^d gavage gestation d6 to 19	-			-			-			10 >40 ^e	40	Parental-↓ body weight Fetal-no effects	4*
Rat inhale 6h/dx5d/w x3w	<0.58	0.58	70-52	<0.58	0.58	44-61	<0.58	0.58	78-72	<0.58	0.58	Cholinergic signs, nasal and eye damage	5
Rat inhale 6h/dx5d/w x13w	0.039	0.22	81-92	0.039	0.22	83-86	0.22	1.0	54-62	<0.039	0.039	Nasal pathology	6
Rat dermal 6h/dx5d/w X4w	1	20	47-54	1	20	75-79	1	20	40	<1	1	skin inflammation, necrosis	7
Rabbit ^d gavage gestation d7 to 19	-			-			-			2	10	Maternal-tremors, salivation in 10 days	8
Rabbit ^d gavage gestation d7 to 19	-			-			-			>8 ^e	-	no effects	9*
Dog gavage 1dx4w	0.2	1.0	73-81	0.2	1.0	70-110	1.0	5	86-52	1.0	5	altered blood chemistry	10

a/ Abbreviations: ChE= cholinesterase, RBC= erythrocyte, inhal= inhalation, h= hours, d= days, w= weeks, y= years, % C= % of control values (male-female) to indicate inhibition at the LOEL, -= data not available. The study selected for risk characterization is indicated in bolded-type.

b/ * after the reference number indicates the study was considered acceptable by DPR according to FIFRA guidelines. References: 1. Lough *et al.*, 1981; 2. Lamb, 1994a; 3. Bio/dynamic, Inc., 1985; 4. Science Applications, Inc., 1984; 5. Rittenhouse, 1985b; Wong, 1986; 6. Griffis, 1986; 7. Rausina and Zimmerman, 1986; 8. Hardy, 1985; 9. FitzGerald, 1985; 10. Batham *et al.*, 1983.

c/ Studies are described in **III.F. REPRODUCTIVE TOXICITY**.

d/ Studies are described in **III.G. DEVELOPMENTAL TOXICITY**.

e/ Highest dose tested.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: Naled caused inhibition of plasma, erythrocyte, and brain ChE activities in rats and dogs. Chronic exposure to naled resulted in mild testicular degeneration, focal mineralization of the spinal cord, and mild splenic siderosis in dogs. At sublethal doses, naled caused decreased body weight gain in mice. Naled was not considered oncogenic in rodents or dogs.

III.D.1. Gavage - Rat

Sprague-Dawley rats (65/sex/group at the start, and reduced to 55/sex/group after 8 weeks) were treated with naled (93.3% pure; 0, 0.2, 2.0, or 10.0 mg/kg/day) daily by gavage for 102 weeks and 105 weeks, respectively, for females and males (Batham *et al.*, 1984; Slagowski, 1987). The survival rates between the control and treated groups were similar, with about 50% of the animals in each group dying from 8 weeks to the end of the study. There were no biologically significant findings in the blood chemistry analysis, body weights, food consumption, organ weights, and macroscopic and histological examination of the tissues (except mammary tumors). There were no overt clinical signs, but slight tremors were observed occasionally after dosing between weeks 36-45 in 1-3 females of the 10 mg/kg/day group. Plasma, erythrocyte, and brain ChE activities showed treatment-related inhibition, though the inhibition of plasma and brain ChE activities were greater than that for erythrocyte ChE (Table 8). The magnitude of plasma or erythrocyte ChE inhibitions when measured at 0.5, 1, 1.5, and 2 years was similar. The NOELs were 0.2 mg/kg/day and 2 mg/kg/day for plasma and erythrocyte ChE inhibition after 0.5 year and 2 years, respectively. The NOEL was 0.2 mg/kg/day for brain ChE inhibition after 2 years. The only oncogenic finding was a slight increased incidence of mammary adenocarcinomas in male rats (Table 9); however, only the trend was statistically significance at $p \leq 0.05$ based on a dose-weighted chi-square trend test. Mammary tumors were also found in the females; however, the incidences were not related to treatment since they were higher in the controls than those in the treated groups. This study was considered acceptable by DPR according to FIFRA guidelines.

III.D.2. Gavage - Mouse

Charles River CD-1 mice (60/sex/group) were given naled (92.7% pure; 0, 3, 15, or 75/50 mg/kg/day) by gavage daily for 89 weeks (International Research and Development Corporation, IRDC, 1984). The highest dose was 75 mg/kg/day, but was reduced to 50 mg/kg/day at week 27 due to mortality (14 mice died). There was an interim sacrifice of 10 mice per sex per group at 52 weeks. No treatment-related effects on the appearance, behavior, food consumption, hematological determinations, organ weight, and macroscopic or microscopic changes were observed. The body weights of the male mice of all the treated groups showed only a slight decrease (97% of control values) though the trend was considered statistically significant. No oncogenic effects were reported. Cholinesterase activity was not measured. The NOEL for the study was 15 mg/kg/day, based on mortality at 75 mg/kg/day. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 8. The inhibition of cholinesterase activity in rats after chronic exposure to naled ^a.

Gender/ Dosage	Mean % Control ChE activity				
	Plasma		Erythrocyte		Brain
	0.5yr	2yr	0.5yr	2yr	2yr
MALES					
0.2 mg/kg/day	102	114	98	111	97
2.0	70**	71	67**	96	76**
10.0	46**	45*	58**	74	40**
FEMALES					
0.2 mg/kg/day	112	136*	96	97	99
2.0	76*	76	87*	73	76**
10.0	44**	50*	92	67**	41**

^{a/} Data from Batham *et al.*, 1984. Statistical significance from control values was * at $p \leq 0.05$, and ** at $p \leq 0.01$ was based on Dunnett's t test.

Table 9. The incidences of mammary tumors in rats after chronic exposure to naled ^a.

Gender/ Tumor types	Dosage (mg/kg/day)			
	0	0.2	2	10
MALES				
Fibroadenoma	1/44 (2%)	0/50 (0%)	0/49 (0%)	0/48 (0%)
Adenoma	0/44 (0%)	0/50 (0%)	0/49 (0%)	0/48 (0%)
Adenocarcinoma	0/44* (0%)	0/50 (0%)	1/49 (2%)	2/48 (4%)
Adenoma and/or adenocarcinoma	0/44* (0%)	0/50 (0%)	1/49 (2%)	2/48 (4%)
FEMALES				
Fibroadenoma	12/54 (22%)	17/44 (39%)	13/53 (25%)	21/55 (38%)
Adenoma	6/54 (11%)	5/44 (11%)	1/53 (2%)	3/55 (5%)
Adenocarcinoma	3/54 (6%)	2/44 (5%)	2/53 (4%)	1/55 (2%)
Adenoma and/or adenocarcinoma	9/54 (17%)	6/44 (14%)	3/53 (6%)	4/55 (7%)

^{a/} Data from Batham *et al.* (1984) and Slagowski (1987). Incidences were expressed as the number of animals bearing tumors per animals at risk. All animals with at least 50 weeks of exposure or alive when the first tumor was detected, whichever came first, were considered at risk. Level of statistical significance, $p \leq 0.05$ (*), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

III.D.3. Gavage - Dog

Beagle dogs (6/sex/group) were dosed with naled (91.4% pure; 0, 0.2, 2.0, or 20.0 mg/kg/day) by gavage daily for 1 year (IRDC, 1986; Slagowski, 1986). Clinical effects observed were dose-related increases in the incidences of soft stool/and or diarrhea, salivation, and emesis. Emesis occurred daily approximately 40 minutes post-dosing, and did not cause significant decreases in body weight gain or food consumption. The other effects were observed as early as the first week, and observations were reported in weekly intervals. One dog in the 20.0 mg/kg/day group was sacrificed on week 50 with weight loss and decreased food consumption probably due to ulcerative gastritis with fibrosis of the gastric mucosa. Cholinesterase activities were inhibited in a dose-related manner (Table 10). Erythrocyte ChE activity was inhibited to a greater extent than plasma or brain ChE activity. Increased length of exposure from 4 weeks to 1 year resulted in a slight increase (0-15%) in the inhibition of plasma and erythrocyte ChE activities. The NOEL for erythrocyte and brain ChE inhibition was 0.2 mg/kg/day.

Hematological parameters (mean erythrocyte, hemoglobin, hematocrit) of the 2.0 and 20.0 mg/kg/day groups were lower (10-25%) than those for controls after 3 months of treatment; the reduction was statistically significant for the majority and all of the measurements for the 2.0 and 20.0 mg/kg/day groups, respectively. Platelet counts were increased by 30-50% in those treated groups after 9 months of treatment. The mean absolute and relative weights of liver (both sexes) and kidneys (females) were increased and were statistically significant ($p \leq 0.05$). Microscopic examination of other organs showed mild testicular degeneration, focal mineralization of the spinal cord, and mild splenic siderosis (Table 11). The NOEL for overall effects was 0.2 mg/kg/day. No oncogenic effects were reported. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 10. The inhibition of cholinesterase activity in dogs after chronic exposure to naled^a.

Gender/ Dosages	Mean % Control ChE activity				
	<u>Plasma</u>		<u>Erythrocyte</u>		<u>Brain</u>
	4wk	1yr	4wk	1yr	1yr
MALES					
0.2 mg/kg/day	83	83	96	84	100
2.0	76*	65**	57*	42*	95
20.0	59**	56**	30*	19*	82**
FEMALES					
0.2 mg/kg/day	79*	70**	96	94	92
2.0	60**	52**	48**	42**	83*
20.0	60**	53**	24**	23**	71**

a/ Data from IRDC., 1986. Statistically significant from control values * at $p \leq 0.05$, and ** at $p \leq 0.01$ was based on Dunnett's t test.

Table 11. Selected systemic effects in dogs after chronic exposure to naled ^a.

Effects	Dosages (mg/kg/day)			
	0	0.2	2.0	20
MALES				
Spinal cord, lumbar mineralization	1/6 (17%)	3/6 (50%)	5/6* (83%)	4/6 (67%)
Spinal cord, thoracic mineralization	0/6 (0%)	1/6 (17%)	1/6 (17%)	1/6 (17%)
Spleen siderosis	0/6 + (0%)	0/6 (0%)	1/6 (17%)	2/6 (33%)
Testis degeneration	0/6 + (0%)	0/6 (0%)	2/6 (33%)	3/6 (50%)
FEMALES				
Spinal cord, lumbar mineralization	0/6 ++ (0%)	0/6 (0%)	1/6 (17%)	4/6* (67%)
Spinal cord, thoracic mineralization	0/6 (0%)	2/6 (33%)	0/6 (0%)	1/6 (17%)
Spleen siderosis	0/6 (0%)	0/6 (0%)	1/6 (17%)	1/6 (17%)

^{a/} Data from IRDC, 1986. NA= not applicable. Level of statistical significance, $p \leq 0.05$ (+,*) or $p \leq 0.01$ (++,), is indicated after each incidence. Significance at the control value was based on dose-weighted chi-square trend test, and pair-wise significance at the dosed groups was for the Fisher's Exact Test.

Table 12. The No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect levels (LOELs) of naled from chronic toxicity studies.

Species/route/duration	Plasma ChE ^a			RBC ChE ^a			Brain ChE ^a			Other Effects			Ref ^b
	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	%C	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects	
Rat gavage 102-105 weeks	2.0	10.0	45-50	2.0	10.0	74-67	0.2	2.0	76-76	2.0	10.0	slight tremors after dosing (females)	1*
Mouse gavage 89 weeks	-			-			-			15	75	mortality (after 27 weeks)	2*
Dog gavage 52 weeks	0.2	2.0	65-52	0.2	2.0	42-42	0.2	2.0	95-83	0.2	2.0	testicular degeneration, spinal cord mineralization, and splenic siderosis	3*

a/ Abbreviations: ChE= cholinesterase, RBC= erythrocyte, % C= % of control values to indicate inhibition at the LOEL, %C=% of control values (male-female) to indicate inhibition at the LOEL, -= data not available. The study selected for risk characterization is indicated in bolded-type.

b/ * after the reference number indicates the study was considered acceptable by DPR according to FIFRA guidelines. References: 1. Batham *et al.*, 1984; 2. IRDC, 1984; 3. IRDC, 1986.

III.E. GENOTOXICITY

Summary: Naled was not genotoxic in *in vitro* and *in vivo* genotoxicity studies. A summary of selected studies is presented in Table 13.

III.E.1. Gene Mutation

The mutagenicity of naled was studied in *in vitro* bacterial assays using *Bacillus subtilis* and *Salmonella typhimurium* (Shiau *et al.*, 1981). Naled (0, 5, 10, 25, or 50 $\mu\text{g}/\text{plate}$) was added to *Bacillus subtilis* strains TKJ5211 and TKJ6321 and *Salmonella typhimurium* strains TA1535 in the absence of S-9 homogenates from rat livers induced with Aroclor 1254. Increased numbers of revertants were observed for all strains. This study was unacceptable since there was insufficient information presented for evaluation as the data were presented only in a graph.

Naled (93.3% pure) was tested with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without Aroclor-induced rat liver preparation, and *E. coli* strain WP2 uvrA (Carver, 1988). The concentrations used in the first trial were 0, 0.003, 0.01, 0.033, 0.1, and 0.33 mg/plate , and in the second trial were 0, 0.01, 0.033, 0.1, 0.33, and 1.0 mg/plate . Although some colony counts were statistically significant, the results were considered negative because data were not reproducible and less than twice the spontaneous rate. This study was considered acceptable by DPR.

Several published studies showed conflicting evidence for mutagenicity in the Ames Assay; however, these studies were considered unacceptable by DPR due to insufficient experimental details. When naled was tested with TA100, TA98, TA1535, TA1537 and TA1538, *E. coli* WP2 with and without metabolic activation system, the result for naled was only indicated as “-” (Moriya *et al.*, 1983). While this study was deficient in providing details of the experiment, the result supports those conducted by Carver (1988). In an assay with TA100, the revertant rate was less than 2 times the background, a result generally considered equivocal for TA100 (Braun *et al.*, 1983). A “weak” response was reported for TA1535 (Hanna and Dyer, 1975). The cause of this response is unknown since the strain was tested in a saturated solution of naled previously incubated overnight at 45°C before test. Neither naled, DDVP, nor other metabolites were measured. In another assay with TA1535 and TA 100, the results were designated as “±”, a notation for ambiguous result by the authors (Byeon *et al.*, 1976).

III.E.2. Structural Chromosomal Aberration

A single dose of naled (92.0% pure; 55, 110, or 220 mg/kg for males; 55, 110, or 290 mg/kg for females) was given to Swiss albino mice (5/sex/group) by gavage (Machado, 1984). Bone marrow smears were made at 24, 48, and 72 hours after treatment. There was no significant increase in the number of micronucleated erythrocytes in any treated groups. Cholinergic signs (convulsions, decreased motor activity, salivation, lacrimation, tremors, weakness, oral and ocular discharge and death) occurred in the 220 mg/kg group, and one male in the 110 mg/kg dose group. This study was considered acceptable by DPR.

Sprague-Dawley rats (4/sex/group) were exposed to naled (purity not stated; 6.17, 20.57, or 61.7 mg/kg for females; 3.88, 12.93, or 38.8 mg/kg for males) in a single dose by

gavage (Carver, 1983). Rats were sacrificed at 6, 24, or 48 hours, and bone marrow cells were examined. There was no significant increase in the number of chromosomal aberrations. This study was considered acceptable by DPR.

III.E.3. Other Genotoxic Effects

Primary rat hepatocytes from male Sprague-Dawley rats were exposed to naled (93.3% pure; 0, 1.0, 2.5, 5.0, 7.5, 10, or 50 $\mu\text{g/ml}$) for 18 hours and tested for unscheduled DNA synthesis (Thilagar, 1988). There was no significant increase in ^3H -thymidine incorporation into hepatocytes treated with naled. This study was considered acceptable by DPR.

C57Bl/6 female mice (120-181/group) were mated to T-strain male mice and then given naled (92.5% pure; 0, 3, 20, or 150 mg/kg/day) by gavage on gestation days 8.5 to 12.5 (Litton Bionetics, Inc., 1984). The strains of parental mice were selected because their mating would result in offspring with melanocyte precursor cells that were heterozygous at 5 specific coat color loci. Mutation at any wild-type allele in these 5 coat color loci would result in mosaic patches on the neonate fur. Ethyl nitrosourea was the positive control of the assay. There was no evidence of mutation in mice treated with naled. This study was unacceptable by DPR because it was not an FIFRA guideline study.

Table 13. Selected genotoxicity studies of naled.

Test types	Route/Exposure Duration	Dose ^a	Effects/Comments	Ref. ^b
<u>1. Gene Mutation</u>				
<i>Salmonella typhimurium</i> TA100, TA98, TA1538, TA1537, TA1536, TA1535 (revertant frequency)	plate	1 mg/plate	-	1*
<u>2. Structural Chromosomal Aberrations</u>				
mouse (bone marrow micronucleus test)	gavage/one dose	290 mg/kg	-	2*
rat (bone marrow chromosomal aberrations)	gavage/one dose	61.7 mg/kg	-	3*
<u>3. Other Genotoxic Effects</u>				
rat hepatocytes (unscheduled DNA synthesis)	plate/18 hours	50 µg/ml	-	4*
mouse (mosaic skin patches)	gavage/ gestation days 8.5 to 12.5	150 mg/kg/day	-	5

a/ The highest dose tested with a negative response indicated as (-).

b/ * after the reference number indicates the study was considered acceptable by DPR according to FIFRA guidelines.
References: 1. Carver, 1988; 2. Machado, 1984; 3. Carver, 1983; 4. Thilagar, 1988; 5. Litton Bionetics, Inc., 1984.

III.F. REPRODUCTIVE TOXICITY

Summary: In a two-generation rat reproductive toxicity study with naled, the only significant parental effect was a dose-related decrease in body weights of all F₁ males during both pre- and post-mating periods. The effects on the pups included decreased survival, body weight, and number of pups at birth.

III.F.1. Gavage - Rat

CD rats (15 males and 30 females/group) were given naled (91.0% pure; 0, 2, 6, or 18 mg/kg/day) by gavage daily for 102-days (pre-mating period, mating, gestation, and lactation period) (Bio/dynamic Inc., 1985). No clinical signs were reported. The reproductive performance of the treated groups was not different from that of the control. The only significant parental effect was a dose-related decrease in the body weights of all treated F₁ males during both pre- and post-mating periods, and the LOEL was 2 mg/kg/day. The difference in the treated and control body weights was statistically significant ($p \leq 0.05$) and was of a similar magnitude from week 30 to 62 of the study (Table 14). There was no effect on food consumption. There was a significant decrease (71-75% of control) in the total number of live pups for only the F_{2b} litter of the 6 and 18 mg/kg/day groups. The mean pup body weights of the F₁ litters from treated parents were significantly less than the controls (82-85% of control) only on days 8 and 12, but not ($\geq 86\%$ of control) on days 4 and 21 of lactation. There was no significant decrease in the body weights of the F₂ litters. The total number of pups at birth was significantly decreased only for the F_{2b} litters. The NOEL for reproductive toxicity in the pups was 2 mg/kg/day based on decreased survival, body weight, and number of pups at birth (Table 14). This study was considered acceptable by DPR according to FIFRA guidelines.

Table 14. The effects of naled in rats in a two-generation reproductive toxicity study ^a.

Effects			Dosages (mg/kg/day)		
			2	6	18
<u>Adult F₁ males body weights</u>					
week 30 - week 62			87-90*	90-93*	84-92*
<u>Total number of pups at birth</u> F ₁ -F _{2b}			104	71*	75*
<u>Mean pup wt (g)</u>	F ₀ -F ₁	day 8	85	82*	84*
		day 12	83*	84*	84*
<u>Total live pups</u> F ₁ -F _{2b}		day 4-12	107	67-68**	84
		day 21 males	93	47**	85
		females	119	90	88

^a/ Data from Bio/dynamic Inc., 1985. Values are % of controls. Levels of significance were * for $p \leq 0.05$, and ** for $p \leq 0.01$ based on Dunnett's t test.

III.G. DEVELOPMENTAL TOXICITY

Summary: Pregnant rats and rabbits showed cholinergic signs after naled exposure. In the presence of maternal toxicity, decreased fetal body weight was the only developmental effect.

III.G.1. Gavage - Rat

Naled formulation (Fly Killer D with 36% naled; 0, 25, 50, or 100 mg/kg/day) was given by gavage to pregnant Wistar rats (15-19/group) from gestation days 6 to 15 (Khera *et al.*, 1979). No adverse effects were reported. This study was considered unacceptable by DPR because there was insufficient information for evaluation.

Sprague-Dawley rats (30/group) were exposed to naled (91.4% pure; 0, 2, 10, or 40 mg/kg/day) by gavage from gestation days 6 to 19 (Science Applications, Inc., 1984). Clinical signs were observed intermittently during the dosing period primarily in the 40 mg/kg/day group, and included tremors, clear discharges from the mouth, dyspnea, and hypoactivity. Tremors and salivation were observed after 1 day and 2 days, respectively, of dosing, and affected the majority of the animals. The corrected mean body weight change (body weight minus gravid uterus and day 6 body weights) of this group was significantly ($p \leq 0.05$) lower (71% of control) than that for the control group. The NOEL for maternal toxicity was 10 mg/kg/day based on cholinergic signs and reduction of body weight gain. No significant developmental effects were observed, and the NOEL was ≥ 40 mg/kg/day. This study was considered acceptable by DPR according to FIFRA guidelines.

III.G.2. Gavage - Rabbit

In a pilot study, New Zealand white rabbits (8/group) were given naled (92.5% pure; 0, 0.2, 2, 10, or 40 mg/kg/day) by gavage on gestation days 7 to 19 (Hardy, 1985). Because toxicity (death and cholinergic signs) in 4 animals dosed with 40 mg/kg after 1 day of dosing, the dose was reduced to 20 mg/kg. However, this group was sacrificed after 3 days due to severe cholinergic signs and death. For the 10 mg/kg/day group, tremors, wobbling motion, loss of coordination, hypersensitivity to tactile and auditory stimuli, salivation, rapid breathing, and dyspnea were observed. For this group, the effects were observed after 10 days of treatment. The acute NOEL for maternal toxicity was 10 mg/kg/day. The developmental effect was a decrease, 87% and 68% ($p < 0.06$) of control values, respectively, in the mean fetal body weights of the 2 and 10 mg/kg/day groups. The mean body weights were 44.9 ± 6.4 g, 35.8 ± 12.5 g, 39.1 ± 4.21 , and 30.5 ± 5.8 g for control, 0.2, 2, and 10 mg/kg/day, respectively. No other developmental effects were observed. The developmental NOEL was 2 mg/kg/day.

In the definitive study, New Zealand white rabbits (20/group) were given naled (92.5% pure; 0, 0.2, 2, or 8 mg/kg/day) by gavage on gestation days 7 to 19 (FitzGerald, 1985). Females were sacrificed on day 29 of gestation. The mean fetal body weights of all treated groups were slightly (5-8%; statistically not significant) higher than those of the control group. No maternal or fetal toxicity was observed and the NOEL was determined to be ≥ 8 mg/kg/day. This study was considered acceptable by DPR according to FIFRA guidelines.

III.H. NEUROTOXICITY

Summary: Naled caused acute neurotoxicity in rats as determined by a Functional Observation Battery and motor activity evaluations. In hens, there was significant inhibition of brain ChE activity and axonal degeneration of the spinal cord, but no delayed neurotoxicity.

III.H.1. Oral - Rat

In a range-finding study, Sprague-Dawley rats were given a single dose of technical naled (92.7% pure) (Lamb, 1994b). The doses studied were: 0.5, 1, 5, 25, 35, 50, 75, 100, 125, 150, 300, 450, 500, 550, and 600 mg/kg with 1 to 4 rats per sex per group. Mortality (death in one or all animals in the group) was observed at doses of 450 mg/kg or higher. At the lower doses, the predominant clinical signs included gait alterations, whole body tremors, reduced forelimb/ hindlimb grasp, exophthalmus and splayed hindlimbs, salivation, and rales. The NOEL for clinical signs was 35 mg/kg. Constricted pupils were observed sporadically in some animals in all groups dosed at 0.5, 1, 5, and 35 mg/kg, but not at 25 mg/kg. There was no control group, and too few animals in each treated group.

Sprague-Dawley rats (12/sex/group; 16/sex/group at the high dose) were given a single dose of technical naled (92.7% pure; 0, 25, 100 or 400 mg/kg) by gavage for the determination of acute neurotoxicity (Lamb, 1993a). Mortality occurred at the 400 mg/kg group as 3 males and 8 females died between 45 minutes after dosing and the next day. The average body weight (day 0 to 7) of this group was also significantly lower (64% of control, $p \leq 0.01$) than the control. 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 and retching). Effects observed in the Functional Observational Battery at ≥ 25 mg/kg included: tremors, exophthalmus, decreased rearing, decreased tail pinch response, and reduced hindlimb resistance (Table 15). While these effects were not statistically significant at 25 mg/kg, they were considered toxicologically significant because of increased incidences or severity at higher doses. At ≥ 100 mg/kg, there were significant effects in sensorimotor activity, neuromuscular, physiological, autonomic, excitability domains in both sexes. These effects were reversed by day 14 to control level. In addition to the observations noted in Table 15, the average body temperature and mean motor activity were lower in the 100 and 400 mg/kg groups. These effects were observed primarily on the day of dosing as there was no remarkable difference in the observations on day 7 or 14 between the control and the treated groups. The acute LOEL was 25 mg/kg for effects observed in the Functional Observational Battery on the day of exposure. This study was considered acceptable by DPR according to FIFRA guidelines.

III.H.2. Additional Studies

A 13-week neurotoxicity study (Lamb, 1994a) is described under **III.C. SUBCHRONIC TOXICITY**.

Table 15. Functional Observational Battery results for rats after acute exposure to naled ^a.

Observations	Treatment Level (mg/kg)							
	Males				Females			
	0	25	100	400	0	25	100	400
Animals Tested	12	12	12	13	12	12	12	8
Home Cage Observations								
<u>Posture:</u>								
Flattened, limbs extended	0	0	4	11*	0	0	8	7*
Alert	3	6	0	0	5	2	0*	0
<u>Convulsions-Clonic:</u>								
Absent	12	12	3*	1*	12	11	0*	0*
Clonic tremors of limbs	0	0	5*	3	0	1	3	0
Whole body tremors	0	0	4	10*	0	0	9*	8*
<u>Tremors:</u>								
None	12	12	3*	1*	12	11	0*	0*
Slight	0	0	7*	6*	0	1	8*	1
Moderate	0	0	2	5*	0	0	3	6*
Marked	0	0	0	1	0	0	1	0
Handling Observations								
<u>Salivation:</u>								
None	12	12	10	6*	12	12	6*	0*
Slight	0	0	2	2	0	0	3	1
Severe	0	0	0	5*	0	0	3	7*
<u>Eye Prominence:</u>								
Normal	12	12	11	11	11	10	8	3*
Exophthalmus	0	0	1	2	1	2	4	5*

^{a/} Data from Lamb, 1993a. All data were for day 0 (day of exposure), unless otherwise indicated.
 * Significantly different from control at $p < 0.05$ using Fisher's Exact Test.

Table 15. Functional Observational Battery results for rats after acute exposure to naled (continued)^a.

Observations	Treatment Level (mg/kg)							
	Males				Females			
	0	25	100	400	0	25	100	400
Animals Tested	12	12	12	13	12	12	12	8
Open Field Observations								
<u>Mobility:</u>								
Normal	12	12	6*	4*	12	12	8	1*
Moderately impaired	0	0	2	6*	0	0	2	5*
<u>Gait:</u>								
Normal	11	11	1*	2*	9	9	0*	0*
Ataxia, sway, rock & lurch	1	1	11*	9*	2	2	9*	4
<u>Convulsions-Clonic:</u>								
Absent	12	12	6*	2*	12	12	4*	0*
Whole body tremors	0	0	4	9*	0	0	7*	8*
<u>Tremors:</u>								
None	12	12	6*	2*	12	12	4*	1*
Slight	0	0	4	5*	0	0	2	1
Moderate	0	0	2	4	0	0	4	5*
Marked	0	0	0	2	0	0	2	1
<u>Gait Score:</u>								
Normal	11	11	1*	2*	9	9	0*	0*
Slight impairment	1	1	9*	3	3	3	5	0
Much impaired	0	0	1	7*	0	0	4	5*
Very impaired	0	0	1	0	0	0	2	1
Severe	0	0	0	1	0	0	1	2
<u>Arousal:</u>								
Very low: stupor, coma	0	0	0	1	0	0	0	0
Low: somewhat stuporous	0	0	0	1	0	0	1	0
Rearing (mean)-Day 0	8.4	7.5	3.2++	1.7++	9.8	9.5	2.8++	0.5++
Day 7	8.4	7.4	7.0	7.5	10.3	8.2	9.6	5.4++

^{a/} Data from Lamb, 1993a. All data were for day 0 (day of exposure), unless otherwise indicated.
 * Significantly different from control at p < 0.05 using Fisher's Exact Test.
 ++ Significantly different from control at p<0.01 using Dunnett's Test.

Table 15. Functional Observational Battery results for rats after acute exposure to naled (continued)^a.

Observations	Treatment Level (mg/kg)							
	Males				Females			
	0	25	100	400	0	25	100	400
Animals Tested	12	12	12	13	12	12	12	8
<u>Sensory Observations</u>								
<u>Approach Response:</u>								
No reaction	0	0	2	5*	0	0	3	6*
Slow	11	12	10	8	10	11	8	2*
<u>Touch Response:</u>								
No reaction	0	0	0	4	0	0	2	5*
<u>Startle Response:</u>								
No reaction	0	0	0	2	0	0	1	2
More energetic response	6	3	5	6	11	11	7	3*
<u>Tail Pinch Response:</u>								
No reaction	0	0	1	6*	0	0	4	5*
More energetic response	5	2	1	1	7	4	1*	1
<u>Pupil Response:</u>								
No pupil response	2	2	10*	5	1	2	9*	7*
Pupil response present	10	10	2*	8	11	10	3*	1*
<u>Air Righting Reflex:</u>								
Normal	12	12	8	8*	11	11	6	3*
Slightly uncoordinated	0	0	3	3	1	1	3	1
Lands on side	0	0	1	1	0	0	1	3*
Lands on back	0	0	0	1	0	0	2	1
<u>Neuromuscular Observations:</u>								
<u>Hindlimb Extensor Strength:</u>								
Reduced hindlimb resistance	0	0	6*	5*	0	1	4	5*
Hindlimb resistance present	12	12	6*	7*	12	11	6*	2*

^{a/} Data from Lamb, 1993a. All data were for day 0 (day of exposure), unless otherwise indicated.
^{*} Significantly different from control at p < 0.05 using Fisher's Exact Test.

III.H.2. Oral - Chicken

In a range-finding study, domestic hens (4/group) were given naled (91.7% pure; 0, 2, 4, 8, or 16 mg/kg/day) orally for 7 days (Beavers and Foster, 1994a). Hens in the high dose group died after the second dose while 2 of 4 hens in the 8 mg/kg/day group died either on day 1 or day 4. Clinical signs (reduced reaction to external stimuli, wing droop, loss of coordination and lower limb weakness) were observed in hens at ≥ 4 mg/kg/day; the NOEL was 2 mg/kg.

In the definitive study, domestic hens (10/group) were given naled (91.7% pure; 0, 0.5, 2.0, or 4.0 mg/kg/day) orally for 28 days and followed by an observation period of 21 days (Beavers and Foster, 1994b). Additional hens (4/group) were treated for the determination of brain ChE and brain and spinal cord neuropathic target esterases (NTE). Delayed neurotoxicity was observed in hens given tri-ortho-cresyl phosphate (TOCP, 35 or 45 mg/kg/day), the positive control. No mortality or clinical signs was observed in the naled groups. A transient decrease in the mean body weight and mean feed consumption was observed in the 4.0 mg/kg/day group during the first week of exposure. Brain ChE activities of the 2.0 and 4.0 mg/kg/day groups were reduced significantly ($p \leq 0.01$) to 71% and 58% of control values, respectively. No depression of neurotoxic esterases or lesions were found in the brain, spinal cord, and sciatic and tibial nerves of the 4.0 mg/kg/day hens. The NOEL was 0.5 mg/kg/day with brain ChE inhibition at ≥ 2.0 mg/kg/day. This study was considered acceptable by DPR according to FIFRA guidelines.

Domestic hens (40 hens) were given a single dose of naled (90% pure; 0 or 42 mg/kg) by gavage, followed by a repeat dose after 21 days (Redgrave *et al.*, 1990). Naled-treated hens were protected with atropine sulphate (10 mg/kg) and 2-PAM (50 mg/kg) prior to dosing. A satellite group was treated with naled at 0, 8 (5 hens/group) and 42 mg/kg (5 hens/group in 2 groups) for assessing brain ChE and NTE. TOCP (500 mg/kg) was used as the positive control. No ataxia or depression of brain NTE was observed. Brain ChE inhibition (45% of control) was significant ($p \leq 0.01$) only for the second 42 mg/kg/day group. Brain ChE activity was inhibited (74-77% of control; not statistically significant) in the 8 mg/kg/day and the first 42 mg/kg/day groups. Axonal degeneration in the spinal cord was observed in the 42 mg/kg group. This study was considered acceptable by DPR according to FIFRA guidelines.

Atropinized domestic hens were given naled (stated not purity) at 117 mg/kg in a single gavage dose (Cox *et al.*, 1978). No delayed neurotoxicity was observed. This study was unacceptable to DPR (no repeat dosage given in absence of response to first dose).

III.I. HUMAN STUDIES

An aerial applicator was exposed to naled (1 ounce/acre) while maintaining the spray plane for mosquito control (Mick *et al.*, 1970). Through a hole in the glove, his skin was exposed and resulted in erythema and followed with blisters, indicating contact dermatitis.

Nine women were exposed to a mixture of naled, captan, and dicofol used to treat a chrysanthemum field (Edmundson and Davies, 1967). Four of those women affected were examined four days after the occurrence. Patch tests showed that only naled induced a positive response (in 3 of 4 women) indicating that naled was a skin sensitizer.

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

IV.A.1. Introduction

The derivation of the critical no-effect levels to be used for risk characterization of naled is discussed in this section. Details of the studies are in **III. TOXICOLOGY PROFILE**. Only those endpoints which are considered of toxicological significance are selected for use in the risk characterization. The no-effect levels may be expressed as NOELs or NOAELs (No-Observed-Adverse-Effect Level). Summary tables for selected toxicity studies considered for critical NOELs are in Tables 4 (acute), 7 (subchronic), and 12 (chronic) respectively.

The non-oncogenic endpoints used in this assessment were cholinergic signs and brain ChE inhibition. The inhibition of brain ChE is considered an adverse effect (U.S. EPA, 1990; Brimijoin, 1992). The correlation of brain ChE inhibition and cholinergic signs depends on the inhibitor and how these endpoints were measured. For example, certain cholinergic signs may be due to inhibition in specific regions of the brain (Nieminen *et al.*, 1990). The level of brain ChE inhibition required to produce these effects may not be representative if the activity is measured in the whole brain. Another consideration is that brain ChE activity is usually measured at the end of the study whereas cholinergic signs may be observed at various time points during the study. On the other hand, the inhibition of plasma ChE activity is generally considered an indication of exposure and not necessarily of toxicity. *In vitro* studies with human plasma showed that naled caused aging of ChE (Mason *et al.*, 1993). The half-lives were 23.6 hours and 5.5 hours at 37°C and 22°C, respectively. After inhibition, a maximum of 25% of the ChE activity was recovered by spontaneous reactivation.

With naled, the NOEL and LOEL for cholinergic signs were the same as those for plasma, erythrocyte, and brain ChE inhibition (Lough *et al.*, 1981; Rittenhouse, 1985b) after short-term exposure (Table 7). In a rat chronic toxicity study, the NOEL (0.2 mg/kg/day) for brain ChE was lower than those for cholinergic signs and plasma and erythrocyte ChE inhibition (Batham *et al.*, 1984) (Table 12).

IV.A.2. Selection of Critical NOELs

The primary routes of exposure for naled were dermal (occupational and residential) and oral (dietary) routes.

IV.A.2.a. Acute Toxicity

For the derivation of the critical NOEL, studies from inhalation exposures were not used because inhalation exposure was a minor component of the total exposure (**Volume II.**). For acute occupational and residential exposures, the average daily dose for inhalation was ≤ 0.68 ug/kg/day (0.03 to 3.8% of total exposure). The limited information on the effects of naled in animals after whole-body inhalation exposure showed the lowest NOEL was 1.29 ug/L (0.22 mg/kg/day) for salivation and respiratory sound in rats after 1-2 exposures to 5.8 ug/L (1.0 mg/kg/day) naled (Griffis, 1986). In another study, the NOEL was < 0.58 mg/kg/day for more

than 20% inhibition of plasma and erythrocyte ChE activity in rats after 5 exposures (whole body) to 0.58 mg/kg/day naled (Rittenhouse, 1985b; Wong, 1986).

To address dermal exposure, dermal toxicity studies were first considered. Of the three rabbit acute dermal toxicity studies reviewed (Narcisse and Cavalli, 1971; Bullock and Narcisse, 1975; Brorby, 1985), the most relevant one was by Brorby (1985) as it provided a detailed description of the effects. In this study, the dermal NOEL for local effects was 125 mg/kg as the skin was described as brown and thickened with necrosis, fibrosis, hyperkeratosis, acanthosis, and necrosis. Using a default factor of 10 for the extrapolation of a NOEL from a LOEL, the estimated NOEL for local effects was 12.5 mg/kg. For clinical signs in this study, the LOEL was also 125 mg/kg with diarrhea, ocular and nasal discharges, and decreased motor activity observed in rabbits within 3 hours of dermal exposure. Using a default factor of 10 to estimate the NOEL and another default factor of 50% to account for absorption, the adjusted dermal estimated NOEL for clinical signs was 6.25 mg/kg. As a reference, the dermal absorption for DDVP is 13% (Jeffcoat, 1990); however, DDVP is more volatile than naled.

The acute oral neurotoxicity study in rats (Lamb, 1993a) was also considered to address the dermal exposure because a Functional Observation Battery was used to evaluate the potential neurotoxicity from cholinesterase inhibition. At 25 mg/kg/day (the LOEL and the lowest dose tested), tremors, exophthalmus, decreased rearing, decreased tail pinch response, and reduced hindlimb resistance were observed (Table 15). The estimated NOEL (ENEL) was 2.5 mg/kg/day based on the LOEL of 25 mg/kg/day with a default factor of 10 for the extrapolation of the NOEL from a LOEL (Dourson and Stara, 1983). This ENEL was not adjusted for absorption since pharmacokinetic studies showed that the absorption was 100% by the oral route. As a comparison, the lowest acute oral NOEL for DDVP was 0.5 mg/kg/day for cholinergic signs (tremors, salivation, neuromuscular deficits) in rats (Lamb, 1992; Lamb, 1993b).

The LOEL from this study (Lamb, 1993a) was of similar magnitude as those observed in pregnant rats (40 mg/kg/day) and pregnant rabbits (20 mg/kg/day) for cholinergic signs (Science Applications, Inc., 1984; Hardy, 1985). While the NOELs of these latter studies were established at 10 mg/kg/day, the severity of the effects indicated that pregnant rats and rabbits were more sensitive than non-pregnant animals. Therefore, it is possible that neurotoxicity would be observed at 10 mg/kg/day if the FOB was administered to the pregnant animals.

Since the ENEL from the oral study (Lamb, 1993a) was based on the Functional Observation Battery, a test designed to detect neurotoxicity, this ENEL of 2.5 mg/kg/day was selected as the critical NOEL for the risk assessment of dermal and oral exposures. The use of this NOEL also addressed potential localized effects to the skin since it is lower than the estimated dermal NOEL of 12.5 mg/kg for local effects (Brorby, 1985).

IV.A.2.b. Subchronic Toxicity

There is no seasonal dietary exposure because naled is used on many commodities available throughout the year. For occupational and residential exposures, the critical NOEL was determined from a dermal toxicity study as the most relevant route of exposure. In a 4-week dermal toxicity study, the NOEL for systemic effects was 1 mg/kg/day for plasma, erythrocyte, and brain ChE inhibition at 20 and 80 mg/kg/day (Table 6) (Rausina and

Zimmerman, 1986). When adjusted for the default absorption factor of 50% and amortized for the week (5 days/ 7 days), the adjusted NOEL was 0.36 mg/kg/day. In comparison, the NOELs from short-term oral toxicity were higher than that for the above study (Table 7). The lowest NOEL was 1.0 mg/kg/day for the inhibition of brain ChE in the rat (47-48% of control) (Lough et al., 1981) and in the dog (52% of control) (Batham et al., 1983).

For local effects, the LOEL was 1.0 mg/kg/day as inflammation and necrosis were noted for this dose in the female rats (Rausina and Zimmerman, 1986). Using a default factor of 10, the estimated NOEL was 0.1 mg/kg/day. The dose was not adjusted for absorption since it was for direct effects on the application site.

IV.A.2.c. Chronic Toxicity

There were no chronic inhalation or dermal toxicity studies; therefore, chronic oral studies were used to determine the critical NOEL for chronic exposure.

For non-oncogenic effects, the critical chronic NOEL was 0.2 mg/kg/day for brain ChE inhibition in both rats ((Batham *et al.*, 1984; Table 8) and dogs (IRDC, 1986; Table 10). This level was also the NOEL for plasma ChE and RBC ChE inhibition and lesions (testicular degeneration, spinal cord mineralization, and splenic siderosis) observed in dogs at 2 mg/kg/day; IRDC, 1986). At higher naled concentrations, tremors were observed in female rats at 10 mg/kg/day (Batham *et al.*, 1984) and mortality in mice at 75 mg/kg/day after 27 weeks of exposure (IRDC, 1984). The critical NOEL (0.2 mg/kg/day) for naled was higher than the NOEL of 0.05 mg/kg/day for DDVP inhibition of brain ChE inhibition in dogs (Markiewicz, 1990).

IV.A.2.d. Weight of Evidence for Oncogenicity

Bioassays of naled did not provide sufficient evidence in animal studies to support the generation of the cancer potency (the slope of the dose-response relationship at the low dose range) for a quantitative characterization of the risk for lifetime exposure to naled. In the chronic study with Sprague-Dawley rats, the only noteworthy tumor was dose-related mammary gland adenocarcinomas in the males. However, the increased incidences were not statistically different from the control incidence (Table 9). Mammary gland adenocarcinoma is a rare tumor type in the male rat with a historical control rate of 0.8% for the conducting laboratory (Lawyer, 1988), compared to the 0% for the concurrent control. There was no increased incidences of tumors in the mouse oncogenicity study.

Furthermore, there was no evidence of naled interaction with macromolecules. Naled was negative in almost all available genotoxicity studies including two (*in vitro* unscheduled DNA synthesis in hepatocytes and *in vivo* chromosomal aberration) conducted with Sprague-Dawley rats, and *in vitro* bioassays with and without metabolic activation.

Results from oncogenicity studies with structurally-related compounds also indicated that naled was unlikely to be oncogenic at low doses (Table 16). DDVP, at doses similar to those used in the naled studies, showed limited evidence of oncogenicity. In the rat bioassay with DDVP, several tumor types (pancreatic adenoma, mammary gland tumors, and mononuclear cell leukemia) were observed in the Fischer rat (Chan, 1989). However, the finding of pancreatic adenoma in male rats was attributed to the use of corn oil as the vehicle and was considered a factor in the increased incidences. The incidence of mammary gland fibroadenoma was elevated only in the low dose female group. In contrast to naled, mammary gland adenomas/adenocarcinomas were not found in the treated males while the incidences for the treated females were similar to the controls. Mononuclear cell leukemia was the only systemic effect determined to be clearly related to DDVP exposure. *In vitro* genotoxicity studies indicated a potential for DDVP to induce DNA and genetic damage in some bacterial and mammalian cell systems. DPR concluded that the evidence was sufficient, though limited, to support the evaluation of DDVP for oncogenicity (Lim *et al.*, 1996). The maximum likelihood estimates and the 95% upper confidence limit for mononuclear cell leukemia were 0.20 and 0.35 mg/kg/day⁻¹, respectively, in terms of human exposure.

U.S. EPA also classified DDVP as a potential oncogen. In a recent meeting, the U.S. EPA SAP concluded that mononuclear cell leukemia was not relevant to humans as it is a common tumor type limited to Fischer 344 rats (Lewis, 1998a). The SAP also considered the pancreatic adenomas to be associated with the corn oil treatment. Based on the finding of forestomach tumors as a result of chronic irritation in mice (Chan, 1989), the SAP concluded that DDVP was a weak oncogen.

Results from oncogenicity studies conducted with trichlorfon also showed that DDVP as a metabolite, has weak oncogenic activity. At concentrations many-fold higher than those used with DDVP (2.9 and 5.7 mg/kg/day) and naled (0.2 to 10 mg/kg/day), trichlorfon (158.9 mg/kg/day) increased the incidences of mononuclear cell leukemia (female), renal tubular adenoma (males), and alveolar and bronchiolar adenoma and carcinomas (both sexes) in Fischer 344 rats. The relevancy of the mononuclear cell leukemia with respect to human exposure has previously been discussed. The increased incidences of renal tubular adenoma, and alveolar/bronchiolar adenoma and carcinoma in the male rats were not statistically significant and were within the range of National Toxicology Program historical control rates (0 to 6%, 0 to 4%, and 0 to 14%, respectively), for this strain of rats. In the mouse study with trichlorfon, increased incidence (not statistically significant) of mammary gland tumors was observed only at the highest dose (2700 ppm, 405 mg/kg/day assuming a consumption rate of 15% of the body weight). The dose-response relationship was, however, non-linear.

Dichloroacetic acid was the only metabolite of naled that showed strong evidence of oncogenicity. U.S. EPA classification for dichloroacetic acid is B2. Liver tumors were observed in rats and mice given >0.5 g/L (~40 mg/kg/day) in the drinking water (DeAngelo *et al.*, 1991 and 1996). The mechanism for tumors was hypothesized to be due to lipid peroxidation. Since the dose required to induce tumor formation is much higher than that likely to be produced *in vivo* after naled exposure, these results alone did not provide sufficient evidence to support further characterization of the oncogenicity potential of naled.

Table 16. Oncogenic effects of naled and related compounds.

	Species/ route	dose (mg/kg/day)	Dosage/ Effects/incidences	Ref ^a																																																				
Naled gavage	Sprague- Dawley rats	0, 0.2, 2, 10	<table><tr><td></td><td>0</td><td>0.2</td><td>2</td><td>10</td></tr><tr><td colspan="5">Mammary gland fibroadenoma</td></tr><tr><td>M</td><td>1/44 (2%)</td><td>0/50</td><td>0/49</td><td>0/48</td></tr><tr><td>F</td><td>12/54 (22%)</td><td>17/44 (39%)</td><td>13/53 (25%)</td><td>21/55 (38%)</td></tr><tr><td colspan="5">Mammary gland adenoma and/or adenocarcinoma</td></tr><tr><td>M</td><td>0/44+</td><td>0/50</td><td>1/49 (2%)</td><td>2/48 (4%)</td></tr><tr><td>F</td><td>9/54 (17%)</td><td>6/44 (14%)</td><td>3/53 (6%)</td><td>4/55 (7%)</td></tr></table>		0	0.2	2	10	Mammary gland fibroadenoma					M	1/44 (2%)	0/50	0/49	0/48	F	12/54 (22%)	17/44 (39%)	13/53 (25%)	21/55 (38%)	Mammary gland adenoma and/or adenocarcinoma					M	0/44+	0/50	1/49 (2%)	2/48 (4%)	F	9/54 (17%)	6/44 (14%)	3/53 (6%)	4/55 (7%)	1																	
		0	0.2	2	10																																																			
Mammary gland fibroadenoma																																																								
M	1/44 (2%)	0/50	0/49	0/48																																																				
F	12/54 (22%)	17/44 (39%)	13/53 (25%)	21/55 (38%)																																																				
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M	0/44+	0/50	1/49 (2%)	2/48 (4%)																																																				
F	9/54 (17%)	6/44 (14%)	3/53 (6%)	4/55 (7%)																																																				
	CD mice	0, 3, 15, 50	No increased incidences in tumors	2																																																				
DDVP gavage	Fischer 344 rats	0, 2.9, 5.7	<table><tr><td></td><td>0</td><td>2.9</td><td>5.7</td></tr><tr><td colspan="4">Pancreatic adenoma</td></tr><tr><td>M</td><td>16/50+ (32%)</td><td>25/49 (51%)*</td><td>30/50 (60%)*</td></tr><tr><td>F</td><td>1/50 (2%)</td><td>1/46 (2%)</td><td>4/50 (8%)</td></tr><tr><td colspan="4">Mononuclear cell leukemia</td></tr><tr><td>M</td><td>11/50+ (22%)</td><td>20/50 (40%)*</td><td>21/50 (42%)*</td></tr><tr><td>F</td><td>17/50 (34%)</td><td>21/48 (44%)</td><td>23/50 (46%)</td></tr><tr><td colspan="4">Mammary gland fibroadenoma</td></tr><tr><td>M</td><td>6/46 (13%)</td><td>1/44 (2%)</td><td>2/46 (4%)</td></tr><tr><td>F</td><td>9/50 (18%)</td><td>19/50 (38%)*</td><td>16/49 (33%)</td></tr><tr><td colspan="4">Mammary gland adenoma and/or adenocarcinoma</td></tr><tr><td>M</td><td>0/46</td><td>0/44</td><td>0/46</td></tr><tr><td>F</td><td>2/50 (4%)</td><td>2/50 (4%)</td><td>1/49 (2%)</td></tr></table>		0	2.9	5.7	Pancreatic adenoma				M	16/50+ (32%)	25/49 (51%)*	30/50 (60%)*	F	1/50 (2%)	1/46 (2%)	4/50 (8%)	Mononuclear cell leukemia				M	11/50+ (22%)	20/50 (40%)*	21/50 (42%)*	F	17/50 (34%)	21/48 (44%)	23/50 (46%)	Mammary gland fibroadenoma				M	6/46 (13%)	1/44 (2%)	2/46 (4%)	F	9/50 (18%)	19/50 (38%)*	16/49 (33%)	Mammary gland adenoma and/or adenocarcinoma				M	0/46	0/44	0/46	F	2/50 (4%)	2/50 (4%)	1/49 (2%)	3
		0	2.9	5.7																																																				
Pancreatic adenoma																																																								
M	16/50+ (32%)	25/49 (51%)*	30/50 (60%)*																																																					
F	1/50 (2%)	1/46 (2%)	4/50 (8%)																																																					
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M	11/50+ (22%)	20/50 (40%)*	21/50 (42%)*																																																					
F	17/50 (34%)	21/48 (44%)	23/50 (46%)																																																					
Mammary gland fibroadenoma																																																								
M	6/46 (13%)	1/44 (2%)	2/46 (4%)																																																					
F	9/50 (18%)	19/50 (38%)*	16/49 (33%)																																																					
Mammary gland adenoma and/or adenocarcinoma																																																								
M	0/46	0/44	0/46																																																					
F	2/50 (4%)	2/50 (4%)	1/49 (2%)																																																					
	B6C3F1 mice	0, 7.1 (males), 14.3, 28.6 (females)	<table><tr><td></td><td>0</td><td>7.1</td><td>14.3</td><td>28.6</td></tr><tr><td colspan="5">Forestomach squamous papilloma or carcinoma</td></tr><tr><td>M</td><td>1/46 (2%)+</td><td>1/50 (2%)</td><td>5/48 (10%)</td><td>NA</td></tr><tr><td>F</td><td>5/44 (11%)+</td><td>NA</td><td>6/44 (14%)</td><td>19/48 (40%)**</td></tr></table>		0	7.1	14.3	28.6	Forestomach squamous papilloma or carcinoma					M	1/46 (2%)+	1/50 (2%)	5/48 (10%)	NA	F	5/44 (11%)+	NA	6/44 (14%)	19/48 (40%)**	3																																
	0	7.1	14.3	28.6																																																				
Forestomach squamous papilloma or carcinoma																																																								
M	1/46 (2%)+	1/50 (2%)	5/48 (10%)	NA																																																				
F	5/44 (11%)+	NA	6/44 (14%)	19/48 (40%)**																																																				
Trichl- orfon diet	Fischer 344 rats	0,129 (males), 158.9 females)	<table><tr><td></td><td>0</td><td>129/158.9</td></tr><tr><td colspan="2">Mononuclear cell leukemia</td></tr><tr><td>M</td><td>24/50 (48%)</td><td>21/50 (42%)</td></tr><tr><td>F</td><td>8/50 (16%)</td><td>17/50 (34%)*</td></tr><tr><td colspan="2">Renal tubular adenoma</td></tr><tr><td>M</td><td>0/50</td><td>3/50 (6%)</td></tr><tr><td>F</td><td>0/50</td><td>0/50</td></tr><tr><td colspan="2">Alveolar/bronchiolar adenoma and carcinoma</td></tr><tr><td>M</td><td>0/50</td><td>4/50 (8%)</td></tr><tr><td>F</td><td>0/50</td><td>3/50 (6%)</td></tr></table>		0	129/158.9	Mononuclear cell leukemia		M	24/50 (48%)	21/50 (42%)	F	8/50 (16%)	17/50 (34%)*	Renal tubular adenoma		M	0/50	3/50 (6%)	F	0/50	0/50	Alveolar/bronchiolar adenoma and carcinoma		M	0/50	4/50 (8%)	F	0/50	3/50 (6%)	4																									
		0	129/158.9																																																					
Mononuclear cell leukemia																																																								
M	24/50 (48%)	21/50 (42%)																																																						
F	8/50 (16%)	17/50 (34%)*																																																						
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F	0/50	0/50																																																						
Alveolar/bronchiolar adenoma and carcinoma																																																								
M	0/50	4/50 (8%)																																																						
F	0/50	3/50 (6%)																																																						
	CD-1 mice	0,66, 245, 750	<table><tr><td></td><td>0</td><td>66</td><td>245</td><td>750 ppm</td></tr><tr><td colspan="5">Mammary gland tumors</td></tr><tr><td>F</td><td>1/50 (2%)</td><td>2/50 (4%)</td><td>0/50</td><td>8/50 (16%)</td></tr></table>		0	66	245	750 ppm	Mammary gland tumors					F	1/50 (2%)	2/50 (4%)	0/50	8/50 (16%)	5																																					
	0	66	245	750 ppm																																																				
Mammary gland tumors																																																								
F	1/50 (2%)	2/50 (4%)	0/50	8/50 (16%)																																																				
DCA ^a	rats, mice		Liver tumors	6																																																				

^a/ Ref: 1. Batham et al., 1984; 2. IRDC, 1984; 3. Chan, 1989; 4. Christenson, 1990 5. Hayes, 1988; 6. DeAngelo et al., 1991 and 1996. DCA=dichloroacetic acid.

^b/ += statistically significant at p <0.05 level based on the trend test. * = statistically significant at p <0.05 level when compared with control values.

Based on the above analysis of the databases for naled and structurally-related compounds, it is clear that there is a difference in the toxicity of a compound when it is given as the parent compound compared to *de novo* synthesis. Compared to naled and trichlorfon, DDVP was more toxic as determined by non-oncogenic and oncogenic endpoints. This difference is likely to be related to the amount of the metabolite produced and whether or not they were further metabolized before reaching the target organs. Additional contributing factors to the difference in response are the species and strains used, routes of administration, and other variations in the experimental protocol between studies.

IV.B. EXPOSURE ASSESSMENT

Human exposure assessments were conducted for non-dietary (ambient air, occupational and residential) and dietary exposures to naled. Estimates of non-dietary exposures for workers and residents were determined by the Worker Health and Safety Branch and are described in detail in Volume II. Only summary information is provided in this section. Dietary exposure (**IV.B.2. Dietary Exposure**) was conducted by the Medical Toxicology Branch.

IV.B.1. Non-Dietary Exposure (Including Ambient Air)

Human exposure to naled from occupational and residential activities were expressed as an absorbed daily dose (ADD), seasonal average daily dose (SADD), and an annual average daily dose (AADD) (Volume II). While SADD and AADD were calculated for all exposure scenarios, some of these estimates (Table 17) were not used in the risk assessment because the exposures were either less than the 30 days or 120 days defined for subchronic (seasonal) and chronic exposures (Sanders, 1998). The seasonal dermal exposure levels, as unabsorbed dose of SADD, was also calculated to address local skin effects. Lifetime exposure estimates were not determined.

The potential exposure to DDVP from the conversion of naled was included in the estimates for field workers only for reasons given in **Volume II. XI-5**. The calculated daily doses were the sum of naled and DDVP levels. Other workers were not expected to be exposed to DDVP following a naled application (**Volume II. XI-5**). Inhalation exposure was a minor component of the total exposure and ranged from 0.03% (backpack applicator) to 3.8% (grape harvester) of total daily exposure (Tables 5, 8, and 9 in **Volume II**). Workers and residents using naled-impregnated flea collars were determined to have no inhalation exposure.

The exposures to ambient air concentration of naled were also estimated from air monitoring of 5 outdoor sites in central Tulare County (ARB, 1995). The highest naled and DDVP levels measured over a 24-hour period were 0.08 and 0.06 $\mu\text{g}/\text{m}^3$, respectively. For adults and children, the calculated ADD for naled were 0.01 $\mu\text{g}/\text{kg}/\text{day}$ and 0.03 $\mu\text{g}/\text{kg}/\text{day}$, respectively (Table 17). The ADD for DDVP were 0.007 $\mu\text{g}/\text{kg}/\text{day}$ and 0.02 $\mu\text{g}/\text{kg}/\text{day}$ for adults and children, respectively. The use of this level in the assessment assumed DDVP was from naled applications alone.

IV.B.1.a. Occupational Exposure

The estimated occupational exposures to naled for workers are listed in Table 17. The only naled-specific exposure information available was from an aerial mosquito application and an exposure study of grape workers. The exposures for mixer/loader, flagger, applicator for agricultural uses, and applicator for non-agricultural uses (except for mosquito control) were based on the arithmetic mean for exposure from the U.S. EPA Pesticide Handlers Exposure Database (PHED). The exposures for field workers (cotton, vegetable crops, and greenhouse) were extrapolated from the dislodgeable foliar residue and dosimetry data for naled workers in vineyards. An estimated maximum release rate and amount of naled in flea collars were used to determine the exposure of animal handlers to the collars. There were no exposure estimates for the applicator of naled on hot pipes or hot plate/pan or workers using a pump sprayer/hydrogun or a thermal/cold fog generator.

Table 17. Estimated occupational and residential exposures to naled ^a.

Activity	Annual Exposure Frequency (days/year)	ADD (ug/kg/day)	SADD (ug/kg/day)	Unabsorbed SADD ^b (ug/kg/day)	AADD (ug/kg/day)
Ambient Air					
Adults		0.01 (0.007DDVP)	- -	- -	- -
Children		0.03 (0.02 DDVP)			
Agricultural Uses					
Mixer/loader- aerial spray	60	189.6	108.3	216.6	20.8
- groundboom	60	31.6	18.1	36.2	3.5
Flagger-aerial spray	60	147.9	84.5	169.0	16.2
Applicator- aerial spray	60	12.1	6.9	13.8	1.3
- airblast	60	97.0	55.4	110.8	10.6
- groundboom	60	12.7	7.3	14.6	1.4
- backpack	60	1290.4	737.3	1474.6	141.4
Field workers- grape girdler/thinner	60	9.0	3.87	7.74	0.74
- grape harvester	150	0.9	0.39	0.78	0.19
- cotton scout	40	2.7	1.16	2.32	0.15
- vegetable harvester	260	14.3	6.15	12.3	5.09
- greenhouse harvester	150	320.1	137.6	275.2	65.8
Non-agricultural Uses- Homeowner uses					
Dog/cat collar	2	317.5	NA	NA	1.74
Hand wand-low pressure	2	2.1	NA	NA	0.01
Backpack sprayer	2	74.5	NA	NA	0.41
Non-agricultural Uses- Occupational uses					
Dog/cat collar	60	63.5	36.3	72.6	6.96
(Veterinarians)	60	3.3	1.88	3.76	0.36
Hand wand-low pressure	60	50.4	28.8	57.6	5.52
Backpack sprayer	60	50.4	28.8	57.6	5.52
Sewage system injection	60	<60.0	34.2	68.4	<6.58
Mosquito control (aerial)					
Residents/Bystanders					
Adults	1	<20	NA	NA	<0.22
Children	1	<20	NA	NA	<0.22

^{a/} Data were from Tables 4, 5, 8, and 9 of Volume II on worker and resident exposure. ADD=Absorbed Daily Dosage, SADD=Seasonal Average Daily Dosage, AADD=Annual Average Daily Dosage, NA=not applicable as exposure was only a few days in the year.

^{b/} The SADD based on 50% absorption factor were multiplied by 2 to calculate the unabsorbed seasonal exposure level. This exposure level will be used in the risk assessment for local skin effects. Since the inhalation exposure component to the SADD was negligible (<4% of total exposure), it was not excluded in the calculation.

For occupational exposure, the backpack applicator had the highest exposure; the ADD, SADD, and AADD were 1290.4 $\mu\text{g/kg/day}$, 737.3 $\mu\text{g/kg/day}$, 1471.6 $\mu\text{g/kg/day}$ and 141.4 $\mu\text{g/kg/day}$, respectively (Table 17). For field workers, the ADD ranged from 0.9 $\mu\text{g/kg/day}$ for the grape harvester to 320.1 $\mu\text{g/kg/day}$ for the greenhouse harvester. The SADD ranged from 0.39 $\mu\text{g/kg/day}$ to 137.6 $\mu\text{g/kg/day}$ for these workers. The AADD ranged from 0.15 $\mu\text{g/kg/day}$ for the cotton scout to 65.8 $\mu\text{g/kg/day}$ for the greenhouse harvester. The seasonal dermal exposure, as the unabsorbed dose of SADD, ranged from 0.78 $\mu\text{g/kg/day}$ for the grape harvester to 1474.6 $\mu\text{g/kg/day}$ for the backpack applicator.

IV.B.1.b. Residential Exposure

The estimated residential exposures to naled for residents are also listed in Table 17. Measured urinary DMP levels from an aerial mosquito application were used to estimate the exposure of residents and bystanders near an application site or reentry into sites after application (Kutz and Strassman, 1977). The exposures for residents and bystanders who were in the vicinity of applications were estimated to be < 20 $\mu\text{g/kg/day}$ for the ADD and < 0.22 $\mu\text{g/kg/day}$ for the AADD.

Homeowners may be exposed to naled from the use of pet collars, hand-wand or backpack sprayer containing naled. The highest residential exposure to naled was for collar users; the ADD and AADD were 317.5 $\mu\text{g/kg/day}$ and 1.74 $\mu\text{g/kg/day}$, respectively (Table 17). Other home uses (hand wand and backpack sprayer) resulted in lower exposures.

IV.B.2. Dietary Exposure

DPR evaluates the risk of exposure of an active ingredient in the diet using separate processes: (1) risk is determined for total exposure based on detected residue levels, and (2) risk is determined for exposure to an individual commodity at the tolerance level (**VI. TOLERANCE ASSESSMENT**). For the evaluation of risk at detected residue levels, the total exposure in the diet is determined for all label-approved crops (raw agricultural commodities), processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. The potential exposure from residues in the water may also be assessed. Tolerances may be established for the parent compound and associated metabolites. DPR considers metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

IV.B.2.a. Introduction

Dietary assessment of naled was conducted for acute and chronic exposures. The potential exposure to DDVP from the degradation of naled was also considered since DDVP is the primary metabolite and is a cholinesterase inhibitor. Tolerances (40 CFR 180.215) are established for residues of naled and DDVP, expressed as naled, resulting from the use of naled on crops and on livestock and poultry (Appendix B).

IV.B.2.b. Residue Database

IV.B.2.b.(1) General Information

The residue data for a dietary exposure assessment are based on DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group as defined by U.S. EPA, or U.S. EPA tolerances are used. Residue levels that exceed established tolerances are not used in the dietary exposure assessments. Over-tolerance incidents are separately investigated by the DPR Pesticide Enforcement Branch. The potential risk from consuming commodities with residues over tolerance levels is evaluated by the Medical Toxicology Branch using an expedited acute risk assessment process.

The DPR sampling programs are priority pesticide and marketplace surveillance. For the priority pesticide program, samples are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both programs are similar and are biased toward factors such as the pattern of pesticide use, the relative number and volume of pesticides typically used on a commodity; the dietary importance of the commodity, and past monitoring results.

At the federal level, the U.S. Food and Drug Administration (FDA) has three programs: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. The U.S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP collects objective, comprehensive pesticide residue data specifically for dietary risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level.

IV.B.2.b.(2) Naled and DDVP Residue Data

Primary Residues

Residue values used for acute and chronic exposures were based on field trials (Sakamoto, 1971; Pensyl, 1994c; Kohn, 1963; Dimaggio, 1971), PDP 1993 to 1994 data (USDA, 1996c), FDA (FDA, 1992-1995), and DPR 1992 to 1994 data (DPR, 1993-1995) (Table 18). When residue data were available from more than one data source, the database with the best experimental design was selected. For naled, the primary database was from the USDA PDP. The U.S. EPA tolerance was used as the residue value for hops since data were not available^b. None of the labeled uses has been found to have residues over the tolerances.

Secondary Residues

Secondary residues may be found in milk, eggs, and meats from the direct application of naled to poultry and cattle, or from the use of treated commodities (safflower, cottonseed, and peas) in the feed. The FDA milk monitoring survey conducted in 1990-1991 showed no detected naled or DDVP residues in the 806 composited milk samples (Trotter and Dickerson, 1993). The metabolism studies in the hen (Cheng, 1983a and b) and goat (Chen, 1982) were

^b Residue data for hops were submitted after the analysis was completed (Valent, 1998). Naled (as DDVP) was below the detection limits for green hops (0.04 ppm) and dried hops (0.08 ppm).

not used because of an inadequate number of animals studied. Therefore, the U.S. EPA tolerance (0.05 ppm) was used for red meat, poultry, and eggs.

Drinking Water

Naled or DDVP residues in the drinking water were not included in the analyses because both compounds readily degrade in the environment (**II.G. ENVIRONMENTAL FATE**).

Residues used for Dietary Exposure

For acute daily exposure, the residue value (except mixtures) was either the detection limit, the 95th percentile of samples (green beans), or the tolerance when there were no data. For almost all raw agricultural commodities (except for green beans), the residue levels for naled or DDVP were below the detection limits. The detection limits of the data sources were: 0.003 ppm for DDVP (PDP), 0.1 ppm for naled and 0.03-0.05 ppm for DDVP (DPR), 0.05-0.1 ppm for naled and 0.02-0.05 ppm for DDVP (FDA), 0.01 ppm for naled and DDVP (field trials). For mixtures such as juices, oils, milk, tomato paste, and tomato puree, 50% of the detection limit was used since both treated and non-treated commodities are commonly mixed during processing. The U.S. EPA tolerances were used for eggs, hops, poultry, and red meat.

The residue values for dietary exposure were the sum of naled and DDVP residue levels. For commodities with naled residues at below the detection limit, the naled residue level was assumed to be zero since naled is readily converted to DDVP (**II.G. ENVIRONMENTAL FATE**). The DDVP residue values were normalized to naled equivalents using the toxicity equivalency factor (TEF) approach since DDVP is more toxic than naled. This approach was valid since the TEF was based on the same endpoints of toxicity. For acute exposure, the TEF was 5-fold based on the NOELs of 2.5 mg/kg/day and 0.5 mg/kg/day, respectively, for naled and DDVP-induced cholinergic signs. For chronic exposure, the TEF was 4-fold based on the NOELs of 0.2 mg/kg/day and 0.05 mg/kg/day, respectively, for naled and DDVP-induced brain cholinesterase inhibition. The calculated residue levels were thus naled equivalents or simply referred to as naled residues in this document:

$$\text{naled equivalent residue} = \text{naled residue or zero} + (\text{DDVP residue} \times \text{TEF})$$

The TEF was not applied to the residue values using the tolerance as the surrogate since the tolerance was the maximum naled and DDVP residues allowed on the commodities.

Table 18. Naled residue values for commodities evaluated for potential dietary exposure.

RAC	Tolerance ^a		Residue Used (ppm) ^b		% crop treated	N ^c	Additional Information ^d	References ^e
	naled	DDVP	Acute	Chronic				
Almond	0.5	0.5	0.035	0.015	1	4	<MDL	1
Beans	0.5	0.5	0.0177	0.00604	100	1165	Acute: 95 th % all beans	2
Broccoli	1.0		0.015	0.006	10	1270	< MDL	2
Brussels Sprouts	1.0		0.15	0.06	100	151	< MDL	3
Cabbage	1.0		0.15	0.06	100	297	< MDL	3
Cauliflower	1.0		0.15	0.06	100	148	< MDL	3
Celery	3.0		0.015	0.006	35	813	< MDL	2
Collards	3.0		0.15	0.06	100	65	< MDL	3
Cottonseed	0.5		0.03	0.025	30	8	< MDL (½ LOQ)	4
Cucumbers	0.5		0.2	0.08	100	780	< MDL	3
Eggs	0.05	0.05	0.05	0.05	60	-	Tolerance	5
Eggplant	0.5		0.15	0.06	100	292	< MDL	3
Grapefruit (fresh & juice)	3.0		0.015	0.006	100	637	Acute mixed=0.0075 ppm	6
Grape (fresh, dry, juice)	0.5		0.015	0.006	10	1300	Acute mixed=0.0075 ppm	2
Hops	0.5		0.5	0.25	100	-	Tolerance	5
Kale	3.0		0.15	0.06	100	46	< MDL	3
Lemon (fresh & juice)	3.0		0.015	0.006	100	1,321	Orange surrogate data	2
Lettuce (head & leaf)	1.0		0.015	0.006	1	1,338	< MDL	2
Melons	0.5		0.2	0.08	100	302	< MDL	3
Milk	0.05	0.02	0.0013	0.001	100	806	FDA special milk survey	7
Mushroom	0.5		0.15	0.06	100	164	≥ MDL	3

^{a/} Tolerances from U.S. EPA 40 CFR 180.215 (naled), 180.235 (DDVP).

^{b/} Residue values were the sum of naled residues and DDVP residues corrected with a toxicity equivalency factor (except when the tolerance was used). Actual values used for chronic exposure included % crop treatment.

^{c/} N = The number of RAC composite samples analyzed from the selected submitted studies or monitoring programs.

^{d/} MDL= minimum detection limit, acute mixed=residue values for acute exposure to mixtures (juice, catsup, paste, oil).

^{e/} References: 1. Sakamoto, 1971; 2. PDP 1993 and 1994 data, USDA, 1996c; 3. DPR 1992 to 1994 data, DPR, 1993-1995; 4. Pensyl, 1994c; 5. U.S. EPA tolerance; 6. PDP 1993 data, USDA, 1996c; 7. Trotter and Dickerson, 1993.

Table 18. Naled residue values for commodities evaluated for potential dietary exposure (continued).

RAC	Tolerance ^a (ppm)		Residue Used (ppm) ^b		% crop treated	N ^c	Additional Information ^d	References ^e
	naled	DDVP	Acute	Chronic				
Orange (& juice)	3.0		0.015	0.006	15	1,321	Acute mixed=0.0075 ppm	1
Peach	0.5		0.015	0.006	1	765	< MDL	1
Peas, succulent	0.5		0.015	0.006	100	433	< MDL	2
Peppers	0.5		0.2	0.08	100	1,131	< MDL	3
Poultry, all tissues	0.05	0.05	0.05	0.05	60	-	Tolerance	4
Pumpkin	0.5		0.25	0.1	100	50	< MDL	5
Red meat, all tissues	0.05	0.02	0.05	0.05	65	-	Tolerance	4
Rice	0.5	0.5	0.25	0.1	1	>100	< MDL	5
Safflower seed (oil)	0.5		0.03	0.025	35	12	< MDL	6
Spinach	3.0		0.2	0.08	1	271	< MDL	3
Squash	0.5		0.15	0.06	100	398	< MDL	3
Strawberry & juice	1.0		0.2	0.06	25	311	Acute mixed = 0.1 ppm	3
Sugar beet (sugar)	0.5		0.035	0.025	10	4	Raw mixed beet roots	7
Swiss Chard	3.0		0.2	0.08	100	59	< MDL	3
Tangerine (& juice)	3.0		0.015	0.006	100	1,321	Orange surrogate data	1
Tomato	0.5		0.15	0.06	10	1000	Acute mixed = 0.075 ppm	3
Turnip, greens	3.0		0.2	0.08	100	16	< MDL	3
Walnut	0.5	0.5	0.25	0.1	100	4	< MDL	5

^a/ Tolerances from U.S. EPA 40 CFR 180.215 (naled) & 180.235 (DDVP).

^b/ Residue values were the sum of naled residues and DDVP residues corrected with a toxicity equivalency factor (except when the tolerance was used). Actual values used for chronic exposure included % crop treatment.

^c/ N = The number of RAC composite samples analyzed from the selected submitted studies or monitoring programs.

^d/ MDL= minimum detection limit, acute mixed=residue values for acute exposure to mixtures (juice, catsup, paste, oil).

^e/ References: 1. PDP 1993 and 1994 data, USDA, 1996c; 2. PDP 1994 data, USDA, 1996c; 3. DPR 1992 to 1994 data, DPR 1993-1995; 4. U.S.EPA tolerance; 5. FDA, 1992-1995; 6. Kohn, 1963; 7. Dimaggio, 1971.

IV.B.2.c. Consumption Data

IV.B.2.c.(1) General Information

The USDA directs the Nationwide Food Consumption Survey (NFCS) and the Continuing Survey of Food Intakes by Individuals (CSFII) (USDA, 1987-1988; USDA, 1989-1992). The NFCS is a geographically stratified probability sampling of U.S. households and is conducted every 10 years (1977-1978 and 1987-1988). The CSFII is an annual survey which reflects the current consumption patterns and has a greater focus on consumption data for population subgroups of concern (e.g., infants and children).

IV.B.2.c.(2) Consumption Database for Naled

The consumption analysis used the three-year data (1989-1990, 1990-1991, and 1991-1992) from the CSFII because they reflected current consumption patterns (USDA, 1989-1992).

IV.B.2.d. Exposure Analysis

Acute and chronic dietary exposure analyses were conducted with the Exposure-4™ and Exposure-1™ software programs, respectively (TAS, Technical Assessment Systems, Inc.). The Exposure-4™ program was used to estimate the distribution of user-day (consumer-day) exposure for the U.S. population and specific subgroups (TAS, 1996a). A user-day is any day in which at least one food from the labeled-approved commodities is consumed. The Exposure-1™ program was used to estimate the annualized average exposure for all members of a designated population subgroup (TAS, 1996b).

IV.B.2.d.(1) Acute Dietary Exposure (Daily)

When the residue values were derived from monitoring programs, the assumption was that the data represent high end residue levels in the diet. The use of the data does not account for the potential change in residue levels due to (1) washing and peeling, and (2) food preparation and processing (e.g., cooking and canning).

Based on the 95th percentile of user-days exposure for all specific population subgroups, the potential acute dietary exposure of naled from all labeled uses ranged from 1.069 $\mu\text{g}/\text{kg}/\text{day}$ (seniors 55+ years old) to 2.635 $\mu\text{g}/\text{kg}/\text{day}$ (children 1-6 years) (Table 19).

IV.B.2.d. (2) Chronic Dietary Exposure (Annual)

Estimates of potential chronic annual dietary exposure used the average measured residue values of all values for each commodity or the tolerance. For commodities with residues at "below detection limit", a value equal to one-half (50%) of the MDL was assigned to each commodity. The DDVP residues were also converted to naled equivalents with a TEF factor of 4 (as discussed above). When the residue values were derived from monitoring programs, the assumption was that the data represent annual average level in the diet.

Percentage of crop treated data (PCT) were used in calculating the average residue levels for some commodities to provide a more realistic estimate of chronic exposure.

Estimates of the PCT were based on the DPR Pesticide Use Report (DPR, 1995-1996), CDFA crop statistic (CDFA, 1993a and b, 1994) and USDA reports (USDA, 1991; 1993; 1994 a, b, and c; 1995 a, b, and c; 1996 a, b, c, and d; 1997). While the pattern of pesticide use is expected to fluctuate from year to year, the PCT was determined from data collected over several years. The highest PCT value, in some cases rounded up to the nearest 5%, was used in the residue profile calculation. The PCTs were 1% (almond, lettuce, peach, rice, and spinach), 10% (broccoli, grape, sugar beet, and tomato), 15% (orange), 25% (strawberry), 30% (cottonseed), 35% (celery, safflower), 60% (poultry, eggs), and 65% (red meats) (Table 18). The PCT represented the probability that a commodity could potentially contain residues. In calculating the average residue level, the remaining (i.e., [100-PCT%]) could then be assumed to contain none or zero residue, instead of at 50% of the MDL.

The potential chronic dietary exposure for all population subgroups ranged from 0.027 $\mu\text{g/kg/day}$ (nursing infants < 1 years old) to 0.251 $\mu\text{g/kg/day}$ (children 1-6 years old) (Table 19).

IV.B.2.d.(3) Lifetime Dietary Exposure

A lifetime dietary exposure to naled was not determined because naled there is insufficient evidence to show that naled was oncogenic in experimental animals (**VI.A.2.d. Weight of Evidence for Oncogenicity**). However, DPR has determined that there is sufficient evidence which showed that DDVP, when given as the parent compound, is oncogenic. To determine the lifetime dietary exposure to DDVP, the databases and tolerances used in this document to determine the acute and chronic exposures for naled were considered inappropriate. The exposure values would be unrealistic since the major component of the total would be contributed by the use of tolerances as the residue levels for meat, poultry, and eggs.

Instead, the recent estimation of DDVP exposure from naled by the U.S. EPA was used. The U.S. EPA was able to obtain more recent residue data and percentage of crop treated data to derive a realistic estimate of exposure (Steinwand, 1998; Hummel, 1998a and b). The total lifetime exposure to DDVP was $3.46 \times 10^{-6} \text{ mg/kg/day}$ with $0.678 \times 10^{-6} \text{ mg/kg/day}$ from naled-derived DDVP, and $2.78 \times 10^{-6} \text{ mg/kg/day}$ from direct DDVP uses (Steinwand, 1998).

Table 19. Potential acute (daily) and chronic (annual) dietary exposures to naled^a.

Population subgroups	Acute Exposure 95th percentile (ug/kg/day)	Chronic Exposure Annualized Average (ug/kg/day) ^b
US Pop. all seasons	1.467	0.132
Pacific Region	1.408	0.127
Hispanics	1.848	0.143
Non-Hispanic Whites	1.374	0.127
Non-Hispanic Blacks	1.556	0.144
Non-Hispanic Other	1.911	0.162
All Infants	2.443	0.100
Infants (nursing, < 1 year)	1.884	0.027
Infants (non-nursing, < 1 year)	2.417	0.131
Children (1-6 years)	2.635	0.251
Children (7-12 years)	1.790	0.175
Females (13+ years) (pregnant, not nursing)	1.192	0.110
Females (13+ years) (nursing)	1.269	0.125
Females (13-19 years) (not pregnant, not nursing)	1.362	0.112
Females (20+ years) (not pregnant, not nursing)	1.118	0.108
Females (13-50 years)	1.166	0.106
Males (13-19 years)	1.236	0.124
Males (20+ years)	1.190	0.117
U.S. Population (16+ years)	1.151	c
Seniors (55+ years)	1.069	0.113

^{a/} Exposure levels were based on naled residues and DDVP residues converted to naled equivalents using toxicity equivalency factor approach. Consumption rates were based on the 1989-1992 USDA CSFII Survey.

^{b/} Residues for some commodities were adjusted for percentage of crop treatment (see Table 18).

^{c/} Exposure estimates for this subgroup were not available from the TAS^R chronic exposure program.

IV.B.3. Combined Exposures

The combined exposures considered exposure from dietary sources with either occupational or residential contributions. The ambient air exposure was not included in the combined exposure since the levels were relatively low (<3%, in nanogram range) compared to those from other routes. For workers of agricultural and non-agricultural uses of naled, the dietary component was based on the exposure of adults (16+ years) and adults (20+) for acute and chronic exposures, respectively. The adult (16+ years) group was selected because 16 years old is the minimum age requirement for workers. Since the TAS program does not calculate chronic exposure for the same age group, the 20+ years old group with the highest exposure was used instead. For dog/cat collar use in homes and children bystanders, the children group with the highest dietary exposure was used. For other home uses, the adult group with the highest exposure was used. The dietary exposure levels were not adjusted for absorption since the absorption by the oral route was 100%. A summary of the dietary exposure levels (from Table 19) used in combined exposure is listed below:

Groups	Acute Exposure ($\mu\text{g/kg/day}$)	Chronic Exposure ($\mu\text{g/kg/day}$)
Workers	1.151 (adults 16+ years old)	0.117 (males 20+ years old)
Residents- collars, children	2.635 (children 1-6 years old)	0.251 (children 1-6 years old)
Residents- other uses, adult	1.362 (females 13-19 years old)	0.125 (females 13+ years old)

IV.B.3.a. Combined Occupational and Dietary Exposures

The combined acute occupational and dietary exposures ranged from 2.1 $\mu\text{g/kg/day}$ (grape harvester) to 1291.6 $\mu\text{g/kg/day}$ (backpack applicator) (Table 20). The combined chronic occupational and dietary exposures ranged from 0.3 $\mu\text{g/kg/day}$ (grape harvester and cotton scout) to 141.5 $\mu\text{g/kg/day}$ (backpack applicator) (Table 21).

IV.B.3.b. Combined Residential and Dietary Exposures

The combined acute residential and dietary exposures ranged from 3.5 $\mu\text{g/kg/day}$ (hand wand applicator) to 320.1 $\mu\text{g/kg/day}$ (children in contact with dog/cat collar) (Table 20). The combined chronic residential and dietary exposures ranged from 0.1 $\mu\text{g/kg/day}$ (hand wand applicator) to 2.0 $\mu\text{g/kg/day}$ (children in contact with dog/cat collar) (Table 21).

Table 20. Potential combined acute occupational, residential, and dietary exposures to naled.

Activity	Non-dietary (ug/kg/day) ^a	Dietary (ug/kg/day) ^b	Total Exposure (ug/kg/day)
Agricultural Uses			
Mixer/loader- aerial spray	189.6	1.151 ^c	190.8
- groundboom	31.6	1.151 ^c	32.8
Flagger-aerial spray	147.9	1.151 ^c	149.1
Applicator- aerial spray	12.1	1.151 ^c	13.3
- airblast	97.0	1.151 ^c	98.2
- groundboom	12.7	1.151 ^c	13.9
- backpack	1290.4	1.151 ^c	1291.6
Field workers- grape girdler/thinner	9.0	1.151 ^c	10.2
- grape harvester	0.9	1.151 ^c	2.1
- cotton scout	2.7	1.151 ^c	3.9
- vegetable crop harvester	14.3	1.151 ^c	15.5
- greenhouse harvester	320.1	1.151 ^c	321.3
Non-agricultural Uses- Homeowner uses			
Dog/cat collar	317.5	2.635 ^d	320.1
Hand wand-low pressure	2.1	1.362 ^e	3.5
Backpack sprayer	74.5	1.362 ^e	75.9
Non-agricultural Uses- Occupational uses			
Dog/cat collar (Veterinarians)	63.5	1.151 ^c	64.7
Hand wand-low pressure	3.3	1.151 ^c	4.5
Backpack sprayer	50.4	1.151 ^c	51.6
Sewage system injection	50.4	1.151 ^c	51.6
Mosquito control (aerial)	60.0	1.151 ^c	61.2
Residents/Bystanders			
Adults	<20	1.362 ^e	<21.4
Children	<20	2.635 ^d	<22.6

a/ Data from Table 17.

b/ Data from Table 19.

c/ Highest exposure for males and females 16+ years old.

d/ Highest exposure for all children groups.

e/ Highest exposure for all adult groups.

Table 21. Potential combined chronic occupational, residential, and dietary exposures to naled.

Activity	Non-dietary (ug/kg/day) ^a	Dietary (ug/kg/day) ^b	Total Exposure (ug/kg/day)
Agricultural Uses			
Mixer/loader- aerial spray	20.8	0.117 ^c	20.9
- groundboom	3.5	0.117 ^c	3.6
Flagger-aerial spray	16.2	0.117 ^c	16.3
Applicator- aerial spray	1.3	0.117 ^c	1.4
- airblast	10.6	0.117 ^c	10.7
- groundboom	1.4	0.117 ^c	1.5
- backpack	141.4	0.117 ^c	141.5
Field workers- grape girdler/thinner	0.74	0.117 ^c	0.7
- grape harvester	0.19	0.117 ^c	0.3
- cotton scout	0.15	0.117 ^c	0.3
- vegetable crop harvester	5.09	0.117 ^c	5.2
- greenhouse harvester	65.8	0.117 ^c	65.9
Non-agricultural Uses- Homeowner uses			
Dog/cat collar	1.74	0.251 ^d	2.0
Hand wand-low pressure	0.01	0.125 ^e	0.1
Backpack sprayer	0.41	0.125 ^e	0.5
Non-agricultural Uses- Occupational uses			
Dog/cat collar	6.96	0.117 ^c	7.1
Hand wand-low pressure	0.36	0.117 ^c	0.5
Backpack sprayer	5.52	0.117 ^c	5.6
Sewage system injection	5.52	0.117 ^c	5.6
Mosquito control (aerial)	<6.58	0.117 ^c	<6.7
Residents/Bystanders			
Adults	<0.22	0.125 ^e	<0.3
Children	<0.22	0.251 ^d	<0.5

a/ Data from Table 17.

b/ Data for percentage of crop treated adjustment from Table 19.

c/ Highest exposure for males and females 20+ years old.

d/ Highest exposure for children groups.

e/ Highest exposure for adult groups.

IV.C. RISK CHARACTERIZATION

The potential health hazard associated with the use of naled was considered for occupational, residential, and dietary exposures. Non-oncogenic effects were characterized in terms of margins of exposure (MOE), defined as the ratio of NOEL to the potential exposure dosage. Based on the current database, naled is not considered oncogenic. The critical NOELs (in terms of adjusted dosages) used to address the various exposure scenarios and routes of exposure for humans are listed in Table 22.

Table 22. Critical NOELs for the risk characterization of naled and DDVP.

Exposure	NOEL or ENEL	LOEL	Effects	Reference
NALED ACUTE (all routes)	2.5(ENEL)	25 mg/kg/day ^a	cholinergic signs (rat, oral)	Lamb, 1993a
SUBCHRONIC (dermal)	<u>systemic effect:</u> 1.0 (adjusted NOEL= 0.36 mg/kg/day) ^b	20 mg/kg/day	brain ChE inhibition (rat, dermal)	Rausina and Zimmerman, 1986
	<u>local effect:</u> 0.1 (ENEL) (adjusted NOEL= 0.07 mg/kg/day) ^c	1 mg/kg/day	inflammation and necrosis (rat, dermal)	
CHRONIC (all routes)	0.2	2 mg/kg/day	brain ChE inhibition (rat and dog, oral)	Batham <i>et al.</i> , 1984; IRDC, 1986
DDVP^d ACUTE -oral	0.5	1.0 mg/kg/day	cholinergic signs (rat, oral)	Lamb, 1992 and 1993b
-inhalation	0.65 mg/kg/day (adjusted NOEL= 0.325 mg/kg/day) ^a	1.0 mg/kg/day	death (rabbit, inhalation)	Thorpe <i>et al.</i> , 1971
CHRONIC -oral	0.05	1.0 mg/kg/day	brain ChE inhibition and signs (dog, oral)	Markiewicz, 1990
Lifetime - oral	q ₁ = 0.2 mg/kg/day ⁻¹ q ₁ *=0.35 mg/kg/day ⁻¹		mononuclear cell leukemia (rat, oral)	Chan, 1989

a/ 100% absorption for oral route, and assumed 50% for inhalation route as used in the Exposure Assessment (Volume II).

b/ The NOEL was adjusted to account for 50% absorption and amortized for daily exposure (5 days/7 days) .

c/ The NOEL was amortized for daily exposures (5 days/7 days) with no absorption correction for effects on application site.

d/ Studies reviewed in the Risk Characterization Document for DDVP (Lim *et al.* 1996).

IV.C.1. Non-Dietary Exposure (Including Ambient Air)

For non-dietary exposure, except ambient air exposure, the critical NOELs for naled were used to evaluate exposure since the exposures were expressed as total naled. For exposure in the ambient air, critical NOELs for naled and DDVP were used since exposures for both compounds were determined. The MOEs for adult and child exposures to naled or DDVP in the ambient air were equal to or greater than 16,250 for the two groups.

IV.C.1.a. Occupational Exposure

For localized effect of naled on the skin, only the seasonal exposures were evaluated since the NOEL for local effects was lower than that for the systemic effect (**IV.A. HAZARD IDENTIFICATION**). The MOEs ranged from 0.05 (backpack applicator) to 90 (grape harvester) (Table 23).

For systemic effects of naled, the MOEs for the mixer/loader and applicator depended on the application method (Table 23). For aerial spray and groundboom mixer/loaders, the MOEs were 13 and 79 for acute exposure, and 3 and 20 for seasonal exposure. The flagger of aerial sprayer had high exposures resulting in acute and seasonal MOEs of 17, and 4, respectively. For all durations of exposure, the MOEs for the exposure of air blast and backpack applicators were 0.5 to 26 and were lower than those (49 to 207) for aerial spray and groundboom applicators.

For field workers, the greenhouse harvesters had the highest exposures with MOEs of 8, 3, and 3 for acute, seasonal, and chronic exposures. The acute and seasonal exposure MOEs were ≥ 93 for grape girdler/thinners, grape harvesters and cotton scouts with relatively low exposures (Table 23). For vegetable crop harvesters, the MOE was 175 for acute, but were 59 and 39 for seasonal and chronic exposures, respectively.

For non-agricultural uses of naled, workers using low pressure hand wand had the lowest exposure. Their MOEs were 758, and 191 for acute and seasonal exposures, respectively (Table 23). The acute MOEs for the other workers were 39 (dog/cat collar handler) and 50 (backpack sprayer and sewage system injection worker). For longer-term exposure, the MOEs were 10 and 13 for these workers. For mosquito control by aerial application, the MOEs were >42 , and 11 for acute and seasonal exposures, respectively.

IV.C.1.b. Residential Exposure

For home uses, the highest acute exposure was from naled-impregnated dog and cat collars with a MOE of 8 (Table 23). The MOEs for acute exposure were 1190 and 34 for exposure to naled from the use of hand wand-low pressure and backpack sprayer, respectively. For residents and bystanders near naled treatment sites, the acute MOEs were >125 .

Table 23. The margins of exposure for potential acute, seasonal, and chronic occupational and residential exposures to naled ^a.

Activity	Acute Exposure MOE ^b	Seasonal Exposure		Chronic Exposure MOE ^e
		dermal MOE ^c	systemic MOE ^d	
Agricultural Uses				
Mixer/loader- aerial spray - groundboom	13 79	0.3 2	3 20	NA NA
Flagger-aerial spray	17	0.4	4	NA
Applicator- aerial spray - airblast - groundboom - backpack	207 26 197 2	5 1 5 0.05	52 6 49 0.5	NA NA NA NA
Field worker- grape girdler/thinner - grape harvester - cotton scout - vegetable crop harvester -greenhouse harvester	278 2778 926 175 8	9 90 30 6 0.3	93 923 310 59 3	NA 1053 NA 39 3
Non-agricultural Uses- Homeowner uses				
Dog/cat collar Hand wand-low pressure Backpack sprayer	8 1190 34	NA NA NA	NA NA NA	NA NA NA
Non-agricultural Uses- Occupational uses				
Dog/cat collar (Veterinarians) Hand wand-low pressure Backpack sprayer Sewage system injection Mosquito control (aerial)	39 758 50 50 >42	1 19 1 1 1	10 191 13 13 11	NA NA NA NA NA
Residents/Bystanders				
Adults	>125	NA	NA	NA
Children	>125	NA	NA	NA

^{a/} Data were from Table 17. NA= not applicable as exposure was less than the 30 days or the 120 days defined as seasonal and chronic exposures, respectively.

^{b/} Margins of exposure were based on an ENEL of 2.5 mg/kg/day for cholinergic signs in rats (Lamb, 1993a).

^{c/} Margins of exposure were based on an adjusted ENEL of 0.07 mg/kg/day for skin effects in rats (Rausina and Zimmerman, 1986).

^{d/} Margins of exposure were based on an adjusted NOEL of 0.36 mg/kg/day for brain ChE inhibition in rats (Rausina and Zimmerman, 1986).

^{e/} Margins of exposure were based on a NOEL of 0.2 mg/kg/day for brain ChE inhibition in rats (Batham *et al.*, 1984; IRDC, 1986).

IV.C.2. Dietary Exposure

For dietary exposure, the critical NOELs for naled were used since the residues (naled and DDVP) in the commodities were expressed as naled equivalents using the toxicity equivalency factor approach (**IV.B.2.b.(3) Total Residues**). For acute and chronic exposures to naled, the MOEs for all population subgroups were greater than ≥ 800 (Table 24).

For lifetime exposure to DDVP (3.46×10^{-6} mg/kg/day) from direct use of DDVP and those derived from naled, the oncogenic risk was 6.9×10^{-7} and 1.2×10^{-6} for q1 and q1*, respectively.

IV.C.3. Combined Exposures

Since the dietary exposure was a minor component of the total naled exposure, the MOEs for combined exposure were essentially those for occupational or residential exposures alone (Table 25).

IV.C.3.a. Combined Occupational and Dietary Exposures

The combined acute occupational and dietary exposure MOEs ranged from 2 (backpack applicator) to 1219 (grape harvester). The combined chronic occupational and dietary exposure MOEs ranged from 3 (greenhouse harvester) to 651 (grape harvester).

IV.C.3.b. Combined Residential and Dietary Exposures

The combined acute residential and dietary exposure MOEs were 8 (children exposed to dog/cat collars), 33 (backpack sprayer), and 722 (hand wand applicator). The MOEs for combined chronic exposures were not calculated since the residential chronic exposure duration was not considered chronic in duration.

Table 24. The margins of exposure for potential acute (daily) and chronic (annual) dietary exposures to naled ^a.

Population subgroups	Acute MOE ^b	Chronic MOE ^c
US Pop. all seasons	1700	1520
Pacific Region	1780	1570
Hispanics	1350	1400
Non-Hispanic Whites	1820	1570
Non-Hispanic Blacks	1610	1390
Non-Hispanic Other	1310	1230
All Infants	1020	2000
Infants (nursing, < 1 year)	1330	7280
Infants (non-nursing, < 1 year)	1030	1530
Children (1-6 years)	950	800
Children (7-12 years)	1400	1140
Females (13+ years) (pregnant, not nursing)	2100	1820
Females (13+ years) (nursing)	1970	1600
Females (13-19 years) (not pregnant, not nursing)	1840	1780
Females (20+ years) (not pregnant, not nursing)	2240	1860
Females (13-50 years)	2140	1880
Males (13-19 years)	2020	1610
Males (20+ years)	2100	1710
U.S. population (16+ years)	2170	d
Seniors (55+ years)	2340	1770

^{a/} Margin of Exposure (MOE) values were based on exposures in Table 19.

^{b/} MOEs were based on an oral NOEL of 2.5 mg/kg/day naled for cholinergic signs in rats (Lamb, 1993a).

^{c/} MOEs were based on an oral NOEL of 0.2 mg/kg/day naled for brain ChE inhibition in rats and dogs (Batham *et al.*, 1984; IRDC, 1986). Chronic exposures were calculated with the residues of some commodities adjusted for percentage of crop treatment.

^{d/} Data not available.

Table 25. The margins of exposure of potential combined acute and chronic occupational, residential, and dietary exposures to naled^a.

Activity	Acute MOE ^b	Chronic MOE ^c
Agricultural Uses		
Mixer/loader- aerial spray - groundboom	13 76	NA NA
Flagger-aerial spray	17	NA
Applicator- aerial spray - airblast - groundboom - backpack	189 25 180 2	NA NA NA NA
Field worker- grape girdler/thinner - grape harvester - cotton scout - vegetable crop harvester - greenhouse harvester	246 1219 649 162 8	NA 651 NA 38 3
Non-agricultural Uses- Homeowner uses		
Dog/cat collar Hand wand-low pressure Backpack sprayer	8 722 33	NA NA NA
Non-agricultural Uses- Occupational uses		
Dog/cat collar (Veterinarians) Hand wand-low pressure Backpack sprayer Sewage system injection Mosquito control (aerial)	39 562 48 48 >41	NA NA NA NA NA
Residents/Bystanders		
Adults Children	>117 >110	NA NA

^{a/} Data were from Table 17.

^{b/} Margins of exposure were based on a NOEL of 2.5 mg/kg/day for cholinergic signs in rats (Lamb, 1993a).

^{c/} Margins of exposure were based on a NOEL of 0.2 mg/kg/day for brain ChE inhibition in rats (Batham *et al.*, 1984; IRDC, 1986). NA= Not applicable as the exposure duration was less than the 120 days defined for chronic exposure.

V. RISK APPRAISAL

V.A. INTRODUCTION

The health risk assessment of naled was conducted for workers and the general population. The exposure scenarios included ambient air (acute exposure only), occupational, residential, and dietary exposures under acute, subchronic (in some cases), and chronic conditions. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in human under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain default assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for naled are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification of naled are those from human studies. However, human case reports (**III.I. HUMAN STUDIES**) did not provide sufficient detail on the dose-response relationship. Results from animal studies were thus used assuming that the effects observed in experimental animals would also be observed in humans.

The critical NOELs were derived from oral studies because lack of appropriate studies by the dermal route (except for seasonal exposure), the primary route for occupational and residential exposure. In addition, there were no dermal and only one inhalation pharmacokinetics studies available to determine the uncertainty for route-to-route extrapolation.

V.B.1. Acute Toxicity

The critical acute NOEL was an estimated ENEL (2.5 mg/kg/day) calculated from a LOEL of 25 mg/kg/day from an oral study and was based on effects (tremors, exophthalmus, decreased rearing, decreased tail pinch response, and reduced hindlimb resistance) from Functional Observation Battery tests in an oral study with rats (Lamb, 1993a) (**III.H.1. Oral - Rat**). The use of an oral study to assess exposure then assumed that there was no difference in the toxicity between routes of exposure. A comparison of the oral critical NOEL with available dermal toxicity studies showed that this was a reasonable assumption. The lowest adjusted dermal ENEL was 6.25 mg/kg for cholinergic signs (diarrhea, ocular and nasal discharges, and decreased motor activity) in rabbits (Brorby, 1985). These effects were more severe than those observed in the Functional Observation Battery tests in the oral study. Thus the difference between the oral ENEL (2.5 mg/kg) and the dermal ENEL (6.25 mg/kg) was only 3-fold. The greater sensitivity in the FOB to detect neurotoxicity may account for the lower ENEL in the oral toxicity study compared with gross observation in the dermal toxicity study.

In the derivation of the ENEL, the acute LOEL for naled was divided by a 10-fold factor, the current DPR default factor to estimate the NOEL from a LOEL. A comparison of the LOEL from this study (25 mg/kg/day; Lamb, 1993a) with other studies showed that it is of similar magnitude as those observed in pregnant rats (40 mg/kg/day) and pregnant rabbits (20 mg/kg/day) for cholinergic signs (Science Applications, Inc., 1984; Hardy, 1985; **III.G. DEVELOPMENTAL TOXICITY**). However, in these studies, the signs at the LOEL were more severe as tremors and salivation affected most of the animals in rat study, and death in the rabbit study. A second consideration is that the findings in the Lamb study (1993a) was based on Functional Observation Battery tests which are designed to detect neurological effects which may not be detected by gross observations. The severity of the effects observed in those two studies with pregnant animals suggested that they are more sensitive than non-pregnant animals. The NOEL for FOB testing may be lower than the 10 mg/kg/day based on gross observations. Therefore, the use of the default factor of 10-fold provided a reasonable estimate of the critical NOEL of 2.5 mg/kg/day.

V.B.3. Subchronic Toxicity

Only one subchronic dermal toxicity study was available to evaluate the dermal exposure of workers. The NOEL for systemic effect was 1 mg/kg/day for brain ChE inhibition in the rat (Rausina and Zimmerman, 1986). The actual amount of naled absorbed in this study was not determined and there was no pharmacokinetics for this route of exposure. The absorption was likely to be relatively high since the magnitude of the plasma, erythrocyte, and brain ChE was comparable to those for an oral study (100% absorption) with a NOEL of 1.0 mg/kg/day and a LOEL of 10 mg/kg/day (Lough *et al.*, 1981). The absorption may have been enhanced due to the injury at the application site which inflammation and necrosis. For this risk assessment, the dermal NOEL was adjusted to account for dermal absorption based on a default factor of 50% as used in the Exposure Assessment (Volume II).

To address local skin effects, an estimated NOEL of 0.1 mg/kg/day was calculated from a LOEL of 1 mg/kg/day (Rausina and Zimmerman, 1986) and a default factor of 10 for the extrapolation of a NOEL from a LOEL. Since the effects at the LOEL was described as minimal to mild, the actual NOEL may be less than 10-fold of the LOEL. If this is the case, then the risks may be overestimated. For mild effects, U.S. EPA generally applies a 3-fold uncertainty factor. However, A more appropriate unit for the dose based on surface area was not calculated since the surface area of application was not given in the study.

V.B.4. Chronic Toxicity

An oral study was also used for chronic exposure because there were no dermal or inhalation chronic toxicity studies. The critical NOEL was 0.2 mg/kg/day for brain ChE inhibition in two species (rats and dogs) (Batham *et al.*, 1984; IRDC, 1986). The impact on the use of an oral NOEL to assess chronic dermal exposure is unknown since there was also no information on the pharmacokinetics of naled after long-term exposure by either route.

V.C. EXPOSURE ASSESSMENT

V.C.1. Non-dietary Exposure (Including Ambient Air)

The uncertainties involved in occupational and residential exposures included the following: (1) the use of the highest air level of naled for ambient air level, (2) use of passive patch dosimetry data to derive the dermal exposure, (3) the use to the U.S. EPA Pesticide Handler Exposure Database, (4) estimation of full workday exposure from partial workday monitoring, (5) default dermal absorption factor of 50%, (6) exposure to DDVP, (7) use of other default factors (body weight, inhalation rate, exposure duration). A detailed discussion is included in the Worker Exposure Assessment (**Volume II**). Many of the uncertainties were considered to have overestimated the exposures.

V.C.2. Dietary Exposure

In the dietary analyses, the exposures for some commodities may be overestimated when certain assumptions were used in the absence of data. One of the source of overestimation was 100% crop treatment for many of the commodities. When data were available, the residue values of some commodities were adjusted to account for percentage of crop treatment which ranged from 1% to 65% (**IV.B.2.d. (2) Chronic Dietary Exposure**, Table 18). Another source of overestimation was the use of tolerance levels as the theoretical residues in or on eggs, hops, meat, and poultry. U.S. EPA has recently completed the evaluation of the tolerances for meat, milk, poultry, and egg and determined that "there is no reasonable expectation of finite residues" of naled in or on these commodities (U.S. EPA, 1999). U.S. EPA plans to revoke their tolerances in a subsequent notice. Because of this proposed action, the dietary exposure assessment for this risk characterization document was re-evaluated without these commodities (data not shown but available if requested). The acute exposures were reduced by 1% (nursing infants) to 14% (U.S. population, Hispanics, non-Hispanic whites and non-Hispanic blacks). The chronic dietary exposures were also reduced and to a greater extent since chronic exposures include non-users of the commodities. The reduction ranged from 48% (all infants) to 71% (males 13-19 years old). Since the MOEs for acute and chronic exposures were ≥ 800 and dietary exposure had little or no impact on the combined exposures, additional refinements to the dietary exposure estimates were not conducted.

V.D. RISK CHARACTERIZATION

The MOEs for potential acute and chronic exposures were based on NOELs for cholinesterase effects in rats or dogs exposed to naled by the oral route. When the NOEL for non-oncogenic effects is based on animal data, a MOE of 100 is generally considered adequate for human health protection against potential acute or chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for interspecies variability. These uncertainty factors assume that humans may be up to 10 times more sensitive to the effects of a chemical than the most sensitive experimental animal; and that there may be up to a 10-fold variation in response between humans. For the discussion of whether or not the exposure exceeded the benchmark level for health concerns, MOE values >90 were considered equivalent to 100 due to the

uncertainty and default assumptions (discussed in **V.B.** and **V.C.**) used in the calculation of the values.

V.D.1. Interspecies Extrapolation

For naled, a quantitative comparison of the sensitivity between humans and experimental animals to naled toxicity was not conducted because of the lack of data on human exposure and toxicity (**III.I. HUMAN STUDIES**). The current DPR default for interspecies extrapolation is a factor of 10-fold with respect to the dose.

V.D.2. Intraspecies Extrapolation

For intraspecies variation in the response to naled, the default factor of 10 was used because human reports did not provide sufficient information to derive another factor.

V.D.3. Non-dietary Exposure (including Ambient Air)

Only the MOEs of grape harvesters were above the benchmark for all exposure durations (Table 23). For other workers, the MOEs were less than 100 for most exposure scenarios (Tables 23). The risks to these workers, in particular the agricultural workers, may be overestimated due to factors discussed in the previous section (**V.C.1. Non-dietary Exposure**) and discussed in details in **Volume II**.

The MOEs for ambient air exposures by adults and children to naled or DDVP were $\geq 16,250$. The MOEs for bystanders and residents near naled treatment sites were greater than 100 (Table 23). While the MOEs for homeowner use of low pressure hand wand were greater than 100, those exposed to naled from flea collars or backpack sprayers had MOEs of less than 100 only for acute exposure.

V.D.4. Dietary Exposure

The MOEs for acute and chronic dietary exposures naled and DDVP were ≥ 800 for all population subgroups (Table 24). The lifetime risks for dietary exposures to DDVP-derived from naled and direct DDVP uses were 6.9×10^{-7} and 1.2×10^{-6} for q1 and q1*, respectively. These MOEs are overestimates of the actual risk because mushroom and rice were included in the analysis; the tolerances for these uses were recently revoked (U.S. EPA, 1998). Additional factors in the overestimation included the assumption of 100% crop treatment for some commodities and the use of tolerance levels as residue levels (**V.C.2. Dietary Exposure**).

V.D.5. Combined Exposure

The combined acute and chronic MOEs were similar in magnitude as those for non-dietary exposure alone (**V.D.3. Non-dietary Exposure**).

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to “upgrade its risk assessment process as part of the tolerance setting procedures” (U.S. EPA, 1997a and b). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, “Pesticides in the Diets of Infants and Children” (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

V.E.1. Pre- and Post- Natal Sensitivity

Under FQPA, U.S. EPA has used the additional uncertainty factor to address incomplete toxicology database and endpoints of concern. However, a final policy on the use of the factor has not been developed by the U.S. EPA.

The database for naled was complete for the evaluation of potential pre- and post-natal sensitivity from exposure. The completeness of the database has been used by the U.S. EPA to remove the FQPA factor. There was no evidence of increased pre- and post-natal sensitivity from developmental or reproductive toxicity. The rat developmental toxicity study showed a maternal NOEL (10 mg/kg/day for cholinergic signs and decreased body weight) lower than that for developmental NOEL (> 40 mg/kg/day for no toxicity) (Science Applications Inc., 1984). In the rabbit developmental toxicity pilot study, the NOEL of 2 mg/kg/day for decreased pup weight was lower than that (10 mg/kg/day) for cholinergic signs in the dams (Hardy, 1985). However, the decrease in the pup weight was not statistically significant in the range-finding study and was not confirmed in the definitive study with more animals. In the definitive study, the NOELs for maternal and developmental toxicity were the same (> 8 mg/kg/day) for no toxicity observed (FitzGerald, 1985). In the rat reproductive toxicity study, the lowest dose (2 mg/kg/day) resulted in decreased body weight in the dams while it was the NOEL for decreased pup survival, body weight, and numbers at birth at higher doses (Bio/dynamic Inc., 1985).

In the toxicity studies reviewed (**III. TOXICOLOGY PROFILE**), naled has not been shown to cause lesions in the brain. The only nervous system-related lesions were focal mineralization of the spinal cord in the dog (IRDC., 1986) and axonal degeneration of the spinal cord in the hen (Redgrave *et al.*, 1990). However, DDVP has been reported to cause decreased brain weights in guinea pig offspring (Mehl *et al.*, 1994). This published study was not considered in the naled RCD but was reviewed for DDVP. In this study, pregnant guinea pigs were exposed to DDVP (15 mg/kg/day or 15 mg/kg/day twice daily at 12-hour intervals) on gestational days 42, 43, and 44; or days 44, 45 and 46. There was a single pregnant dam per dosing regimen and one litter per pups (4 in each litter) was analyzed for the effect on the brain weight. Other organophosphates tested were trichlorfon (125 mg/kg/day, days 42, 43 and 44), ethyl-trichlorfon (125 mg/kg/day, days 4, 45 and 46), ethyl-trichlorfon (138 and 121 mg/kg/day, days 42 and 44), soman and TOCP. The data showed treatment with trichlorfon

and dichlorvos during gestation days of the brain growth spurt caused significantly lower total brain weight and lower weight for selected regions of the brain (cerebellum, medullar, diencephalon, and quadrigemina). There was no effect on enzyme activities (glutamate decarboxylase, choline acetyltransferase, and acetylcholinesterase) in the brain. The major problem with the data interpretation was that only a single dam was treated for each dosing regimen. Since the doses used in this study are much higher than the critical acute NOEL (2.5 mg/kg/day)^c used for risk characterization, an additional uncertainty factor would not be necessary at this time.

In the naled reregistration document, U.S. EPA has determined that the additional uncertainty factor should be removed (Rowland to Whitby, 1998). This decision, however, did not include any consideration of the above DDVP study (Mehl *et al.*, 1994).

The U.S. EPA SAP reviewed this study in the determination of whether an additional uncertainty factor was needed for DDVP exposure (Lewis, 1998a). Consistent with the DPR review, the SAP was concerned that the data came from only one litter. The Panel concluded that the study could not be used to determine developmental toxicity. However, it “suggests the possibility of a developmental effect on the brain”. Because of uncertainties associated with developmental neurotoxicity and patterns of human exposure, the Panel decided to retain the additional uncertainty factor. However, the Panel was divided as to whether the factor was a 10-fold or 3-fold factor. In the draft risk assessment for DDVP, U.S. EPA proposed a 3-fold factor to address the potential increased sensitivity to DDVP by infants and children.

V.E.2. Aggregate Exposures

Aggregate exposure is discussed in **V.D.5. Combined Exposure**. In this risk assessment, aggregate exposure was considered for occupational and dietary, as well as residential and dietary exposures. This approach is different than that practiced by the U.S. EPA. The FQPA mandated aggregate exposures of home, food, and drinking water, but not the exposure from work.

V.E.3. Cumulative Toxicity

This risk characterization document addressed risks from naled exposure as well as DDVP, a toxicologically active metabolite of naled. The potential exposure to DDVP in the diet from trichlorfon is limited since trichlorfon residues may be present only in imported cattle meat and by-products.

There is a potential for cumulative toxicity between naled and other organophosphates. In the recent FIFRA SAP meeting, the proposed U.S. EPA policy is that cholinergic toxicities of organophosphates are expressed through the common mechanism of interactions with ChE, and consequently, the toxicities of these pesticides should be considered as a group for cumulative risk assessments (Lewis, 1998b). In addition to the toxicological considerations, the

^cIn terms of moles, the DDVP and trichlorfon doses used in the studies were 68 $\mu\text{mole/kg/day}$ and 486 $\mu\text{mole/kg/day}$ compared to the naled acute NOEL of 6.6 $\mu\text{mol/kg/day}$.

extent of coexistence of these chemicals in the environment should also be included to develop a realistic assessment of the cumulative risk of multiple chemical exposures. U.S. EPA is currently in the process of developing the methodology to address this issue.

V.E.4. Endocrine Effects

There is no known naled-induced endocrine disruption effect at this time.

VI. TOLERANCE ASSESSMENT

VI.A. INTRODUCTION

VI.A.1. U.S. EPA

U.S. EPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities (Section 409 of FFDCA). A tolerance is the legal maximum residue concentration of a pesticide which is allowed in a raw agricultural commodity and processed food. The tolerances are established at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from chronic dietary exposure (U.S. EPA, 1991). The data requirements for tolerances include: (1) residue chemistry, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 1996). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and formulations proposed (U.S. EPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (U.S. EPA, 1997a and b). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. The tolerances must be health-based and the same standards are used to establish tolerances for both the raw agricultural commodities and their processed forms. FQPA required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, the evaluations of the tolerance must take into account: (1) aggregate exposure from all non-occupational sources, (2) effects from cumulative exposure to the pesticide and other substances with common mechanisms of toxicity, (3) effects of *in utero* exposure; and (4) potential for endocrine disrupting effects (**V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT**).

Under FQPA, U.S. EPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (U.S. EPA, 1997c). Previously, U.S. EPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the U.S. EPA uses a tiered approach and the assessment includes all label-use commodities.

VI.A.2. California

In California, U.S. EPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides. In these assessments, the tolerance for each specific commodity is evaluated individually and is discussed in the following sections. For a pesticide registered for use on multiple commodities, tolerance assessments are conducted for only a group of selected fruits and vegetables. Generally,

commodities are selected from all the uses based on the potential for high levels of exposure. While the tolerance assessment was limited to the tolerances for naled, there is a potential for cumulative toxicity with other organophosphates at or lower than the respective tolerances. As discussed in **V.E.3. Cumulative Toxicity**, U.S. EPA is developing the methodology to address multiple chemical exposures. Once available, the tolerance assessment for naled may have to be reevaluated.

For naled, the tolerances for 19 commodities were analyzed: broccoli, cauliflower, celery, cucumber, grape, grapefruit, kale, lettuce, lemon, milk, orange, peach, pepper, rice, spinach, strawberry, Swiss chard, tangerine and tomato. They were selected because of high consumption rates, high frequency of consumption, or high tolerance levels. The acute NOEL of 2.5 mg/kg/day for cholinergic signs in rats was used to calculate the margin of exposures (Table 22; Lamb, 1993a).

VI.B. ACUTE EXPOSURE

An acute exposure assessment is conducted for each individual label-approved commodity at the tolerance. The TAS Exposure-4™ software program and the 1989-1992 CSFII consumption databases were used in this assessment. The acute tolerance assessment does not routinely address multiple commodities all at tolerance levels because the probability of consuming multiple commodities that are all at the tolerance level significantly decreases as the number of commodities included in the assessment increases. A list of all the tolerances is in Appendix B.

The MOE values for the exposures of all population groups to the tolerances were greater than 100 except for the following commodities: orange, grapefruit, and spinach (Table 26). The lowest MOE was 6 for the consumption of oranges at the tolerance by nursing infants (< 1 year old) and the exposure was 0.41 mg/kg/day. The 95th percentile consumption rate for oranges was 136 g/kg/day and only 2 of the 8 users were at this percentile or higher. This rate is likely an overestimation since it was 10-times higher than those for non-nursing infants (16 g/kg/day) with a larger population (11 of 62 users). However, the MOEs for non-nursing infant and those for children (76 of 1134 users) were 51-56, also less than the benchmark of 100.

The MOEs for the grapefruit at the tolerance were less than 100 for non-Hispanic Blacks and children (7-12 years old). For both population subgroups, the users with consumption at the 95th percentile were about 8% of total users in the subgroup (11/141 and 6/88 total users for non-Hispanic Blacks and children 7-12 years old, respectively). The consumption rates at this percentile were considered reasonable. For children, the 95th percentile and mean consumption rates were 12.4 g/kg/day and 4.3 g/kg/day (or ½ medium size grapefruit per 22 kg child). For non-Hispanic Blacks, the 95th percentile and mean consumption rates were 11.6 g/kg/day and 3.7 g/kg/day (or 1 medium size grapefruit per 60 kg person).

The MOE for spinach at the tolerance was less than 100 only for children (1-6 years). There were 7 users (of 47 total users) at the 95th percentile consumption rate of 14.1 g/kg/day. The mean consumption rate was 4.5 g/kg/day or 45 g of spinach for a 10 kg child. This rate was considered reasonable since the average serving size is 90 g for boiled spinach.

VI.C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities is not conducted because it is highly improbable that an individual would habitually consume single or multiple commodities with pesticide residues at tolerance levels. This conclusion is supported by data from both federal and DPR pesticide monitoring programs which show that <1% of all sampled commodities have residue levels at or above the established tolerance (DPR, 1989-1995).

Table 26. The margins of exposure for potential acute dietary exposure to naled based on residues at tolerance levels.

Population subgroups	Margins of Exposure ^a		
	Orange	Grapefruit	Spinach
US Pop. all seasons	>100	>100	>100
Pacific Region	>100	>100	>100
Hispanics	92	>100	>100
Non-Hispanic Whites	>100	>100	>100
Non-Hispanic Blacks	>100	72	>100
Non-Hispanic Other	>100	>100	>100
All Infants	51	>100	>100
Infants (nursing, < 1 year)	6	>100	>100
Infants (non-nursing, < 1 year)	52	>100	>100
Children (1-6 years)	56	>100	59
Children (7-12 years)	>100	67	>100
Females (13+ years) (pregnant, not nursing)	>100	>100	>100
Females (13+ years) (nursing)	>100	>100	>100
Females (13-19 years) (not pregnant, not nursing)	>100	92	>100
Females (20+ years) (not pregnant, not nursing)	>100	>100	>100
Females (13-50 years)	>100	>100	>100
Males (13-19 years)	>100	>100	>100
Males (20+ years)	>100	>100	>100
Seniors (55+ years)	>100	>100	>100

^{a/} Margin of exposure was calculated based on the acute NOEL of 2.5 mg/kg/day for cholinergic signs in rats (Lamb, 1993a) and the 95th percentile of potential acute dietary exposure estimates using the 1989-1992 Continuing Survey of Food Intake of Individuals.

VII. CONCLUSIONS

The risk of potential exposure to naled was evaluated for occupational, residential, dietary, and combined uses. It was based on toxicity observed in experimental animal studies and was expressed as the margin of exposure. The benchmark MOE traditionally considered as adequate for the protection of human health is a MOE of 100 when based on no-effect levels from experimental animal toxicity studies. It is essential that the significance of the MOEs be viewed in the context of the limitations and uncertainties discussed.

Based on the currently available toxicity and exposure information, DPR concluded that the MOEs for skin effects for all workers from seasonal exposure were less than the benchmark. For systemic effects, scenarios and workers or residents with MOEs of less than the benchmark were:

- (1) acute exposure only: homeowners using flea collars or backpack sprayers;
- (2) seasonal exposure only: aerial spray applicators and groundboom applicators; grape girdler/thinners, cotton scouts, hand-wand sprayer workers; aerial mosquito control workers;
- (3) acute and seasonal exposures: aerial spray and groundboom mixer/loaders, aerial spray flaggers, airblast and backpack applicators, veterinarians, backpack sprayer (non-agricultural use), and sewage system injection workers;
- (4) seasonal and chronic exposures: vegetable crop harvesters; and
- (5) acute, seasonal, and chronic exposures: greenhouse harvesters.

For dietary exposure, the MOEs for acute and chronic dietary exposures to naled and DDVP residues were greater than the benchmark of 100. The oncogenic risk for lifetime exposure to DDVP derived from naled and DDVP direct uses were $\leq 1.2 \times 10^{-6}$. In combined exposures, MOEs were essentially those from non-dietary routes since the dietary exposure was relatively low and had minimal impact on the total combined exposure.

The MOEs for residues at tolerances were greater than the benchmark for most commodities with the exceptions of oranges (infants and children 1-6 years), grapefruit (Non-Hispanic blacks, and children 7-12 years), and spinach (children 1-6 years).

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VIII. APPENDICES

APPENDIX A

Summary of Dichlorvos Risk Characterization Document

The summary of DDVP risk characterization is based on the risk characterization document (Lim *et al.*, 1996) and Addenda (Lim, 1997; Lim, 1998).

I. INTRODUCTION

I.A. Chemical Identification

DDVP is an organophosphate insecticide used for the control of pests in enclosed spaces such as buildings and residents, on pets, on vegetables in greenhouses, on commodities during post-harvest storage, and on livestock. From 1991 to 1993, approximately 4,000-5,000 pounds of DDVP were used each year for structural and livestock pest control. DDVP exerts its toxicological activity primarily through the inhibition of acetylcholinesterase activity. Clinical signs associated with its toxicity included salivation, diarrhea, tremors, and death.

I.B. Regulatory History

DDVP is currently under Special Review by the U.S. Environmental Protection Agency (USEPA). In 1989, the Scientific Advisory Panel of the USEPA recommended that DDVP oncogenicity classification be changed from a B2 carcinogen to a C carcinogen. Because of oncogenic risks, most of the food tolerances have been revoked. A revocation of tolerances for bagged or packaged nonperishable commodities has been proposed. In 1993, the registrants of DDVP in California voluntarily canceled the use on fresh vegetables.

I.C. Environmental Fate

DDVP is not likely to persist in the environment since it is volatile, does not bind to soil, and is hydrolyzed. The half-life of DDVP was 5.2 days in aqueous buffered solution at pH 7. The half-lives ranged from 9 to 20 days for DDVP in tap water with pH 7.5 to 8.1. DDVP was also degraded by soil microorganisms with a half-life of 10.2 hours. After foliar application, DDVP residues on the leaves may be volatilized, hydrolyzed, and absorbed into the plants.

II. TOXICOLOGY PROFILE

II.A. Pharmacokinetics

DDVP was rapidly absorbed by the oral, intravenous, intraperitoneal, and inhalation routes and slowly absorbed by the dermal route. After absorption, the radioactivity distributed to major organs including the liver and kidneys. DDVP was metabolized completely by ester hydrolysis and demethylation. Initial metabolites were mono- and dimethyl phosphates, and desmethyl DDVP. Once formed, they may be further metabolized. Final metabolites were either incorporated in tissues or excreted. Major routes of excretion were in the urine and in the exhaled air, while to a lesser extent in the feces and in the milk. Excretion routes, tissue distribution, and urinary metabolites in rats were similar following inhalation or oral exposures.

II.B. Acute Toxicity

DDVP was more toxic than its metabolites as determined by the magnitude of the 72 hour lethal dose after intraperitoneal administration. Human exposure of DDVP by ingestion and from the use of no-pest strips resulted in the inhibition of plasma and erythrocyte cholinesterase (ChE) activities. Acute effects observed in laboratory animals from oral or inhalation exposures included diarrhea, irritability, salivation, lethargy, pupillary constriction, tremors, decreased neuromuscular functions, and death.

II.C. Subchronic Toxicity

Subchronic exposures to DDVP resulted in the inhibition of brain, erythrocyte, or/and plasma ChE activities in humans, rats, mice, dogs, and cows. Clinical signs observed in laboratory animals were tremors, diarrhea, decreased body weight gain, increased frequency of salivation and urine staining in rats, and increased activity and urination in dogs. Other effects included statistically significant decreases in red blood cell parameters (cell counts, hemoglobin, and hematocrit) in rats. Lactating rats and milk cows showed ChE activity depression and cholinergic signs, but ChE inhibition was not observed in the offspring.

II.D. Chronic Toxicity and Oncogenicity

DDVP inhibited plasma, erythrocyte, and brain ChE activities. Other non-oncogenic effects included hepatocellular lesions (vacuoles in the cytoplasm, cell swelling, prominence of cell membranes), reduced body weight, emesis, salivation, and ataxia. Oncogenic effects observed in rats and mice were pancreatic adenoma; mononuclear cell leukemia; mammary gland carcinoma, fibroadenoma, and adenoma; forestomach papillomas and carcinomas; and pituitary adenomas. DDVP also increased tumor growth rate in rats given leukemia transplant.

II.E. Genotoxicity

DDVP was genotoxic in some *in vitro* systems, including assays with *Salmonella* TA 100 strain and *Schizosaccharomyces pombe*, mouse lymphoma forward mutation assay, and unscheduled DNA synthesis assay using human epithelial cells. However, DDVP was not genotoxic in the micronucleus, dominant lethal, *in vivo* chromosomal aberrations, and *in vivo* sister chromatid exchange assays. Studies conducted in the presence and absence of a liver preparation (S-9 fraction) showed that the decrease in genotoxicity in the presence of the preparation may be due to the inactivation of DDVP by liver esterases. Methylated DNA was detected in tissues of mice given DDVP by intraperitoneal injection, but not in rat tissues when DDVP was given by inhalation.

II.F. Reproductive Toxicity

Exposure of rats to DDVP in the water during reproduction resulted in the inhibition of plasma, erythrocyte, and brain ChE. Clinical signs were observed in both parents and offsprings. Other toxicity included decreased body weights and decreased water

consumption. Re-mating of the F₁ females after the F₂ generation showed that decreased estrous cycling and increased incidence of abnormal estrus cycling. Mice exposed to DDVP-containing resin strips showed only plasma ChE depression and no effect on reproduction.

II.G. Developmental Toxicity

DDVP did not caused developmental toxicity in rats, mice, or rabbits. Cholinergic signs (tremors, ataxia, diarrhea, and other effects) were observed in the pregnant rats and rabbits.

II.H. Neurotoxicity

Possible adverse effects of nerve fiber degeneration and spinal cord degeneration were observed in chickens treated with DDVP. No acute delayed neurotoxicity in hens was reported, except at lethal doses. Acute neurotoxicity study in the rat given DDVP by gavage resulted in cholinergic effects which included gait alteration, constricted pupils, tremors, and salivation.

III. RISK ASSESSMENT

III.A. Hazard Identification

The No-Observed-Effects Levels (NOELs) from both inhalation and oral studies, and oncogenic risk from an oral study were used to evaluate the health hazards from potential exposure by workers and the general population to DDVP. For non-oncogenic endpoints, acute and chronic inhalation and dietary exposures were considered. For oncogenic endpoints, inhalation and dietary exposures to DDVP were assessed.

For acute inhalation exposure, the definitive NOEL was 1.25 $\mu\text{g/L}$ or 0.65 mg/kg-day (NOEL adjusted for exposure duration and respiration rate). The NOEL was based on death in pregnant rabbits after 2 days of inhalation exposure to a LOEL of 2 $\mu\text{g/L}$ DDVP.

For oral exposure, the acute NOEL was 0.5 mg/kg-day based on erythrocyte ChE inhibition in humans. The NOELs for chronic toxicity were based on the inhibition of brain ChE activity in a one-year dog oral study and a two-year rat inhalation study. The adjusted NOELs for inhalation and oral routes were 0.025 mg/kg-day, and 0.05 mg/kg-day, respectively.

Oncogenic risk was determined based on the finding of mononuclear cell leukemia in rats given DDVP by gavage for 2 years. The human equivalent potency factors were 0.20 mg/kg-day⁻¹ for q₁ and 0.35 mg/kg-day⁻¹ for q₁*, the 95th percentile upper confidence limit.

III.B. Exposure Assessment

The potential health hazard associated with the use of DDVP was considered for occupational, residential, and dietary exposures under acute, chronic, and lifetime scenarios.

The population subgroups exposed to DDVP in the work place were workers involved in warehouse fumigation, livestock applications, and structural applications. Residential exposures to DDVP were due to the use of liquid sprays, foggers, no-pest strips, and flea collars. Dietary exposures to DDVP were due to the use on raw agricultural commodities (RAC), livestock, and processed foods. Estimates for chronic dietary exposure by USEPA were also assessed.

IV. RISK APPRAISAL

The margins of exposure (MOEs) for non-oncogenic effects from acute, chronic, and lifetime occupational exposures were less than 100 for the workers involved in warehouse fumigation, livestock applications, and structural applications. The lifetime oncogenic risk for the workers was $> 1 \times 10^{-6}$.

For residential exposure, the MOEs for non-oncogenic effects were greater than 100 only for structural residents (chronic and lifetime), and pet owners (acute, chronic, and lifetime). For other uses, the MOEs were less than 100. The lifetime oncogenic risk for the residents under all exposure scenarios was $> 1 \times 10^{-6}$.

For dietary exposure assessment using either USEPA or DPR exposure estimates, the MOEs for non-oncogenic effects were at or greater than 100 for all population subgroups for acute and chronic exposure. For lifetime exposure to all commodities, the oncogenic risk for the U.S. population was $< 1 \times 10^{-6}$ for both DPR and USEPA estimates.

For combined exposures in the work place and at home, the MOEs for non-oncogenic effects for all the workers were less than 100 and the lifetime oncogenic risk $> 1 \times 10^{-6}$.

V. TOLERANCE ASSESSMENT

The MOEs for the acute exposure based on individual tolerances on RACs and livestock products were greater than 100.

VI. CONCLUSIONS

The toxicological risk of potential exposure to DDVP was evaluated for occupational, residential, dietary and combined uses based on the inhibition of brain ChE activity, clinical signs, and the finding of mononuclear cell leukemia in animal studies. Using the conventional benchmark levels, a margin of safety of at least 100 (laboratory animal studies) or 10 (human studies) for non-oncogenic effects and a risk level of 1×10^{-6} or less for oncogenic effects are generally considered sufficiently protective of human health. The exposure levels of only a few groups meet those benchmark levels. Groups which have exposure levels which do not meet the benchmark levels are: all people occupationally exposed to DDVP alone and in combination with home exposure on an acute, chronic, and lifetime basis; and people exposed through residential use on an acute, chronic, and lifetime basis.

APPENDIX B

U.S. ENVIRONMENTAL PROTECTION AGENCY TOLERANCES

U.S. EPA has established tolerances for the residues of naled and its conversion product, DDVP, expressed as naled, in or on the following raw agricultural commodities (CFR 40 180.215):

<u>Commodity</u>	<u>Parts per million</u>	<u>Commodity</u>	<u>Parts per million</u>
almonds (hulls)	0.5	kale	3
almonds (nuts)	0.5	legumes, forage	10
beans (dry)	0.5	lemons	3
beans (succulent)	0.5	lettuce	1
beets, sugar, roots	0.5	melons	0.5
beets, sugar, tops	0.5	milk	0.05
broccoli	1	mushrooms	0.5
brussels sprouts	1	oranges	3
cabbage	1	peaches	0.5
cattle, fat	0.05	peas (succulent)	0.5
cattle, mbyp	0.05	peppers	0.5
cattle, meat	0.05	poultry, fat	0.05
cauliflower	1	poultry, mbyp	0.05
celery	3	poultry, meat	0.05
collards	3	pumpkins	0.5
cottonseed	0.5	rice	0.5
cucumbers	0.5	safflower, seed	0.5
eggplant	0.5	sheep, fat	0.05
eggs	0.05	sheep, mbyp	0.05
goats, fat	0.05	sheep, meat	0.05
goats, mbyp	0.05	spinach	3
goats, meat	0.05	squash, summer	0.5
grapefruit	3	squash, winter	0.5
grapes	0.5	strawberries	1
grasses, forage	10	Swiss chard	3
hogs, fat	0.05	tangerines	3
hogs, mbyp	0.05	tomatoes	0.5
hogs, meat	0.05	turnips, tops	3
hops	0.5	walnuts	0.5
horses, fat	0.05		
horses, mbyp	0.05		
horses, meat	0.05		

A tolerance of 0.5 ppm has been established for naled residues in or on all raw agricultural commodities from the use of naled for area pest (mosquito and fly) control.

mbyp= meat by product

APPENDIX C

TOXICOLOGY SUMMARIES

(The following is an electronic copy of the summary of toxicology data for naled. Actual signed copy may be obtained from the Registration Branch).

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

NALED

SB 950-041, Tolerance #00215
Chemical Code: 418

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

DATA GAP STATUS

Chronic rat:	(See "Combined rat", below).
Chronic dog:	No data gap, possible adverse effect.
Combined rat:	No data gap, possible adverse effect.
Oncogenicity mouse:	No data gap, no adverse effect.
Reproduction rat:	No data gap, possible 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.
Chromosomal aberration:	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 & hen.

Toxicology One-liners are attached: "***" indicates an acceptable study, "**Bold face**" of volume/record number indicates a possible adverse effect.

Revised by F. Martz, 1/21/88; Kishiyama, Parker, Gee, 10/12/88; Kishiyama, Gee, 5/24/89; Silva, 2/7/91, 7/27/94, 11/8/94, 1/9/96.

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

Rectified with Library printout through record #: 131952 & in volume #: 215-143.

FILE Name: T960109

II. TOXICOLOGY ONE-LINERS

COMBINED CHRONIC FEEDING/CARCINOGENICITY 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 (J. Wong, 3/28/85). Again unacceptable, lacked dose level justification (C. Aldous, 1/24/86). This was satisfied by first rebuttal, but still unacceptable. A review (F. Martz, 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 (F. Martz, 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). (JSK & J. Parker, 10/07/88).

043 022768. Exact duplicate of #037591 above.

032 928896. SBSCS31275E, rebuttal to combined rat study, record #037591-98 above; Prior review of report (C. Aldous, 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. (F. Martz, 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. (F. Martz, 1/21/88).

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

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 (G. Patterson, 11/7/86); review of supplemental data by F. Martz (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. (F. Martz, 5/22/87).

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. (J. Wong, 4/1/85 ; F. Martz, 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. (Gee, 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 CDFA and should be submitted. (Kishiyama, 5/23/89 and Gee, 5/24/89).

TERATOGENICITY 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. (C. Aldous, 1/17/86).

EPA One-Liner: Teratogenic NOEL > 40 mg/kg/day (HDT), Fetotoxic NOEL > 40 mg/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. (F. Martz, 7/29/87).

TERATOGENICITY 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 C. Aldous (1/16/86) as unacceptable, needing justification of dosage levels. Upgraded to ACCEPTABLE by F. Martz, 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. (F. Martz, 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. (Kishiyama, Gee, 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. (J. Wong, 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. I I. O-O-Dimethyl-O-(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. (J. Wong, 3/28/85 and Gee, 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. (J. Wong, 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. (J. Wong, 3/28/85 and Gee, 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 mg/plate by spot test, 0 to 50 mg/plate with 30 minutes preincubation; 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. (J. Wong, 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 C57Bl/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. (J. Wong, 4/1/85 and J. Remsen (Gee), 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. (F. Martz, 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. (J. Wong, 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. Gee, 5/23/89.

CHROMOSOMAL ABERRATION

** 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. (J. (Remsen) Gee, 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. (J. Wong, 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/REPAIR

** 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 mg/ml for 18 hours. Under study conditions, Naled did not induce unscheduled DNA synthesis in rat hepatocytes. ACCEPTABLE. (Kishiyama, 5/22/89 and Gee, 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-O-(1,2-Dibromo-2,2-Dichloroethyl)-Phosphate and Two O-Ether Derivatives of Trichlorfon," (Chem.-Biol. Interactions, 43: 361-370, 1983, Braun et al.). Naled (no purity information), 10 or 40 mM/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. (J. Wong, 3/28/85).

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

NEUROTOXICITY

Rangefinding Study:

127 130856 "A Rangefinding 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.** M. Silva, 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. M. Silva, 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.** M. Silva, 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). M. Silva, 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). (C. Aldous, 1/21/86).

No EPA One-Liner available.

SBSCS31275E: Rebuttal to neurotoxicity study referenced above. No new or useful information provided, study remains UNACCEPTABLE. (F. Martz, 7/28/87). No record number. CDFA 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 . (J. Wong, 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:CDBR 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 \geq 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, exophthalmus and splayed hindlimbs at \geq 75 mg/kg, salivation at \geq 300 mg/kg and hypoactivity at \geq 450 mg/kg (peak effects at 0.5 hr post-dosing). At \leq 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. M. Silva, 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, 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, males & 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. M. Silva, 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:CDBR 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. M. Silva, 7/21/94.

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 ug/L; possible adverse effect: corneal and nasal lesions; supplemental data. (H. Green and G. Patterson, 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 ug/L (6 h/day, 5d/week for 13 weeks). In addition, 10 rats/sex (control and 6.0 ug/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 ug/L. Average BDCA concentrations: 0, 0.18, 0.31 & 0.93 ug/L. Average MMAD at 5.8 ug/L = 2.4 um, at 1.29 & 0.23 ug/L < 0.7 um (most of the naled was in vapor).

Observations: Toxicity was determined by daily clinical observations, weekly body weights and food consumptions, 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 weighs & histopathological examinations. There were no treatment-related mortalities. Females at 6.0 ug/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 $\leq 10\%$. Both sexes showed an increase in clinical signs of cholinesterase inhibition at 6.0 ug/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 ug/L. It remained low in the recovery animals.
2. Mean Plasma ChE: Significantly decreased in both sexes at ≥ 1.2 ug/L. Male levels remained low throughout the 6 week recovery period, where females were reversed at 3 weeks recovery.
3. Mean Brain ChE: Significantly decreased at 6.0 ug/L in both sexes (some reversal by 6 weeks recovery but still a significant decrease).

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

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

Histopathology: Nasal pathology was observed in treated animals:

Effect Observed	Naled Concentration (ug/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	0	1	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 ug/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 ug/L (RBC and plasma ChE were significantly decreased at ≥ 1.2 ug/L and brain ChE was significantly decreased at 6.0 ug/L.) These data are supplemental. M. Silva, 8/17/94

APPENDIX D

CALCULATIONS

1. Dosage estimation for animals from an inhalation study (exposure level in ppm):

$$mg/kg-day = mg/m^3 \times respiration\ rate (m^3/kg-day) \times \frac{hours\ exposed}{24\ hours} \times \frac{days\ exposed/week}{7\ days} \times AF$$

For this equation, 1 $\mu g/L$ in air is equivalent to 1 mg/m^3 . The term for number of days exposed per week/7 days is used in the calculation only for studies when the animals were not dosed every day. The dosage was not corrected for absorption (absorption factor, AF). Only the dosages used in the calculation of MOE are corrected for 50% inhalation absorption rate.

The default respiration rates used are: 0.46 $m^3/kg-day$ for children, 0.26 $m^3/kg-day$ for human adults, 0.96 $m^3/kg-day$ for rats, 0.54 $m^3/kg-day$ for rabbits, and 1.80 $m^3/kg-day$ for mice (Zielhuis and van der Kreek, 1979).

For example: Using the NOEL of 1.14 $\mu g/L$ from Rittenhouse (1983a),

$$\frac{1.14\ mg}{m^3} \times \frac{0.96\ m^3}{kg-day} \times \frac{4.3\ hours}{24\ hours} = 0.20\ mg/kg-day$$

2. Dosage estimation for animals in a dietary study (exposure level expressed as ppm in the diet):

$$\mu g/kg-day = ppm\ (\mu g/g) \times FR\ (g/day) \times \frac{1}{body\ weight\ (kg)} \times \frac{days\ exposed/week}{7\ days}$$

The food consumption rate (FR) is derived either from the reports or the standard default is used. The standard default is based on body weight, 15% for mouse, 5% for rat, and 3% for rabbit.

3. Margin of Safety:

$$Margin\ of\ Safety = \frac{NOEL}{exposure\ level}$$

APPENDIX E

ACUTE DIETARY ANALYSIS- NALED AND DDVP EXPOSURE

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Section 3 Registration

Residue file name: NALEDACT

Analysis date: 05-07-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

COMMENT 1: Total naled (+ DDVP). DDVP 5XTEF. Juices & oils: ND=1/2 LOD

COMMENT 2: Analysis using naled acute NOEL. Most current residues.

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
13	N	GRAPES	0.015000	1.00	1.00	PDP2yr
14	N	GRAPES-RAISINS	0.015000	1.00	1.00	PDP2yr
15	N	GRAPES-JUICE	0.007500	1.00	1.00	PDP2yr
17	N	STRAWBERRIES	0.200000	1.00	1.00	DPR3yr
22	K	GRAPEFRUIT-PEELED FRUIT	0.015000	1.00	1.00	PDP1yr
23	K	GRAPEFRUIT-JUICE	0.007500	2.10	1.00	PDP1yr
26	K	LEMONS-PEELED FRUIT	0.015000	1.00	1.00	PDP0sr
27	K	LEMONS-PEEL	0.001500	1.00	1.00	PDP0sr
28	K	LEMONS-JUICE	0.007500	2.00	1.00	PDP0sr
33	K	ORANGES-JUICE-CONCENTRATE	0.007500	6.70	1.00	PDP2yr
34	K	ORANGES-PEELED FRUIT	0.015000	1.00	1.00	PDP2yr
35	K	ORANGES-PEEL	0.015000	1.00	1.00	PDP2yr
36	K	ORANGES-JUICE	0.007500	1.80	1.00	PDP2yr
38	K	TANGERINES	0.015000	1.00	1.00	PDP0sr
39	K	TANGERINES-JUICE	0.007500	2.30	1.00	PDP0sr
40	R	ALMONDS	0.035000	1.00	1.00	REG-f
48	R	WALNUTS	0.250000	1.00	1.00	FDA
65	M	PEACHES	0.015000	1.00	1.00	PDP2yr
66	M	PEACHES-DRIED	0.015000	7.00	1.00	PDP2yr
125	A	HOPS	0.500000	1.00	1.00	EPA
141	J	CANTALOUPE-NECTAR	no consumption in survey			
142	J	CANTALOUPE-PULP (MUSKMELON)	0.200000	1.00	1.00	DPR3yr
143	J	CASABAS	0.200000	1.00	1.00	DPR3yr
144	J	CRENSHAW	no consumption in survey			
145	J	HONEYDEW MELONS	0.200000	1.00	1.00	DPR3yr
146	J	PERSIAN MELONS	no consumption in survey			
147	J	WATERMELON	0.200000	1.00	1.00	DPR3yr
148	J	CUCUMBERS	0.200000	1.00	1.00	DPR3yr
149	J	PUMPKIN	0.250000	1.00	1.00	FDA
150	J	SQUASH-SUMMER	0.150000	1.00	1.00	DPR3yr
151	J	SQUASH-WINTER	0.150000	1.00	1.00	DPR3yr
154	I	EGGPLANT	0.150000	1.00	1.00	DPR3yr
155	I	PEPPERS-SWEET (GARDEN)	0.200000	1.00	1.00	DPR3yr
157	I	PEPPERS-OTHER	0.200000	1.00	1.00	DPR3yr
159	I	TOMATOES-WHOLE	0.150000	1.00	1.00	DPR3yr
160	I	TOMATOES-JUICE	0.075000	1.50	1.00	DPR3yr
161	I	TOMATOES-PUREE	0.075000	3.30	1.00	DPR3yr
162	I	TOMATOES-PASTE	0.075000	5.40	1.00	DPR3yr
163	I	TOMATOES-CATSUP	0.075000	2.50	1.00	DPR3yr
166	E	CELERY	0.015000	1.00	1.00	PDP2yr
168	F	BROCCOLI	0.015000	1.00	1.00	PDP2yr
169	F	BRUSSELS SPROUTS	0.150000	1.00	1.00	DPR3yr
170	F	CABBAGE-GREEN AND RED	0.150000	1.00	1.00	DPR3yr
171	F	CAULIFLOWER	0.150000	1.00	1.00	DPR3yr
172	F	COLLARDS	0.150000	1.00	1.00	DPR3yr
173	F	CABBAGE-CHINESE/CELERY/BOK CHO	0.150000	1.00	1.00	DPR3yr
174	F	KALE	0.150000	1.00	1.00	DPR3yr
176	E	LETTUCE-LEAFY VARIETIES	0.015000	1.00	1.00	PDP2yr
182	E	LETTUCE-UNSPECIFIED	0.015000	1.00	1.00	PDP2yr
186	E	SPINACH	0.200000	1.00	1.00	DPR3yr
187	E	SWISS CHARD	0.200000	1.00	1.00	DPR3yr
188	C	TURNIPS-TOPS	0.200000	1.00	1.00	DPR3yr
192	E	LETTUCE-HEAD VARIETIES	0.015000	1.00	1.00	PDP2yr
227	G	BEANS-DRY-GREAT NORTHERN	no consumption in survey			

228	G	BEANS-DRY-KIDNEY	0.017700	1.00	1.00	PDPgbs
229	G	BEANS-DRY-LIMA	0.017700	1.00	1.00	PDPgbs
230	G	BEANS-DRY-NAVY (PEA)	0.017700	1.00	1.00	PDPgbs
231	G	BEANS-DRY-OTHER	0.017700	1.00	1.00	PDPgbs
232	G	BEANS-DRY-PINTO	0.017700	1.00	1.00	PDPgbs
233	G	BEANS-SUCCULENT-LIMA	0.017700	1.00	1.00	PDP2yr
234	G	BEANS-SUCCULENT-GREEN	0.017700	1.00	1.00	PDP2yr
235	G	BEANS-SUCCULENT-OTHER	0.017700	1.00	1.00	PDP2yr
236	G	BEANS-SUCCULENT-YELLOW/WAX	0.017700	1.00	1.00	PDP2yr
240	G	PEAS (GARDEN)-DRY	0.015000	1.00	1.00	PDPpsr
241	G	PEAS (GARDEN)-GREEN	0.015000	1.00	1.00	PDPlyr
249	G	BEANS-DRY-BROADBEANS	0.017700	1.00	1.00	PDPgbs
250	G	BEANS-SUCCULENT-BROADBEANS	no consumption in survey			
251	G	BEANS-DRY-PIGEON BEANS	no consumption in survey			
253	G	BEANS-UNSPECIFIED	0.017700	1.00	1.00	PDPgbs
256	G	BEANS-DRY-HYACINTH	no consumption in survey			
257	G	BEANS-SUCCULENT-HYACINTH	no consumption in survey			
258	G	BEANS-DRY-BLACK EYE PEAS/COWPEA	0.017700	1.00	1.00	PDPgbs
259	G	BEANS-DRY-GARBANZO/CHICK PEA	0.017700	1.00	1.00	PDPgbs
261	A	MUSHROOMS	0.150000	1.00	1.00	DPR3yr
270	O	RICE-ROUGH (BROWN)	0.250000	1.00	1.00	FDA
271	O	RICE-MILLED (WHITE)	0.250000	1.00	1.00	FDA
282	B	BEET SUGAR	0.035000	1.00	1.00	REG-fp
290	A	COTTONSEED-OIL	0.030000	1.00	1.00	REG-fp
291	A	COTTONSEED-MEAL	0.030000	1.00	1.00	REG-fp
294	A	SAFFLOWER-SEED	no consumption in survey			
295	A	SAFFLOWER-OIL	0.030000	1.00	1.00	REG-fp
315	A	GRAPES-WINE AND SHERRY	0.007500	1.00	1.00	PDP2yr
318	X	MILK-NONFAT SOLIDS	0.001300	1.00	1.00	FDA2ch
319	X	MILK-FAT SOLIDS	0.001300	1.00	1.00	FDA2ch
320	X	MILK SUGAR (LACTOSE)	0.001300	1.00	1.00	FDA2ch
321	U	BEEF-MEAT BYPRODUCTS	0.050000	1.00	1.00	EPA
322	U	BEEF(ORGAN MEATS)-OTHER	0.050000	1.00	1.00	EPA
323	U	BEEF-DRIED	0.050000	1.00	1.00	EPA
324	U	BEEF(BONELESS)-FAT	0.050000	1.00	1.00	EPA
325	U	BEEF(ORGAN MEATS)-KIDNEY	0.050000	1.00	1.00	EPA
326	U	BEEF(ORGAN MEATS)-LIVER	0.050000	1.00	1.00	EPA
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.050000	1.00	1.00	EPA
328	U	GOAT-MEAT BYPRODUCTS	no consumption in survey			
329	U	GOAT(ORGAN MEATS)-OTHER	0.050000	1.00	1.00	EPA
330	U	GOAT(BONELESS)-FAT	no consumption in survey			
331	U	GOAT(ORGAN MEATS)-KIDNEY	no consumption in survey			
332	U	GOAT(ORGAN MEATS)-LIVER	no consumption in survey			
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	no consumption in survey			
334	U	HORSE	no consumption in survey			
336	U	SHEEP-MEAT BYPRODUCTS	no consumption in survey			
337	U	SHEEP(ORGAN MEATS)-OTHER	no consumption in survey			
338	U	SHEEP(BONELESS)-FAT	0.050000	1.00	1.00	EPA
339	U	SHEEP(ORGAN MEATS)-KIDNEY	no consumption in survey			
340	U	SHEEP(ORGAN MEATS)-LIVER	no consumption in survey			
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	1.00	EPA
342	U	PORK-MEAT BYPRODUCTS	0.050000	1.00	1.00	EPA
343	U	PORK(ORGAN MEATS)-OTHER	no consumption in survey			
344	U	PORK(BONELESS)-FAT	0.050000	1.00	1.00	EPA
345	U	PORK(ORGAN MEATS)-KIDNEY	no consumption in survey			
346	U	PORK(ORGAN MEATS)-LIVER	0.050000	1.00	1.00	EPA
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	1.00	EPA
355	V	TURKEY-BYPRODUCTS	0.050000	1.00	1.00	EPA
356	V	TURKEY-GIBLETS (LIVER)	0.050000	1.00	1.00	EPA
357	V	TURKEY-(BONELESS)-FAT	0.050000	1.00	1.00	EPA
358	V	TURKEY-(BONELESS)LEAN/FAT FREE	0.050000	1.00	1.00	EPA
359	V	TURKEY-UNSPECIFIED	no consumption in survey			
360	V	POULTRY-OTHER-LEAN (FAT FREE)	0.050000	1.00	1.00	EPA
361	V	POULTRY-OTHER-GIBLETS(LIVER)	no consumption in survey			
362	V	POULTRY-OTHER-FAT	0.050000	1.00	1.00	EPA
363	X	EGGS-WHOLE	0.050000	1.00	1.00	EPA

364	X	EGGS-WHITE ONLY	0.050000	1.00	1.00	EPA
365	X	EGGS-YOLK ONLY	0.050000	1.00	1.00	EPA
366	V	CHICKEN-BYPRODUCTS	no consumption in survey			
367	V	CHICKEN-GIBLETS(LIVER)	0.050000	1.00	1.00	EPA
368	V	CHICKEN (BONELESS)-FAT	0.050000	1.00	1.00	EPA
369	V	CHICKEN(BONELESS)LEAN/FAT FREE	0.050000	1.00	1.00	EPA
379	B	BEET SUGAR-MOLASSES	no consumption in survey			
383	F	CABBAGE-SAVOY	no consumption in survey			
384	E	CELERY JUICE	0.020000	1.00	1.00	PDP2yr
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	0.050000	1.00	1.00	EPA
392	N	GRAPES-JUICE-CONCENTRATE	0.007500	1.00	1.00	PDP2yr
398	X	MILK-BASED WATER	0.001300	1.00	1.00	FDA2ch
402	M	PEACHES-JUICE	0.007500	1.00	1.00	PDP2yr
405	G	PEAS-SUCCULENT/BLACKEYE/COWPEA	0.015000	1.00	1.00	PDP1yr
408	O	RICE-BRAN	0.250000	1.00	1.00	FDA
409	O	RICE-WILD	0.250000	1.00	1.00	FDA
416	N	STRAWBERRIES-JUICE	0.100000	1.00	1.00	DPR3yr
420	K	TANGERINES-JUICE-CONCENTRATE	no consumption in survey			
423	I	TOMATOES-DRIED	0.150000	14.30	1.00	DPR3yr
424	U	VEAL-(BONELESS)-FAT	0.050000	1.00	1.00	EPA
425	U	VEAL-(BONELESS)-LEAN (FAT FREE	0.050000	1.00	1.00	EPA
426	U	VEAL-(ORGAN MEATS)-KIDNEY	no consumption in survey			
427	U	VEAL-(ORGAN MEATS)-LIVER	no consumption in survey			
428	U	VEAL-(ORGAN MEATS)-OTHER	no consumption in survey			
429	U	VEAL-DRIED	no consumption in survey			
430	U	VEAL-MEAT BYPRODUCTS	no consumption in survey			
431	R	WALNUT OIL	no consumption in survey			
436	J	WATERMELON-JUICE	no consumption in survey			
441	K	GRAPEFRUIT-JUICE-CONCENTRATE	0.007500	8.26	1.00	PDP1yr
442	K	LEMONS-JUICE-CONCENTRATE	0.007500	11.40	1.00	PDP0sr
448	K	GRAPEFRUIT PEEL	no consumption in survey			
449	V	TURKEY-(ORGAN MEATS)-OTHER	0.050000	1.00	1.00	EPA

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Section 3 Registration

Residue file name: NALEDACT

Analysis date: 05-07-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Initial estimate of user-days as % of person-days in survey = 100.00%

COMMENT 1: Total naled (+ DDVP). DDVP 5XTEF. Juices & oils: ND=1/2 LOD

COMMENT 2: Analysis using naled acute NOEL. Most current residues.

U.S. POP - ALL SEASONS

Daily Exposure Analysis 1/

(mg/kg body-weight/day)

per Capita per User

Mean	0.000513	0.000515
Standard Deviation	0.000514	0.000514
Standard Error	0.000003	0.000003

Percent of Person-Days that are User-Days = 99.68%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000107	23,468	90.00	0.001094	2,285
20.00	0.000167	14,990	95.00	0.001467	1,704
30.00	0.000225	11,128	97.50	0.001874	1,334
40.00	0.000287	8,697	99.00	0.002474	1,010
50.00	0.000362	6,907	99.50	0.003025	826
60.00	0.000456	5,485	99.75	0.003764	664
70.00	0.000581	4,304	99.90	0.004675	535
80.00	0.000765	3,267			

WESTERN REGION

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000506	0.000509
Standard Deviation	0.000486	0.000486
Standard Error	0.000006	0.000006

Percent of Person-Days that are User-Days = 99.43%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000102	24,467	90.00	0.001094	2,286
20.00	0.000166	15,025	95.00	0.001435	1,742
30.00	0.000225	11,118	97.50	0.001816	1,377
40.00	0.000291	8,591	99.00	0.002367	1,056
50.00	0.000368	6,789	99.50	0.002893	864
60.00	0.000461	5,428	99.75	0.003272	764
70.00	0.000581	4,305	99.90	0.003923	637
80.00	0.000763	3,275			

1/ Analysis based on all participant-days in NFCS 1989-92 survey.

2/ Margin of Exposure = NOEL/ Dietary Exposure.

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

HISPANICS

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000623	0.000628
Standard Deviation	0.000619	0.000619
Standard Error	0.000011	0.000011

Percent of Person-Days that are User-Days = 99.35%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000113	22,049	90.00	0.001398	1,789
20.00	0.000191	13,089	95.00	0.001848	1,353
30.00	0.000269	9,279	97.50	0.002349	1,064
40.00	0.000347	7,205	99.00	0.002797	894
50.00	0.000433	5,773	99.50	0.003810	656
60.00	0.000553	4,518	99.75	0.004198	595
70.00	0.000718	3,483	99.90	0.004646	538
80.00	0.000933	2,680			

NON-HISPANIC WHITES

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000492	0.000493
Standard Deviation	0.000480	0.000479
Standard Error	0.000003	0.000003

Percent of Person-Days that are User-Days = 99.75%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000107	23,291	90.00	0.001040	2,404
20.00	0.000165	15,145	95.00	0.001374	1,819
30.00	0.000221	11,291	97.50	0.001738	1,439
40.00	0.000281	8,896	99.00	0.002322	1,077
50.00	0.000353	7,090	99.50	0.002887	866
60.00	0.000442	5,651	99.75	0.003530	708
70.00	0.000561	4,460	99.90	0.004245	589
80.00	0.000731	3,420			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

NON-HISPANIC BLACKS

Daily Exposure Analysis
(mg/kg body-weight/day)
per Capita per User

Mean	0.000524	0.000526
Standard Deviation	0.000535	0.000535
Standard Error	0.000008	0.000008

Percent of Person-Days that are User-Days = 99.61%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000095	26,362	90.00	0.001201	2,082
20.00	0.000157	15,959	95.00	0.001556	1,607
30.00	0.000218	11,450	97.50	0.001968	1,271
40.00	0.000280	8,931	99.00	0.002386	1,048
50.00	0.000359	6,968	99.50	0.002943	850
60.00	0.000456	5,480	99.75	0.003661	683
70.00	0.000594	4,206	99.90	0.004448	562
80.00	0.000788	3,171			

NON-HISPANIC OTHER

Daily Exposure Analysis
(mg/kg body-weight/day)
per Capita per User

Mean	0.000737	0.000744
Standard Deviation	0.000846	0.000847
Standard Error	0.000026	0.000026

Percent of Person-Days that are User-Days = 99.06%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000110	22,772	90.00	0.001540	1,623
20.00	0.000206	12,162	95.00	0.001911	1,308
30.00	0.000308	8,111	97.50	0.002695	928
40.00	0.000399	6,267	99.00	0.005168	484
50.00	0.000516	4,850	99.50	0.006326	395
60.00	0.000672	3,723	99.75	0.006968	359
70.00	0.000850	2,940	99.90	0.007121	351
80.00	0.001072	2,332			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Section 3 Registration

Residue file name: NALEDACT

Analysis date: 05-07-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

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NURSING INFANTS (<1 YEAR)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000171	0.000312
Standard Deviation	0.000489	0.000626
Standard Error	0.000039	0.000074

Percent of Person-Days that are User-Days = 54.71%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000004	606,580	90.00	0.000898	2,784
20.00	0.000005	543,470	95.00	0.001884	1,327
30.00	0.000005	492,255	97.50	0.002565	975
40.00	0.000008	328,945	99.00	0.002664	938
50.00	0.000014	174,749	99.50	0.002697	927
60.00	0.000018	136,558	99.75	0.002714	921
70.00	0.000319	7,825	99.90	0.002724	918
80.00	0.000461	5,418			

NON-NURSING INFANTS (<1)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000700	0.000704
Standard Deviation	0.000835	0.000836
Standard Error	0.000039	0.000040

Percent of Person-Days that are User-Days = 99.44%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000020	123,494	90.00	0.001789	1,397
20.00	0.000027	93,961	95.00	0.002417	1,034
30.00	0.000153	16,391	97.50	0.002916	857
40.00	0.000291	8,597	99.00	0.003409	733
50.00	0.000412	6,075	99.50	0.004386	570
60.00	0.000592	4,226	99.75	0.005261	475
70.00	0.000938	2,666	99.90	0.005627	444
80.00	0.001159	2,156			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

FEMALES (13+/PREG/NOT NSG)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000415	0.000415
Standard Deviation	0.000386	0.000386
Standard Error	0.000020	0.000020

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000083	30,226	90.00	0.000906	2,759
20.00	0.000116	21,537	95.00	0.001192	2,097
30.00	0.000162	15,457	97.50	0.001612	1,551
40.00	0.000212	11,810	99.00	0.001825	1,370
50.00	0.000283	8,845	99.50	0.001896	1,319
60.00	0.000378	6,616	99.75	0.002048	1,221
70.00	0.000504	4,964	99.90	0.002143	1,167
80.00	0.000631	3,963			

FEMALES (13+/NURSING)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000517	0.000517
Standard Deviation	0.000398	0.000398
Standard Error	0.000027	0.000027

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000101	24,862	90.00	0.000985	2,539
20.00	0.000167	14,977	95.00	0.001269	1,971
30.00	0.000261	9,562	97.50	0.001658	1,508
40.00	0.000340	7,351	99.00	0.001822	1,372
50.00	0.000424	5,903	99.50	0.001980	1,262
60.00	0.000512	4,886	99.75	0.002110	1,185
70.00	0.000652	3,837	99.90	0.002431	1,028
80.00	0.000830	3,010			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

CHILDREN (1-6 YEARS)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000998	0.000999
Standard Deviation	0.000878	0.000878
Standard Error	0.000014	0.000014

Percent of Person-Days that are User-Days = 99.96%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000244	10,237	90.00	0.002059	1,214
20.00	0.000352	7,099	95.00	0.002635	949
30.00	0.000465	5,377	97.50	0.003413	732
40.00	0.000583	4,289	99.00	0.004337	576
50.00	0.000737	3,394	99.50	0.004905	510
60.00	0.000934	2,677	99.75	0.005844	428
70.00	0.001167	2,142	99.90	0.006965	359
80.00	0.001510	1,656			

CHILDREN (7-12 YEARS)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000709	0.000709
Standard Deviation	0.000583	0.000583
Standard Error	0.000010	0.000010

Percent of Person-Days that are User-Days = 99.98%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000183	13,630	90.00	0.001429	1,750
20.00	0.000268	9,343	95.00	0.001790	1,396
30.00	0.000352	7,099	97.50	0.002208	1,132
40.00	0.000438	5,707	99.00	0.002789	896
50.00	0.000547	4,573	99.50	0.003321	753
60.00	0.000674	3,711	99.75	0.003739	669
70.00	0.000846	2,954	99.90	0.004850	515
80.00	0.001085	2,304			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

MALES (13-19 YEARS)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000479	0.000479
Standard Deviation	0.000399	0.000399
Standard Error	0.000010	0.000010

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000125	19,933	90.00	0.000967	2,587
20.00	0.000184	13,593	95.00	0.001236	2,022
30.00	0.000240	10,403	97.50	0.001547	1,616
40.00	0.000296	8,444	99.00	0.001922	1,301
50.00	0.000372	6,712	99.50	0.002182	1,146
60.00	0.000443	5,639	99.75	0.002740	912
70.00	0.000558	4,480	99.90	0.003286	761
80.00	0.000711	3,516			

FEMALES (13-19 YRS/NP/NN)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000465	0.000466
Standard Deviation	0.000462	0.000462
Standard Error	0.000011	0.000011

Percent of Person-Days that are User-Days = 99.80%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000102	24,508	90.00	0.000962	2,599
20.00	0.000153	16,384	95.00	0.001362	1,836
30.00	0.000201	12,412	97.50	0.001679	1,489
40.00	0.000263	9,501	99.00	0.002069	1,208
50.00	0.000332	7,527	99.50	0.003307	756
60.00	0.000413	6,060	99.75	0.003832	652
70.00	0.000522	4,787	99.90	0.004155	602
80.00	0.000702	3,562			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Section 3 Registration

Residue file name: NALEDACT

Analysis date: 05-07-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

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MALES (20+ YEARS)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000443	0.000443
Standard Deviation	0.000376	0.000375
Standard Error	0.000004	0.000004

Percent of Person-Days that are User-Days = 99.90%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000111	22,523	90.00	0.000921	2,714
20.00	0.000165	15,156	95.00	0.001190	2,101
30.00	0.000216	11,564	97.50	0.001440	1,736
40.00	0.000268	9,315	99.00	0.001833	1,364
50.00	0.000331	7,549	99.50	0.002175	1,150
60.00	0.000412	6,067	99.75	0.002444	1,023
70.00	0.000519	4,816	99.90	0.002882	867
80.00	0.000661	3,779			

FEMALES (20+ YEARS/NP/NN)

Daily Exposure Analysis

(mg/kg body-weight/day)

per Capita per User

Mean	0.000410	0.000411
Standard Deviation	0.000380	0.000380
Standard Error	0.000003	0.000003

Percent of Person-Days that are User-Days = 99.81%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000086	29,171	90.00	0.000873	2,864
20.00	0.000138	18,155	95.00	0.001118	2,236
30.00	0.000186	13,418	97.50	0.001397	1,789
40.00	0.000241	10,357	99.00	0.001768	1,414
50.00	0.000302	8,282	99.50	0.002114	1,183
60.00	0.000378	6,616	99.75	0.002427	1,030
70.00	0.000478	5,230	99.90	0.003102	806
80.00	0.000627	3,985			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

SENIORS (55+)

Daily Exposure Analysis
(mg/kg body-weight/day)

per Capita per User

Mean	0.000399	0.000400
Standard Deviation	0.000358	0.000358
Standard Error	0.000004	0.000004

Percent of Person-Days that are User-Days = 99.86%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000091	27,456	90.00	0.000842	2,970
20.00	0.000139	18,022	95.00	0.001069	2,339
30.00	0.000183	13,632	97.50	0.001326	1,886
40.00	0.000233	10,719	99.00	0.001717	1,456
50.00	0.000297	8,431	99.50	0.002063	1,212
60.00	0.000370	6,758	99.75	0.002409	1,038
70.00	0.000467	5,348	99.90	0.003011	830
80.00	0.000610	4,102			

PACIFIC REGION

Daily Exposure Analysis
(mg/kg body-weight/day)

per Capita per User

Mean	0.000507	0.000508
Standard Deviation	0.000472	0.000472
Standard Error	0.000007	0.000007

Percent of Person-Days that are User-Days = 99.65%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000107	23,385	90.00	0.001086	2,301
20.00	0.000170	14,711	95.00	0.001408	1,776
30.00	0.000227	11,010	97.50	0.001771	1,411
40.00	0.000292	8,569	99.00	0.002308	1,083
50.00	0.000369	6,776	99.50	0.002903	861
60.00	0.000462	5,414	99.75	0.003233	773
70.00	0.000586	4,270	99.90	0.003506	713
80.00	0.000768	3,255			

ACUTE EXPOSURE (EX4) ANALYSIS FOR NALED

Residue file name: NALEDACT

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 2.500000 mg/kg body-wt/day

Section 3 Registration

Analysis date: 05-07-1999

ALL INFANTS

Daily Exposure Analysis
(mg/kg body-weight/day)

per Capita per User

Mean	0.000543	0.000630
Standard Deviation	0.000787	0.000815
Standard Error	0.000032	0.000036

Percent of Person-Days that are User-Days = 86.19%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000015	169,772	90.00	0.001671	1,497
20.00	0.000019	134,920	95.00	0.002443	1,023
30.00	0.000036	68,636	97.50	0.002723	918
40.00	0.000212	11,797	99.00	0.002970	842
50.00	0.000353	7,084	99.50	0.003887	643
60.00	0.000490	5,105	99.75	0.004791	522
70.00	0.000819	3,051	99.90	0.005660	442
80.00	0.001063	2,351			

FEMALES (13-50 YEARS)

Daily Exposure Analysis
(mg/kg body-weight/day)

per Capita per User

Mean	0.000425	0.000426
Standard Deviation	0.000391	0.000391
Standard Error	0.000004	0.000004

Percent of Person-Days that are User-Days = 99.81%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000089	27,949	90.00	0.000899	2,781
20.00	0.000143	17,486	95.00	0.001166	2,144
30.00	0.000196	12,768	97.50	0.001496	1,672
40.00	0.000252	9,938	99.00	0.001871	1,336
50.00	0.000311	8,026	99.50	0.002195	1,139
60.00	0.000391	6,401	99.75	0.002578	970
70.00	0.000494	5,064	99.90	0.003295	759
80.00	0.000646	3,868			

APPENDIX F

CHRONIC DIETARY ANALYSIS- PERCENT CROP TREATED ADJUSTED

Chronic Exposure (EX1) Analysis for Naled

Section 3 Registration

RESIDUE FILE NAME: NALEDC6T

ANALYSIS DATE: 05-07-1999

NFCS Combined 89-92 DATA

EPA Reference dose (RfD, chronic) = 0.002000 mg/kg body-wt/day

DPR NOEL (Chronic) = 0.200000 mg/kg body-wt/day

COMMENT 1: Total naled (+ DDVP).DDVP 4XTEF.Juices & oils: ND=1/2LOD. %PCT

COMMENT 2: Analysis using naled chronic NOEL. Yes %PCT. Most current residues.

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
13	N	GRAPES	0.006000	1.00	0.10	PDP2yr
14	N	GRAPES-RAISINS	0.006000	1.00	0.10	PDP2yr
15	N	GRAPES-JUICE	0.006000	1.00	0.10	PDP2yr
17	N	STRAWBERRIES	0.060000	1.00	0.25	DPR3yr
22	K	GRAPEFRUIT-PEELED FRUIT	0.006000	1.00	1.00	PDP1yr
23	K	GRAPEFRUIT-JUICE	0.006000	2.10	1.00	PDP1yr
26	K	LEMONS-PEELED FRUIT	0.006000	1.00	1.00	PDP0sr
27	K	LEMONS-PEEL	0.006000	1.00	1.00	PDP0sr
28	K	LEMONS-JUICE	0.006000	2.00	1.00	PDP0sr
33	K	ORANGES-JUICE-CONCENTRATE	0.006000	6.70	0.15	PDP2yr
34	K	ORANGES-PEELED FRUIT	0.006000	1.00	0.15	PDP2yr
35	K	ORANGES-PEEL	0.006000	1.00	0.15	PDP2yr
36	K	ORANGES-JUICE	0.006000	1.80	0.15	PDP2yr
38	K	TANGERINES	0.006000	1.00	1.00	PDP0sr
39	K	TANGERINES-JUICE	0.006000	2.30	1.00	PDP0sr
40	R	ALMONDS	0.015000	1.00	0.01	REG-f
48	R	WALNUTS	0.100000	1.00	1.00	FDA
65	M	PEACHES	0.006000	1.00	0.01	PDP2yr
66	M	PEACHES-DRIED	0.006000	7.00	0.01	PDP2yr
125	A	HOPS	0.250000	1.00	1.00	EPA1/2
141	J	CANTALOUPE-NECTAR	0.080000	1.00	1.00	DPR3yr
142	J	CANTALOUPE-PULP (MUSKMELON)	0.080000	1.00	1.00	DPR3yr
143	J	CASABAS	0.080000	1.00	1.00	DPR3yr
144	J	CRENSHAW	0.080000	1.00	1.00	DPR3yr
145	J	HONEYDEW MELONS	0.080000	1.00	1.00	DPR3yr
146	J	PERSIAN MELONS	0.080000	1.00	1.00	DPR3yr
147	J	WATERMELON	0.080000	1.00	1.00	DPR3yr
148	J	CUCUMBERS	0.080000	1.00	1.00	DPR3yr
149	J	PUMPKIN	0.100000	1.00	1.00	FDA
150	J	SQUASH-SUMMER	0.060000	1.00	1.00	DPR3yr
151	J	SQUASH-WINTER	0.060000	1.00	1.00	DPR3yr
154	I	EGGPLANT	0.060000	1.00	1.00	DPR3yr
155	I	PEPPERS-SWEET(GARDEN)	0.080000	1.00	1.00	DPR3yr
157	I	PEPPERS-OTHER	0.080000	1.00	1.00	DPR3yr
159	I	TOMATOES-WHOLE	0.060000	1.00	0.06	DPR3yr
160	I	TOMATOES-JUICE	0.060000	1.50	0.06	DPR3yr
161	I	TOMATOES-PUREE	0.060000	3.30	0.06	DPR3yr
162	I	TOMATOES-PASTE	0.060000	5.40	0.06	DPR3yr
163	I	TOMATOES-CATSUP	0.060000	2.50	0.06	DPR3yr
166	E	CELERY	0.006000	1.00	0.35	PDP2yr
168	F	BROCCOLI	0.006000	1.00	0.10	PDP2yr
169	F	BRUSSELS SPROUTS	0.060000	1.00	1.00	DPR3yr
170	F	CABBAGE-GREEN AND RED	0.060000	1.00	1.00	DPR3yr
171	F	CAULIFLOWER	0.060000	1.00	1.00	DPR3yr
172	F	COLLARDS	0.060000	1.00	1.00	DPR3yr
173	F	CABBAGE-CHINESE/CELERY/BOK CHO	0.060000	1.00	1.00	DPR3yr
174	F	KALE	0.060000	1.00	1.00	DPR3yr
176	E	LETTUCE-LEAFY VARIETIES	0.006000	1.00	0.01	PDP2yr
182	E	LETTUCE-UNSPECIFIED	0.006000	1.00	0.01	PDP2yr
186	E	SPINACH	0.080000	1.00	0.01	DPR3yr
187	E	SWISS CHARD	0.080000	1.00	1.00	DPR3yr
188	C	TURNIPS-TOPS	0.080000	1.00	1.00	DPR3yr
192	E	LETTUCE-HEAD VARIETIES	0.006000	1.00	0.01	PDP2yr

227	G	BEANS-DRY-GREAT NORTHERN	0.006040	1.00	1.00	PDPgbs
228	G	BEANS-DRY-KIDNEY	0.006040	1.00	1.00	PDPgbs
229	G	BEANS-DRY-LIMA	0.006040	1.00	1.00	PDPgbs
230	G	BEANS-DRY-NAVY (PEA)	0.006040	1.00	1.00	PDPgbs
231	G	BEANS-DRY-OTHER	0.006040	1.00	1.00	PDPgbs
232	G	BEANS-DRY-PINTO	0.006040	1.00	1.00	PDPgbs
233	G	BEANS-SUCCULENT-LIMA	0.006040	1.00	1.00	PDP2yr
234	G	BEANS-SUCCULENT-GREEN	0.006040	1.00	1.00	PDP2yr
235	G	BEANS-SUCCULENT-OTHER	0.006040	1.00	1.00	PDP2yr
236	G	BEANS-SUCCULENT-YELLOW/WAX	0.006040	1.00	1.00	PDP2yr
240	G	PEAS (GARDEN)-DRY	0.006000	1.00	1.00	PDPpsr
241	G	PEAS (GARDEN)-GREEN	0.006000	1.00	1.00	PDP1yr
249	G	BEANS-DRY-BROADBEANS	0.006040	1.00	1.00	PDPgbs
250	G	BEANS-SUCCULENT-BROADBEANS	0.006040	1.00	1.00	PDP2yr
251	G	BEANS-DRY-PIGEON BEANS	0.006040	1.00	1.00	PDPgbs
253	G	BEANS-UNSPECIFIED	0.006040	1.00	1.00	PDPgbs
256	G	BEANS-DRY-HYACINTH	0.006040	1.00	1.00	PDPgbs
257	G	BEANS-SUCCULENT-HYACINTH	0.006040	1.00	1.00	PDP2yr
258	G	BEANS-DRY-BLACKEYE PEAS/COWPEA	0.006040	1.00	1.00	PDPgbs
259	G	BEANS-DRY-GARBANZO/CHICK PEA	0.006040	1.00	1.00	PDPgbs
261	A	MUSHROOMS	0.060000	1.00	1.00	DPR3yr
270	O	RICE-ROUGH (BROWN)	0.100000	1.00	0.01	FDA
271	O	RICE-MILLED (WHITE)	0.100000	1.00	0.01	FDA
282	B	BEET SUGAR	0.025000	1.00	0.10	REG-fp
290	A	COTTONSEED-OIL	0.025000	1.00	0.30	REG-fp
291	A	COTTONSEED-MEAL	0.025000	1.00	0.30	REG-fp
294	A	SAFFLOWER-SEED	0.025000	1.00	0.35	REG-fp
295	A	SAFFLOWER-OIL	0.025000	1.00	0.35	REG-fp
315	A	GRAPES-WINE AND SHERRY	0.006000	1.00	0.10	PDP2yr
318	X	MILK-NONFAT SOLIDS	0.001000	1.00	0.65	FDA2ch
319	X	MILK-FAT SOLIDS	0.001000	1.00	0.65	FDA2ch
320	X	MILK SUGAR (LACTOSE)	0.001000	1.00	0.65	FDA2ch
321	U	BEEF-MEAT BYPRODUCTS	0.050000	1.00	0.65	EPA
322	U	BEEF(ORGAN MEATS)-OTHER	0.050000	1.00	0.65	EPA
323	U	BEEF-DRIED	0.050000	1.00	0.65	EPA
324	U	BEEF(BONELESS)-FAT	0.050000	1.00	0.65	EPA
325	U	BEEF(ORGAN MEATS)-KIDNEY	0.050000	1.00	0.65	EPA
326	U	BEEF(ORGAN MEATS)-LIVER	0.050000	1.00	0.65	EPA
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.050000	1.00	0.65	EPA
328	U	GOAT-MEAT BYPRODUCTS	0.050000	1.00	0.65	EPA
329	U	GOAT(ORGAN MEATS)-OTHER	0.050000	1.00	0.65	EPA
330	U	GOAT(BONELESS)-FAT	0.050000	1.00	0.65	EPA
331	U	GOAT(ORGAN MEATS)-KIDNEY	0.050000	1.00	0.65	EPA
332	U	GOAT(ORGAN MEATS)-LIVER	0.050000	1.00	0.65	EPA
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	0.050000	1.00	0.65	EPA
334	U	HORSE	0.050000	1.00	0.65	EPA
336	U	SHEEP-MEAT BYPRODUCTS	0.050000	1.00	0.65	EPA
337	U	SHEEP(ORGAN MEATS)-OTHER	0.050000	1.00	0.65	EPA
338	U	SHEEP(BONELESS)-FAT	0.050000	1.00	0.65	EPA
339	U	SHEEP(ORGAN MEATS)-KIDNEY	0.050000	1.00	0.65	EPA
340	U	SHEEP(ORGAN MEATS)-LIVER	0.050000	1.00	0.65	EPA
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	0.65	EPA
342	U	PORK-MEAT BYPRODUCTS	0.050000	1.00	0.65	EPA
343	U	PORK(ORGAN MEATS)-OTHER	0.050000	1.00	0.65	EPA
344	U	PORK(BONELESS)-FAT	0.050000	1.00	0.65	EPA
345	U	PORK(ORGAN MEATS)-KIDNEY	0.050000	1.00	0.65	EPA
346	U	PORK(ORGAN MEATS)-LIVER	0.050000	1.00	0.65	EPA
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	0.65	EPA
355	V	TURKEY-BYPRODUCTS	0.050000	1.00	0.60	EPA
356	V	TURKEY-GIBLETS (LIVER)	0.050000	1.00	0.60	EPA
357	V	TURKEY-(BONELESS)-FAT	0.050000	1.00	0.60	EPA
358	V	TURKEY-(BONELESS)LEAN/FAT FREE	0.050000	1.00	0.60	EPA
359	V	TURKEY-UNSPECIFIED	0.050000	1.00	0.60	EPA
360	V	POULTRY-OTHER-LEAN (FAT FREE)	0.050000	1.00	0.60	EPA
361	V	POULTRY-OTHER-GIBLETS(LIVER)	0.050000	1.00	0.60	EPA
362	V	POULTRY-OTHER-FAT	0.050000	1.00	0.60	EPA

363	X	EGGS-WHOLE	0.050000	1.00	0.60	EPA
364	X	EGGS-WHITE ONLY	0.050000	1.00	0.60	EPA
365	X	EGGS-YOLK ONLY	0.050000	1.00	0.60	EPA
366	V	CHICKEN-BYPRODUCTS	0.050000	1.00	0.60	EPA
367	V	CHICKEN-GIBLETS(LIVER)	0.050000	1.00	0.60	EPA
368	V	CHICKEN (BONELESS)-FAT	0.050000	1.00	0.60	EPA
369	V	CHICKEN(BONELESS)LEAN/FAT FREE	0.050000	1.00	0.60	EPA
379	B	BEET SUGAR-MOLASSES	0.025000	1.00	0.10	REG-fp
383	F	CABBAGE-SAVOY	0.060000	1.00	1.00	FDA
384	E	CELERY JUICE	0.016000	1.00	0.35	PDP2yr
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	0.050000	1.00	0.60	EPA
392	N	GRAPES-JUICE-CONCENTRATE	0.006000	1.00	0.10	PDP2yr
398	X	MILK-BASED WATER	0.001000	1.00	0.65	FDA2ch
402	M	PEACHES-JUICE	0.006000	1.00	0.01	PDP2yr
405	G	PEAS-SUCCULENT/BLACKEYE/COWPEA	0.006000	1.00	1.00	PDP1yr
408	O	RICE-BRAN	0.100000	1.00	0.01	FDA
409	O	RICE-WILD	0.100000	1.00	0.01	FDA
416	N	STRAWBERRIES-JUICE	0.060000	1.00	0.25	DPR3yr
420	K	TANGERINES-JUICE-CONCENTRATE	0.006000	7.35	1.00	PDPosr
423	I	TOMATOES-DRIED	0.060000	14.30	0.06	DPR3yr
424	U	VEAL-(BONELESS)-FAT	0.050000	1.00	0.65	EPA
425	U	VEAL-(BONELESS)-LEAN (FAT FREE	0.050000	1.00	0.65	EPA
426	U	VEAL-(ORGAN MEATS)-KIDNEY	0.050000	1.00	0.65	EPA
427	U	VEAL-(ORGAN MEATS)-LIVER	0.050000	1.00	0.65	EPA
428	U	VEAL-(ORGAN MEATS)-OTHER	0.050000	1.00	0.65	EPA
429	U	VEAL-DRIED	0.050000	1.00	0.65	EPA
430	U	VEAL-MEAT BYPRODUCTS	0.050000	1.00	0.65	EPA
431	R	WALNUT OIL	0.100000	1.00	1.00	FDA
436	J	WATERMELON-JUICE	0.080000	1.00	1.00	DPR3yr
441	K	GRAPEFRUIT-JUICE-CONCENTRATE	0.006000	8.26	1.00	PDPl1yr
442	K	LEMONS-JUICE-CONCENTRATE	0.006000	11.40	1.00	PDPosr
448	K	GRAPEFRUIT PEEL	0.006000	1.00	1.00	PDPl1yr
449	V	TURKEY-(ORGAN MEATS)-OTHER	0.050000	1.00	0.60	EPA

Chronic Exposure (EX1) Analysis for Naled

Section 3 Registration

RESIDUE FILE NAME: NALEDC6T

ANALYSIS DATE: 05-07-1999

NFCS Combined 89-92 DATA

EPA Reference dose (RfD, chronic) = 0.002000 mg/kg body-wt/day

DPR NOEL (Chronic) = 0.200000 mg/kg body-wt/day

COMMENT 1: Total naled (+ DDVP).DDVP 4XTEF.Juices & oils: ND=1/2LOD. %PCT

COMMENT 2: Analysis using naled chronic NOEL. Yes %PCT. Most current residues.

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE		
	mg/kg body-wt/day	Margin of Exposure 1/	Percent of RfD
U.S. POP - 48 STATES - ALL SEASONS	0.000132	1,520	6.6%
U.S. POPULATION - SPRING SEASON	0.000129	1,554	6.4%
U.S. POPULATION - SUMMER SEASON	0.000152	1,320	7.6%
U.S. POPULATION - AUTUMN SEASON	0.000125	1,602	6.2%
U.S. POPULATION - WINTER SEASON	0.000120	1,673	6.0%
NORTHEAST REGION	0.000140	1,432	7.0%
MIDWEST REGION	0.000127	1,577	6.3%
SOUTHERN REGION	0.000132	1,512	6.6%
WESTERN REGION	0.000128	1,568	6.4%
PACIFIC REGION	0.000127	1,569	6.4%
HISPANICS	0.000143	1,401	7.1%
NON-HISPANIC WHITES	0.000127	1,569	6.4%
NON-HISPANIC BLACKS	0.000144	1,394	7.2%
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000162	1,234	8.1%
ALL INFANTS	0.000100	1,997	5.0%
NURSING INFANTS (<1 YEAR OLD)	0.000027	7,276	1.4%
NON-NURSING INFANTS (<1 YEAR OLD)	0.000131	1,530	6.5%
CHILDREN (1-6 YEARS)	0.000251	796	12.6%
CHILDREN (7-12 YEARS)	0.000175	1,144	8.7%
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000112	1,784	5.6%
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000108	1,857	5.4%
FEMALES (13-50 YEARS)	0.000106	1,882	5.3%
FEMALES (13+/PREGNANT/NOT NURSING)	0.000110	1,816	5.5%
FEMALES (13+/NURSING)	0.000125	1,597	6.3%
MALES (13-19 YEARS)	0.000124	1,608	6.2%
MALES (20+ YEARS)	0.000117	1,709	5.9%
SENIORS (55+)	0.000113	1,769	5.7%

1. Margin of Exposure = DPR NOEL / Dietary Exposure

Chronic Exposure (EX1) Analysis for Naled

Section 3 Registration

RESIDUE FILE NAME: NALEDC6T

ANALYSIS DATE: 05-07-1999

NFCS Combined 89-92 DATA

EPA Reference dose (RfD, chronic) = 0.002000 mg/kg body-wt/day

DPR NOEL (Chronic) = 0.200000 mg/kg body-wt/day

COMMENT 1: Total naled (+ DDVP).DDVP 4XTEF.Juices & oils: ND=1/2LOD. %PCT

COMMENT 2: Analysis using naled chronic NOEL. Yes %PCT. Most current residues.

CRITICAL COMMODITY CONTRIBUTION ANALYSIS FOR
CHILDREN (1-6 YEARS)

Total Exposure = 0.0002514 mg/kg body-wt/DAY

CROP GROUPS WITH TOTAL EXPOSURE CONTRIBUTION > 5%

FOODS/FOODFORMS WITH EXPOSURE CONTRIBUTION > 5%

CROP GROUP	mg/kg	% of Total	Margin of	Percent
FOOD	body-wt/day	Exposure	Expos. 1/	of RfD
FOODFORM				
FRUITING VEGETABLES (EXCL. CUCURBITS)				
TOTAL FOR CROP GROUP	0.0000161	6.40%	12,433	0.8%
FRUITING VEGETABLES (CUCURBITS)				
WATERMELON	0.0000164	6.51%	12,229	0.8%
TOTAL FOR CROP GROUP	0.0000341	13.55%	5,870	1.7%
RED MEAT				
BEEF(BONELESS)-FAT	0.0000139	5.53%	14,400	0.7%
BEEF(BONELESS)-LEAN (FAT/FREE)	0.0000484	19.25%	4,134	2.4%
PORK(BONELESS)-LEAN (FAT FREE)	0.0000198	7.89%	10,080	1.0%
TOTAL FOR CROP GROUP	0.0000905	36.01%	2,210	4.5%
POULTRY				
CHICKEN(BONELESS)LEAN/FAT FREE	0.0000266	10.56%	7,532	1.3%
TOTAL FOR CROP GROUP	0.0000351	13.96%	5,700	1.8%
DAIRY PRODUCTS				
EGGS-WHOLE	0.0000302	12.03%	6,616	1.5%
MILK-BASED WATER	0.0000150	5.95%	13,365	0.7%
TOTAL FOR CROP GROUP	0.0000485	19.31%	4,120	2.4%
TOTAL FOR CROP GROUPS LISTED ABOVE:	0.0002243	89.23%	892	11.2%

1. Margin of Exposure = DPR NOEL / Dietary Exposure

APPENDIX G

PEER REVIEW COMMENTS AND RESPONSES

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street
Sacramento, CA 95814-5624

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
2151 Berkeley Way, Annex 11
Berkeley, California 94704

DATE: August 31, 1998

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S
DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE PESTICIDE
ACTIVE INGREDIENT NALED

The purpose of this memorandum is to update our memorandum dated June 16, 1998, in which we provided general comments on the draft naled risk characterization document (RCD) prepared by the Department of Pesticide Regulation (DPR). Naled is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (SB 950) and also is a candidate for evaluation under the Toxic Air Contaminant Identification and Control Act of 1983 (AB 1807). One active metabolite and degradation product of naled, dichlorvos (DDVP), is listed under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the State of California to cause cancer.

This memorandum provides more detailed explanation of our general concerns as well as additional specific comments on the draft naled RCD. This current, more detailed memorandum should replace the June 16, 1998, memorandum. As before, upon completion of our review of the draft RCD for naled we conclude that significant revisions of the draft are required.

In reviewing the draft RCD for naled, we considered the following information: 1) the draft naled RCD (May 7, 1998); 2) the draft human pesticide exposure assessment for naled prepared by the Worker Health and Safety Branch (December 19, 1997); 3) the summary of the

Gary T. Patterson, Ph.D., Chief
August 31, 1998
Page 2

draft dichlorvos RCD (October 19, 1994); 4) U.S. Environmental Protection Agency (U.S. EPA) tolerances; 5) the calculations (dosage estimation for animals from an inhalation study, dosage estimation for animals in a dietary study, and margin of safety); 6) the available toxicology summaries from DPR; 7) the acute dietary analysis of acute exposure to naled and DDVP; 8) the chronic dietary analysis of chronic exposure to naled and DDVP; and 9) the results of our literature search.

Thank you for the opportunity to comment on the draft RCD for naled. The comments are provided as follows. If you have any questions about our comments, please contact me or Dr. Michael J. DiBartolomeis at (510) 540-3063.

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Gary T. Patterson, Ph.D., Chief
August 31, 1998
Page 3

bcc: Robert Howd
Jolanta Bankowska

GENERAL COMMENTS

The draft risk characterization document for naled includes a summary and critique of the data available in DPR's registration data base. The appendices include somewhat more detailed information. We found the inclusion of summary tables helpful in accessing some of the more critical information.

Literature Search

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of naled and its major breakdown products. Pertinent information published in the open literature, in addition to information submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. If a complete search was conducted, and no relevant data were identified, we recommend that this be made clear in the naled RCD before it is finalized.

We conducted a literature search for naled, dichlorvos and their major breakdown products using the current 1998 on-line and CD-ROM based resources including MedLine/ToxLine and the Registry of Toxic Effects of Chemical Substances (RTECS), the Integrated Risk Information System (IRIS) and the Hazardous Substances Data Bank (HSDB). This allowed us to determine if any pertinent literature had been omitted in the RCD. We would be happy to share the assembled information. In order to assist you in revising the draft RCD, we have cited selected published works at the end of this report that may be worth considering in your overall evaluation.

Assessment of Cancer Risks

In the draft RCD (Volume I), the evaluation of potential oncogenicity from exposure to naled was based on three currently available chronic gavage studies (in rats, mice and dogs) and on genotoxicity tests. There were no oncogenic effects reported in the gavage studies in mice (Charles River CD-1) and dogs (Beagles).

In the rat study (Sprague-Dawley) the oncogenic findings were noted in both males and females. In male rats, the findings consisted of a slightly increased incidence of mammary adenocarcinomas at 2 (1/49) and 10 mg/kg-day (2/49). However, only the trend was statistically significant at $p \leq 0.05$ based on a dose-weighted chi-square trend test. There were a variety of mammary tumors observed in female rats (fibroadenomas, adenomas and adenocarcinomas). The results in female rats were determined in the draft RCD as "not related to treatment since they were higher in the controls than those in the treated groups." This statement appears to be correct for adenomas and adenocarcinomas but not for fibroadenomas where the incidence of tumors was higher in all treated groups in comparison with control animals (naled RCD, Volume I, Table 9, page 32). Overall, the rat study was considered to be negative in the draft RCD.

The lack of strong evidence of oncogenic effects from exposure to naled is in contrast to the carcinogenic effects produced in studies with dichlorvos (DDVP), the main toxicologically active metabolite and degradation product of naled. Oncogenic effects were shown in two long-term gavage studies in rats and mice (DPR, 1994). Tumors observed in rats (F344/N) included: pancreatic adenomas (statistically significant in males), mononuclear leukemia (statistically significant in males, clear dose-response trend in females), and mammary gland tumors (carcinoma, fibroadenoma, and adenoma) in females (statistically significant at the dose level of 2.9 mg/kg-day). Oncogenic changes produced in mice (B6C3F1) consisted of forestomach tumors such as squamous papillomas and squamous cell carcinomas (statistically significant in males and females) (DPR, 1994).

According to the draft RCD for naled, it has been concluded that only mononuclear leukemia is clearly related to DDVP exposure (Volume I, page 48). In the draft RCD, the findings of mammary gland fibroadenomas were considered equivocal evidence for oncogenicity, and the increased incidence of pancreatic adenomas following DDVP exposure was considered to be related to the use of corn oil as the vehicle.

According to the evaluation of the available tests on gene mutations, chromosomal aberrations and DNA effects provided in the draft RCD, naled was not found to be genotoxic in either *in vitro* or *in vivo* studies (naled RCD, Volume I, page 36). We find the results of these studies to be equivocal. Some of the results suggest "conflicting evidence for mutagenicity" while results of other studies provide some evidence for positive responses. The latter were disregarded in the draft RCD because "there was insufficient information presented for evaluation." In some cases, the observed positive responses were not statistically significant and therefore the results were considered to be negative. In considering the database as a whole, however, we conclude that the combination of the positive and the equivocal studies provides some evidence that naled is genotoxic. Consequently, there is still some uncertainty regarding the genotoxicity of naled.

In contrast, DDVP was genotoxic in some *in vitro* systems, including assays with *Salmonella TA 100* strain and *Schizosaccharomyces pombe*, mouse lymphoma forward mutation assay, and unscheduled DNA synthesis assay using human epithelial cells. DDVP was not genotoxic in the micronucleus, dominant lethal, *in vivo* chromosomal aberrations, and *in vivo* sister chromatid exchange assays (IRIS, 1998).

DDVP is currently under Special Review by U.S. EPA. In 1989, the Scientific Advisory Board of U.S. EPA recommended that the DDVP oncogenicity classification be changed from a B2 carcinogen to a C carcinogen. Most of the food tolerances for DDVP have been revoked. In 1993 the registrants of DDVP in California voluntarily canceled its use on fresh vegetables.

Our review of the data presented in the draft RCD for naled indicates that the issue of the potential carcinogenicity of naled should be more thoroughly addressed. Oncogenicity data on DDVP should not be disregarded in the overall evaluation of potential oncogenicity for naled. The carcinogenicity of the major metabolite of naled, DDVP, represents an important uncertainty regarding the carcinogenicity of naled. We understand the scientific challenge for risk

assessment presented by the limited evidence of carcinogenicity provided by the bioassays of naled coupled with the clearly positive outcome from bioassays of its major metabolite DDVP.

We recommend that the naled RCD more broadly address the uncertainties in identifying oncogenic hazard and characterizing cancer risk from exposure to naled. Comparison of the protocols and conditions of oncogenicity studies performed for DDVP and naled would be useful. Issues like the dose-equivalent of DDVP from naled administration compared to the DDVP dose in the positive cancer assays, different laboratory conditions and different strains of animals used to assess oncogenic potential of naled and DDVP may contribute to understanding the different toxicological outcomes for these two compounds. It should be noted that mammary tumors were produced in the oncogenicity study with naled (Sprague-Dawley rats) as well as in the oncogenicity study with DDVP (F344/N rats). It would also be useful to analyze more thoroughly the pharmacokinetic behavior of naled under different experimental conditions. In addition, separate exposure data for DDVP derived from naled are available to calculate DDVP-related cancer risk from naled use.

In summary, we conclude that for risk assessment purposes, there is limited evidence for the carcinogenicity of naled in bioassays. This comes from direct evidence from the development of rare mammary tumors in male rats exposed to naled and the supporting evidence from the carcinogenicity of DDVP, the primary metabolite of naled, which caused an increase in the incidence of mammary tumors in a second strain of rats. At present, the difference between the stronger evidence of carcinogenicity of the primary metabolite and the relatively limited evidence of carcinogenicity for the parent compound has no scientific explanation and should be investigated further before concern over the carcinogenicity of naled can be dismissed. In the interim, since DDVP is the major metabolite of naled, we recommend that naled be considered a potential carcinogen and the cancer risk from exposures to DDVP resulting from naled exposures be assessed before finalizing the naled RCD. This assessment should also consider residues of DDVP on agricultural commodities following naled applications (e.g., consumer exposure) and traces of DDVP as a degradation product or as a metabolite of naled (e.g., occupational exposure).

Weight-of-Evidence for Carcinogenicity

The issue of potential carcinogenicity from exposure to naled deserves special attention because of the contrasting results from oncogenicity testing of naled and its major metabolite DDVP. In addition to the suggestions presented above, to better characterize the uncertainties regarding naled carcinogenicity, we recommend that the structure-activity relationship also be addressed in the RCD for naled and its breakdown products. Consequently it should be noted that DDVP is structurally related to dichloropropene (a probable human carcinogen), which causes forestomach squamous cell tumors in rats and mice, lung tumors in mice and neoplastic nodules in the livers of rats (IRIS, 1998; HSDB, 1998).

The discussion of the weight-of-evidence for potential carcinogenicity from naled can be broadened by addressing the issue of carcinogenic effects caused by another organophosphorous compound, trichlorfon. DDVP is also a major metabolite and breakdown product of trichlorfon.

It is noteworthy that trichlorfon (tested as a parent compound) caused numerous oncogenic effects such as renal tubular adenomas, alveolar/bronchiolar adenomas and mononuclear cell leukemia in Fisher 344 rats. The latter carcinogenic effect is unequivocally related to the exposure of rats to DDVP (DPR, 1995).

Another metabolite of naled with clear evidence for carcinogenicity (in mice) is dichloroacetic acid (DCAA) (DeAngelo *et al.*, 1991; 1996). U.S. EPA considers DCAA as a probable human carcinogen (B2). This evaluation is based on an increased incidence of hepatocellular adenomas and carcinomas in male and female mice (B6C3F1). Hyperplastic liver nodules, which are expected to progress into hepatocellular adenomas and carcinomas, were increased in both mice and rats.

Choice of Critical NOELs for Risk Assessment

The draft RCD provides assessment of health risk only from exposures to naled under acute and chronic conditions. We support the choice of the studies for these evaluations. However we recommend that further explanation be provided in the RCD as to why these studies are the most appropriate for risk assessment.

The acute exposure assessment is based on an "estimated no-effect-level (ENEL)" of 2.5 mg/kg-day calculated from a lowest-observed-effect-level (LOEL) of 25 mg/kg-day established in an acute oral study in rats. The LOEL was divided by a default factor of 10 for the extrapolation of the no-observed-effect-level (NOEL) from an LOEL. The LOEL is based on tremors, exophthalmus and "other effects" (naled RCD, Volume I, page 67, "Risk Appraisal" under "Acute Toxicity"). It is not clear what are the "other effects" because they are not listed. The subject study is described in Volume I, page 41, paragraph 3, under "Neurotoxicity." However there is no indication there that this study was chosen for risk assessment. It is also difficult to quickly identify this study while reading the section on "Risk Appraisal" (page 67). We recommend that references to the study being discussed be inserted in the appropriate sections.

We also recommend that references to the chronic studies chosen as a basis for risk assessment be inserted in the appropriate sections. These were chronic gavage studies in rats and dogs in which the NOEL is 0.2 mg/kg-day established for brain ChE inhibition.

Seasonal Exposure Assessment

The draft naled RCD concludes that there are no seasonal occupational or residential exposures (Volume I, page 47, last paragraph), and no seasonal dietary exposure. We agree that there are no dietary or residential seasonal exposures. However, in the light of the broad agricultural use of naled on many commodities, especially cotton, estimates of seasonal occupational exposures is still important. We recommend that the RCD (Volumes I and II) be revised to include such an estimate.

Uncertainty Factor for Children's Exposures

The draft naled RCD (Volume I, page 69) addresses the requirements of the Food Quality Protection Act of 1996 (FQPA). This legislation mandates U.S. EPA to ensure that tolerances for pesticides on food are safe for children. Specific requirements include: 1) the use of an extra 10-fold safety factor to account for potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determines, based on reliable data, that a different margin of exposure would be safe, and 2) consideration of the available information on aggregate exposure from all nonoccupational sources, the effects of cumulative exposure to the pesticide and other substances with a mechanism of toxicity in common, the effects of *in utero* exposure, and the potential for endocrine disrupting effects.

In the draft RCD, an additional uncertainty factor to account for pre- and postnatal developmental toxicity and the completeness of the database was not incorporated. The draft document states that "The database for naled was complete for the evaluation of potential pre- and post-natal sensitivity from exposure" and that "There was no evidence of increased pre- and post-natal sensitivity from developmental or reproductive toxicity." We recommend reevaluation of the potential pre- and post-natal toxicity to naled and the completeness of the database for the following reasons:

- 1) Existing testing requirements do not specifically (and/or adequately) address pre- and postnatal sensitivity. The existing developmental and reproductive toxicity studies do not completely nor specifically test for related toxicity endpoints. This especially applies to the lack of testing for potential neurobehavioral (postnatal) effects which may be of importance for chemicals affecting the central nervous system.
- 2) There was a decrease in fetal body weight in a pilot rabbit study at a NOEL of 2 mg/kg-day while the acute NOEL for maternal toxicity was established at a higher level of 10 mg/kg-day (naled RCD, Volume I, page 40).
- 3) DDVP, the major metabolite of naled (and trichlorfon) was shown to cause severe reduction in brain weight in guinea pig offspring (examined at birth) when administered between day 42 and 46 of gestation (DeAngelo *et al.* 1991).

Based on the evidence of pre- and post-natal toxicity and the existing level of uncertainty regarding the adequacy of the testing requirements for pre- and postnatal toxicity, we recommend that the use of an additional uncertainty factor to account for pre- and postnatal sensitivity be reconsidered.

Exposure Assessment

The draft RCD demonstrates potential for excess exposure to naled and its metabolite DDVP under several conditions. However, the draft exposure assessment (Volume II) does not account for the higher acute and subchronic toxicity of DDVP in occupational exposures to naled even though separate measurements of naled and DDVP are available. Because DDVP is four to

five times more acutely toxic than naled, exposures to the two chemicals should not have been considered equivalent, and simply added, in calculating exposures to grape harvesters. Because the same data were used in estimating exposures for other conditions, such as greenhouse work, combined toxicity calculations [naled + (5 x DDVP)] would also have been appropriate in these cases.

The draft RCD provides only limited discussion of the range and distribution of potential occupational exposures. The draft exposure assessment states that “the values assumed for the application rate and for the daily usage were already at their (practical) maximum” (Volume II, page 24). This is an inadequate scientific explanation. At the maximal application rate and practical maximum daily use, there will still be a range of exposures due to differences in work practices, as shown in every exposure study.

The draft document also states “Because of the great variability inherent in the PHED data, the upper-end values would be unrealistically high to use....” This statement is not scientifically justified. Information on page six of the draft exposure assessment indicates that there have been exposures in California associated with systemic effects and low cholinesterase levels as would be expected from upper-bound exposures. The data indicate 79 cases of systemic effects out of 137 total cases of naled illness or injury reports between 1982 and 1995. Ten of these cases reported low ChE levels. We recommend that the risk characterization attempt to associate these effects (and the probability of such effects) with exposures and the use practices as a critical part of the total evaluation.

SPECIFIC COMMENTS

Risk Characterization Document, Volume I

Page 1, paragraph 4. The statement that “Under some environmental conditions, naled may be completely metabolized to carbon dioxide” and the statement on page 7, paragraph 1 “Depending on the environmental conditions, naled may be completely metabolized to carbon dioxide” should be supported by providing examples of such “conditions.” We are not clear how this would occur. Bromochlorophosphates cannot be transmuted to CO₂. The use of the word “metabolized” does not appear to be appropriate in conjunction with “environmental conditions.”

Page 2, paragraph 4. Typographical error. The word “decreased” should be changed to “decrease.”

Page 7. The section on “Environmental Fate” might be easier to follow if it were reorganized to separately address terrestrial fate, aquatic fate and atmospheric fate. A conclusion regarding the potential for ground water contamination should be stated in this section.

Page 17, paragraph 1. Chemical name of temephos [(phosphorothioic acid, O, O’-(thiodi-4,1-phenylene) O, O, O’ O’-tetramethyl ester)] should be provided.

Page 21, second paragraph. The concentration of naled in the formulation reported here appears to be very low for a 91.5% pure mix (compare with other formulations described in this section). One possibility is that it should be 1.14 mg/L rather than 1.14 µg/L. If this is true, then the conclusion that there were high levels of DDVP (compared with other studies) and the study is only supplemental appears to be invalid.

Page 50, last paragraph. The approach of not using pesticide residue levels discovered to be over tolerance in dietary risk calculations is not mathematically or conceptually valid. Without adequate justification to support a different method, all data should be used. For naled, if no over-tolerance residues occurred it should be specified somewhere in the document. This approach has also caused an additional problem on page 53, second paragraph, where it is stated that "The TEF was not applied to the tolerance since the tolerance was the maximum naled and DDVP residues allowed on the commodities." If the data indicate a mixture of naled and DDVP in the product, then the evaluation should reflect this.

Pages 54-55, Table 17. Listing or referring to DDVP tolerances would be useful here, since both naled and DDVP levels are used in the calculations.

Page 58, first paragraph. We agree that using the tolerance level for estimating cancer risk for carcinogens in foods would overestimate risk. Nevertheless, this is not in itself a reason for not including an estimate of cancer risk from dietary exposures in the naled RCD. Instead, more appropriate residue level estimates should be utilized for calculating a lifetime cancer risk for DDVP derived from naled. As above, we recommend including a cancer risk assessment in the revised RCD for naled.

Page 69, first paragraph. The draft RCD states that the uncertainty factors of 10 "assume that the average human is 10 times more sensitive...than the most sensitive experimental animal, and that a sensitive individual is 10 times more susceptible than an average individual." The scientific rationale for use of these defaults in risk assessment could be stated more clearly. Use of a factor of 10 for intra-species extrapolation assumes that the average human may be up to 10 times more sensitive than the average animal in the most sensitive species or strain which happens to have been tested. Also, a sensitive individual may be up to 10 times more sensitive than an average individual. It is the uncertainty in the database and methods that supports the use of these factors, not the assumption that humans are in fact more sensitive, nor that there are individuals 10 times more sensitive than the average. The most important aspect of this difference in interpretation is that additional data may lead to modification (increasing or decreasing) of these factors when appropriate data are available. We recommend rewriting this paragraph.

Pages 70, Section V.E.3. It is appropriate that the draft RCD acknowledges that while cumulative exposures to organophosphates (which have similar mechanisms of action) should be considered, the methodology for this is still under development. Simultaneous exposure to chemicals with the same mechanism of action provides support for the need to include an additional uncertainty factor to protect infants and children.

Page 72, Section VI.B. As stated in the draft RCD, the exposure of infants at the tolerance level represents an inadequate margin of exposure (MOE) with several MOEs reported to be in the range of 51 to 56, and possibly lower if different assumptions and approaches were used. We recommend that the RCD include further discussion regarding the impact of co-exposures to other organophosphate pesticides that would further decrease this MOE, resulting in a finite probability of cholinergic effects when such potent organophosphate cholinesterase inhibitors are widespread in our food supply.

Risk Characterization Document, Volume II

Page 4, pesticide usage. It should be explicitly stated that pesticide usage estimates do not include household uses of naled, including use in animal flea and tick collars. The present wording of "79% of the total annual usage was on cotton" should be revised to "79% of the reportable usage was on cotton." No estimates are available for total usage in the 12 registered flea and tick collars, although this may represent a significant portion of total population exposures. We recommend rewording this paragraph to include a statement to this effect.

Page 5. The title of Table 3 "Raw agricultural commodities with the 8 highest (for the majority years) percent usage from 1991 through 1995" is confusing, and should be renamed for clarity. It is unclear whether the title refers to the highest usage of naled in pounds as a percent of total naled use by year, or the percent by total acres treated, or the percent of the individual crops treated. If this is based on use by pounds, it appears that for the years 1993 through 1995 use on grapes decreased five-fold, orange and safflower use did not change, use on broccoli doubled and use on cotton increased 20-fold. The interpretation of use is critical to further the discussions of population exposures and risks. If true, it appears that high-exposure use on grapes is decreasing, while the use on cotton, a low exposure use, is increasing. It would be reasonable to discuss this issue in the revised RCD.

Page 7. For naled, the default dermal absorption rate of 50% is appropriate in the absence of data. Because of its relatively high vapor pressure, the actual level of dermal absorption might be lower than 50%.

Page 11. The estimate of total naled exposure of human volunteers based on their urinary excretion of dimethyl phosphate (DMP) "within 3 hours after the application" is not fully justified in the draft document. For example, no scientific information was provided on the proportion of exposure by inhalation compared to dermal absorption, which would influence the duration of the total exposure to naled, the rate of systemic absorption of naled, and the rate of its metabolism and excretion. The calculation of total exposure based on two-hour excretion of the chloroethyl metabolite (the leaving group) in rats after a bolus oral exposure, compared to the excretion of DMP (the moiety which binds to cholinesterase) after a mixed-route human exposure for an unknown duration, is not justifiable. The apparent assumption in the first paragraph that the concentration of DMP in the urine collected "within 3 hours" applies to the entire day's urine volume is similarly not supportable. Furthermore, the last paragraph on this page identifies some uncertainties in the human exposure data that appear to invalidate the data for use in risk assessment. We recommend deleting the discussion.

Pages 14-18. Exposure estimates of field workers are based on experiments in grapes. The assumption that crops such as cotton, strawberries and citrus trees achieve the same foliage residue levels as grapes does not appear to be appropriate considering the different amounts of foliage for the different crops. We recommend presenting data or at least including a discussion of residue level data obtained from other pesticide applications to provide better estimates and to support the calculations. In addition, adding the exposures to naled and DDVP together without correction for the greater toxicity of DDVP is not scientifically justified given the availability of data. If the respective potencies are accounted for in the calculation, the combined effective naled exposure is significantly greater than what is presented in the draft document. We recommend correcting the exposure estimates based on a relative potency consideration.

Page 22, fourth paragraph. The assumption that an individual would be exposed to 100% of the active ingredient lost from an animal collar over 90 days (presumably in normal use) probably overestimates risks. Obtaining measurements of residues coming off during handling would help reduce the uncertainty in this assumption. Acknowledgment of this in the revised exposure assessment would be helpful if the data cannot be easily obtained.

Page 23, next to last paragraph. We recommend providing additional discussion in the revised exposure assessment in support of the assumption that it is appropriate to use exposure estimates from backpack sprayers for those who treat sewage systems via injection.

Page 24, third paragraph. The use of maximal application rates (pounds/acre) and amounts of daily usage (acres/day) does not constitute an adequate evaluation of the maximum likely exposures. Under experimental conditions, measured exposures typically vary over 100-fold. Exposure estimates that do not incorporate the range of likely exposures do not provide adequate perspective on why some applicators become symptomatic, while others do not. We recommend including this information in the revised exposure assessment to better document the types of pesticides and application methods that constitute worker hazards.

Page 24, last paragraph. It is stated that "Adverse effects occur only when plasma levels in the target organ exceed a critical level." This statement generally refers to a chemical that acts in a reversible manner; it is less relevant for a kinetically irreversible mechanism of action such as the organophosphate acetylcholinesterase (AChE) inhibitors. Effects of the di-O-methyl organophosphates like naled are cumulative over at least a couple of days. One estimate is that spontaneous reactivation of di-O-methyl-phosphorylated AChE occurs at a rate of about 1% per hour. Resynthesis of AChE occurs at different rates for different tissues, but may be as much as 10% per day in some neuronal reservoirs. The sum of reactivation, resynthesis, and acute tolerance determines most of the cumulative toxicity potential of organophosphate exposures (metabolic changes with repeated exposures are also important for some organophosphates). The relatively slow recovery rate is responsible for the fact that the acute NOEL of naled is 2.5 mg/kg-day, while the chronic NOEL is much lower at 0.2 mg/kg-day. Based on these considerations, we conclude that the entire discussion in this last paragraph on page 24 is not justified and should be deleted.

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Department of Pesticide Regulation



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MEMORANDUM

TO: Gary Patterson, Supervising Toxicologist

VIA: Keith Pfeifer, Senior Toxicologist

FROM: Lori O. Lim, Staff Toxicologist

DATE: February 26, 1999

SUBJECT: Naled

Attached are my responses to OEHHA comments to the Naled Risk Characterization Document (May 7, 1998). There are two major areas of concern: (1) oncogenicity of naled and related compounds, and (2) additional uncertainty factor under the Food Quality Protection Act. Reevaluation of the data showed that there was insufficient weight of evidence to consider naled for oncogenicity and an additional uncertainty factor was not needed, as previously concluded in the RCD. Additional discussion will be provided in the revised RCD.

GENERAL COMMENTS

page 1, Literature Search: The RCD should indicate whether a complete literature was conducted.

A complete literature search was conducted at the initiation of the RCD. Because of the length of time elapsed between the initiation and completion of the final draft, any literature search will be outdated by the time the draft reaches the peer reviewers. As a practice, every effort was made to include relevant published literature in the RCD.

page 1, second paragraph under Assessment of Cancer Risks: "... fibroadenomas where the incidence of tumors were higher in all treated groups in comparison with control animals..."

MT/DPR considers this statement inaccurate. The incidences of fibroadenoma were only increased in the female groups. In the male, the incidences were 1/44, 0/50, 0/49, and 0/48 for control, 0.2, 2, and 10 mg/kg/day, respectively. The incidences for the same tumor type in the female were 12/54 (22%), 17/44 (39%), 13/53 (25%), and 21/55 (38%) for control to high doses. These increased incidences in the treated groups were, however, not statistically significant and did not show any dose-response relationship.

page 2, first paragraph: The lack of strong evidence of oncogenic effects from exposure to naled is in contrast to the carcinogenic effects produced in studies with dichlorvos (DDVP)..."

This statement and the rest of the paragraph implied that there was strong evidence for the oncogenicity of DDVP. MT/DPR considers the oncogenicity evidence for DDVP as limited. As discussed in the RCD, the pancreatic adenomas were likely associated with the use of corn oil as the vehicle. The increased incidence of mononuclear leukemia (MCL) was significant (* at $p < 0.05$ in the table below) only for the males. It is debatable whether the female data showed a "clear" dose response as interpreted by OEHA. The increased incidences for leukemia were not statistically significantly different from the control. As for mammary gland tumors (combined), the increased incidences were also not statistically significant and the incidence (35%) at the high dose was lower than that (42%) at the low dose.

Tumor type	0	2.9 mg/kg/day	5.7 mg/kg/day
Leukemia (MCL)			
males	11/50 (22%)	20/50 (40%)*	21/50 (42%)*
females	17/50 (34%)	21/48 (44%)	23/50 (46%)
Mammary gland tumors			
males (fibroadenomas only)	6/46 (13%)	1/44 (2%)	2/46 (4%)
females	11/50 (22%)	20/48 (42%)	17/49 (35%)

Squamous papillomas and carcinomas of the forestomach in rats treated with DDVP were likely a localized effect due to chronic irritation at the site. The U.S. EPA FIFRA Scientific Advisory Panel (SAP) recently evaluated the evidence for DDVP oncogenicity (Lewis, 1998). The Panel considered MCL an invalid response for human risk assessment because it is one of the "most common background tumor types" for the Fischer rats. Furthermore, MCL occurs at high background rate and variability. Based on the forestomach tumors data, the Panel concluded that DDVP was a weak oncogen acting via a secondary or indirect mechanism.

page 2, third paragraph: DPR considered naled not genotoxic since the studies which sufficient detail for evaluation showed negative results. Other studies with inadequate details for evaluation were not considered. OEHHHA regarded those latter studies as providing positive and equivocal evidence and therefore, naled is potentially genotoxic.

MT/DPR disagrees with the OEHHHA conclusion. The database is summarized below. Naled was not genotoxic in five different types of assays. Other studies (under Equivocal results), all were conducted in *in vitro* bacterial assays and provided "conflicting evidence" for genotoxicity. Since the reports of these studies did not provide sufficient detail, neither the "positive" nor "negative" results could not be evaluated. It should be noted these studies were evaluated by Dr. Jeff Wong who had extensive experience conducting bacterial assays, in particular the Ames's assay. While some studies not described in details in the main text of the RCD, these studies were described in the Toxicology Summary in the Appendix.

a. Negative results:

1. Ames assay with TA1535, TA1537, TA98, and TA100; *E.coli* WP2 (Carver, 1988), in the presence and absence of metabolic enzymes (liver S-9).
2. *in vivo* micronuclei assay with Swiss albino mice (Machado, 1984).
3. *in vivo* chromosomal aberrations with Sprague-Dawley rats (Carver, 1983).
4. *in vitro* unscheduled DNA synthesis with Sprague-Dawley rat hepatocytes (Thilagar, 1988).
5. *in vivo* mutation assay with C57bl/6 mice (Litton Bionetics, Inc., 1984).
6. Ames assay with TA100, TA98, TA1535, TA1537 and TA1538, *E.coli* WP2 with and without metabolic activation system (Moriya et al., 1983). Result for naled was only indicated as "-". While this study was deficient in providing details of the experiment, the result supports those conducted by Carver (1988).
7. Ames assay with TA1537, TA1538, and TA98 with and without metabolic activation system (Braun et al., 1983).
8. Ames assay with 10 of 11 bacterial (*E. coli* and *Salmonella*) strains without metabolic activation system (Hanna and Dyer 1975).
9. Ames assay with TA1538 and TA98 with and without metabolic activation system (Byeon et al., 1976).

b. Equivocal results

1. Ames assay with TA100 (Braun et al., 1983). The revertant rate was less than 2 times the background, a result generally considered equivocal for TA100.
2. Ames assay with TA1535 was reported to show a "weak" response (Hanna and Dyer, 1975). The result is difficult to interpret since the strain was tested in a saturated solution of naled

previously incubated overnight at 45°C before test. Neither naled, DDVP, nor other metabolites were measured.

3. Ames assay with TA1535 and TA 100 (Byeon et al., 1976). The results, for with and without metabolic activation system, were designated as "±", a notation for ambiguous result by the authors.

4. Ames assay with Ames assay TKJ6321 and TKJ5211 (*B. subtilis*), TA1535. Data was presented in a graph with zero revertants for the control and no data analysis (Shiau et al., 1981).

MT/DPR considered the overall database showed naled without significant genotoxic potential. The negative genotoxicity data provides support to the MT/DPR conclusion that there is insufficient evidence for oncogenicity.

page 2, last paragraph, to top of page 3: "Oncogenicity data on DDVP should not be disregarded in the overall evaluation of potential oncogenicity for naled". DDVP bioassay showed "clearly" positive outcome.

The oncogenicity of DDVP was considered in the evaluation of potential oncogenicity for naled. MT/DPR does not agree that DDVP bioassay showed "clearly" positive outcome. See previous response on the oncogenicity of DDVP for *page 2, first paragraph*.

page 3, second and third paragraphs: More comparison should be made between naled and DDVP studies before the oncogenicity of naled can be dismissed. The difference in response in the chronic bioassays has not scientific explanation.

In the RCD, MT/DPR made comparisons between naled and DDVP studies, and both databases were considered in the determination of the oncogenicity of naled. Since DDVP is not the only metabolite and was further metabolized in animals given naled, the difference in the outcome was expected when either DDVP or naled was given as the parent compound.

page 3, third paragraph: OEHHA considered the bioassays provided limited evidence for naled oncogenicity based on direct evidence from rare mammary tumors in male rats and supporting evidence from DDVP which also caused mammary tumors.

MT/DPR agrees that mammary gland adenocarcinomas in male rats is a rare tumor type and that the increased incidence after naled treatment as biologically significant. However, the low incidence and lack of statistical significance by pair-wise comparison did not support further consideration for oncogenicity. Furthermore, this type of tumor was not found in the DDVP study where only fibroadenomas were reported.

page 3, third paragraph: cancer risk from exposure to DDVP-derived from naled should be considered.

In the revised RCD, MT/DPR plans to include this determination for dietary exposure to DDVP based on more recent residue databases. The lifetime risks for occupational exposure to DDVP will have to be addressed by the WH&S Branch.

page 3 under Weight-of-Evidence for Carcinogenicity: The discussion of naled oncogenicity should be broadened to include dichloropropene, trichlorfon, and dichloroacetic acid.

A weight-of-evidence for carcinogenicity section will be added to the revised RCD. MT/DPR determined that there was no clear evidence of oncogenicity and therefore did not support the generation of a cancer potency for quantitative characterization of the risk from lifetime exposure.

1. Two chronic toxicity studies with naled conducted in 2 species and both gender did not showed sufficient evidence of oncogenicity.
 - a. No treatment-related tumors in mice after chronic exposure to naled (highest dose tested was 50 mg/kg/day) by gavage.
 - b. In Sprague-Dawley rats exposed to naled (2 and 10 mg/kg/day) by gavage, the only noteworthy tumor was mammary gland adenocarcinomas in the males. However, the increased incidences were not statistically different from the control incidence.
2. Mammary gland adenocarcinoma is a rare tumor type in male rats. The historical control rate for mammary adenocarcinoma in the male was 0.8% for the conducting laboratory, compared to the 0% for the concurrent control.
3. There was no evidence of naled interaction with macromolecules. Naled was negative in almost all available genotoxicity studies including two (*in vitro* unscheduled DNA synthesis in hepatocytes and *in vivo* chromosomal aberration) conducted with Sprague-Dawley rats.
4. Oncogenicity has been shown in structurally-related compounds but was limited to common tumor types and at high doses.
 - a. DDVP- a metabolite of naled
 - (1) Significantly increased the incidences of mononuclear cell leukemia in male Fischer 344 rats treated with DDVP (2.9 and 5.7 mg/kg/day).
 - (2) Both positive and negative results reported in genotoxicity studies.
 - (3) MT/DPR evaluated the oncogenic risk from DDVP exposure.
 - (4) U.S. EPA cancer classification for DDVP is Cq. In a recent meeting, the U.S. EPA SAP considered it a weak oncogen based on forestomach tumors due to chronic irritation (Lewis, 1998). MCL was considered by the Panel as not relevant to humans as it is a common tumor type limited to Fischer 344 rats.
 - b. Trichlorfon- metabolize to DDVP
 - (1) Increased incidences of MCL in female Fischer 344 rats and mammary tumors (not statistically significant) in female mice.
 - (2) Significantly increased incidences of tumor occurred only at the highest dose tested (158.9 mg/kg/day in the rat, and 750 mg/kg/day in the mouse). The doses were much higher than those used in DDVP or naled studies.
 - c. Dichloroacetic acid- a metabolite of naled
 - (1) U.S. EPA classification for dichloroacetic acid is B2.

(2) Liver tumors were observed in rats and mice given >0.5 g/L (~40 mg/kg/day) in the drinking water.

(3) Mechanism for tumors has been hypothesized to be due to lipid peroxidation.

page 4. Choice to Critical NOELs for Risk Assessment: OEHHA agrees with the selection of the studies but more explanation and details of the studies should be provided.

In the revised RCD, additional details will be added as suggested.

page 4. Seasonal Exposure Assessment: Seasonal occupational exposure should be considered.

In the revised RCD, seasonal exposure will be considered.

page 5. Uncertainty Factor for Children's Exposures: OEHHA recommends the use of an additional uncertainty factor.

MT/DPR considered the reasons given by OEHHA for the additional uncertainty factor. This section will be revised to include these considerations.

1. Existing testing requirements do not specifically address pre- and postnatal sensitivity.

MT/DPR agrees that the existing testing guidelines do not specifically test for sensitivity. However, the database for required studies is considered complete, a criteria that U.S. EPA used to remove the factor.

2. There was a decrease in fetal body weight at a NOEL lower than that for maternal toxicity.

While the pup body weight was decreased when compared to the control, the decrease was not statistically significant in the range-finding study. Furthermore, the change was not confirmed in the definitive study with more animals.

3. DDVP caused severe reduction in brain weight in guinea pig offspring (DeAngelo et al., 1991)

The correct citation for this study should be Mehl et al., 1994. This study was not considered in the naled RCD but was reviewed for DDVP. The data showed decreased brain weights in pups exposed to DDVP (15 mg/kg/day or 15 mg/kg/day twice-a-day) or trichlorfon (125 mg/kg/day) given pregnant rabbits on gestational days 44, 45, and 46. The major problem with the data interpretation was that only a single dam was treated for each dosing regimen. Since the doses used in this study are much higher than the critical acute NOEL (2.5 mg/kg/day)¹ used for risk characterization, an additional uncertainty factor is not needed.

¹In terms of moles, the DDVP and trichlorfon doses used in the studies were 68 umole/kg/day and 486 umole/kg/day compared to the naled acute NOEL of 6.6 umole/kg/day.

In the naled reregistration document, U.S. EPA has determined that the additional uncertainty factor should be removed (Rowland to Whitby, 1998). This decision, however, did not include any consideration of the above DDVP study.

The U.S. EPA SAP reviewed this study in the determination of whether an additional uncertainty factor was needed for DDVP exposure (Lewis, 1998). Consistent with the MT/DPR review, the SAP was concerned that the data came from only one litter. The Panel concluded that the study could not be used to determine developmental toxicity. However, it "suggests the possibility of a developmental effect on the brain". Because of uncertainties associated with developmental neurotoxicity and patterns of human exposure, the Panel decided to retain the additional uncertainty factor. However, the Panel was divided as to whether the factor was a 10-fold or 3-fold factor. In the draft risk assessment for DDVP, U.S. EPA proposed to use a 3-fold factor.

page 5, Exposure Assessment

(Comments to be addressed by WH&S).

SPECIFIC COMMENTS

1. *on RCD page 1, paragraph 4:* Details were not given because the cited paragraphs are summaries. Instead of "metabolized", "degraded" will be used.

2. *on RCD page 2, paragraph 4:* The typographical error will be corrected.

3. *on RCD page 7:* This is the current format for all RCD generated by Medical Toxicology. a statement on exposure in the drinking water is already included under **IV.B.2.b.(2) Naled and DDVP Residue Data**.

4. *on RCD page 17:* The chemical name for temephos will be added.

5. *on RCD page 21:* The concentration is correct, no change is needed.

6. *on RCD page 50, last paragraph:* There is no overtolerance residues for naled and all measured values were below the detection limits. The cited sentence on TEF will be clarified.

7. *on RCD page 54-44, table 17:* The use of DDVP tolerance level will be clarified.

8. *on RCD page 58, first paragraph:* The dietary oncogenic risk of DDVP derived from naled will be added. This is possible now because the U.S. EPA has obtained more current residue data and processing information which allowed the determination of more realistic exposure estimates.

9. *on RCD page 69, first paragraph:* The discussion on the uncertainty factors will be clarified.

10. *on RCD page 70, Section V.E.3:* The discussion on the uncertainty factor for cumulative toxicity will be expanded.

11. on RCD page 72 Section VI.B.: Additional discussion on cumulative toxicity will be added.

Oncogenic effects of naled and related compounds.

	Species/ route	dose (mg/kg/day)	Dosage/ Effects/incidences	Ref ^a																																																				
Naled gavage	Sprague- Dawley rats	0, 0.2, 2, 10	<table><tr><td></td><td>0</td><td>0.2</td><td>2</td><td>10</td></tr><tr><td>Mammary gland fibroadenoma</td><td></td><td></td><td></td><td></td></tr><tr><td>M</td><td>1/44 (2%)</td><td>0/50</td><td>0/49</td><td>0/48</td></tr><tr><td>F</td><td>12/54 (22%)</td><td>17/44 (39%)</td><td>13/53 (25%)</td><td>21/55 (38%)</td></tr><tr><td>Mammary gland adenoma and/or adenocarcinoma</td><td></td><td></td><td></td><td></td></tr><tr><td>M</td><td>0/44+</td><td>0/50</td><td>1/49 (2%)</td><td>2/48 (4%)</td></tr><tr><td>F</td><td>9/54 (17%)</td><td>6/44 (14%)</td><td>3/53 (6%)</td><td>4/55 (7%)</td></tr></table>		0	0.2	2	10	Mammary gland fibroadenoma					M	1/44 (2%)	0/50	0/49	0/48	F	12/54 (22%)	17/44 (39%)	13/53 (25%)	21/55 (38%)	Mammary gland adenoma and/or adenocarcinoma					M	0/44+	0/50	1/49 (2%)	2/48 (4%)	F	9/54 (17%)	6/44 (14%)	3/53 (6%)	4/55 (7%)	1																	
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F	9/54 (17%)	6/44 (14%)	3/53 (6%)	4/55 (7%)																																																				
	CD-1mice	0, 3, 15, 50	no increased incidences in tumors	2																																																				
DDVP gavage	Fischer 344 rats	0, 2.9, 5.7	<table><tr><td></td><td>0</td><td>2.9</td><td>5.7</td></tr><tr><td>Pancreatic adenoma</td><td></td><td></td><td></td></tr><tr><td>M</td><td>16/50+ (32%)</td><td>25/49 (51%)*</td><td>30/50 (60%)*</td></tr><tr><td>F</td><td>1/50 (2%)</td><td>1/46 (2%)</td><td>4/50 (8%)</td></tr><tr><td>Mononuclear cell leukemia</td><td></td><td></td><td></td></tr><tr><td>M</td><td>11/50+ (22%)</td><td>20/50 (40%)*</td><td>21/50 (42%)*</td></tr><tr><td>F</td><td>17/50 (34%)</td><td>21/48 (44%)</td><td>23/50 (46%)</td></tr><tr><td>Mammary gland fibroadenoma</td><td></td><td></td><td></td></tr><tr><td>M</td><td>6/46 (13%)</td><td>1/44 (2%)</td><td>2/46 (4%)</td></tr><tr><td>F</td><td>9/50 (18%)</td><td>19/50 (38%)*</td><td>16/49 (33%)</td></tr><tr><td>Mammary gland adenoma and/or adenocarcinoma</td><td></td><td></td><td></td></tr><tr><td>M</td><td>0/46</td><td>0/44</td><td>0/46</td></tr><tr><td>F</td><td>2/50 (4%)</td><td>2/50 (4%)</td><td>1/49 (2%)</td></tr></table>		0	2.9	5.7	Pancreatic adenoma				M	16/50+ (32%)	25/49 (51%)*	30/50 (60%)*	F	1/50 (2%)	1/46 (2%)	4/50 (8%)	Mononuclear cell leukemia				M	11/50+ (22%)	20/50 (40%)*	21/50 (42%)*	F	17/50 (34%)	21/48 (44%)	23/50 (46%)	Mammary gland fibroadenoma				M	6/46 (13%)	1/44 (2%)	2/46 (4%)	F	9/50 (18%)	19/50 (38%)*	16/49 (33%)	Mammary gland adenoma and/or adenocarcinoma				M	0/46	0/44	0/46	F	2/50 (4%)	2/50 (4%)	1/49 (2%)	3
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	B6C3F1 mice	0, 7.1 (males), 14.3, 28.6 (females)	<table><tr><td></td><td>0</td><td>7.1</td><td>14.3</td><td>28.6</td></tr><tr><td>forestomach squamous papilloma or carcinoma</td><td></td><td></td><td></td><td></td></tr><tr><td>M</td><td>1/46 (2%)+</td><td>1/50 (2%)</td><td>5/48 (10%)</td><td>NA</td></tr><tr><td>F</td><td>5/44 (11%)+</td><td>NA</td><td>6/44 (14%)</td><td>19/48 (40%)**</td></tr></table>		0	7.1	14.3	28.6	forestomach squamous papilloma or carcinoma					M	1/46 (2%)+	1/50 (2%)	5/48 (10%)	NA	F	5/44 (11%)+	NA	6/44 (14%)	19/48 (40%)**	3																																
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Trichloron diet	Fischer 344 rats	0,129 (males), 158.9 females)	<table><tr><td></td><td>0</td><td>129/158.9</td></tr><tr><td>Mononuclear cell leukemia</td><td></td><td></td></tr><tr><td>M</td><td>24/50 (48%)</td><td>21/50 (42%)</td></tr><tr><td>F</td><td>8/50 (16%)</td><td>17/50 (34%)*</td></tr><tr><td>Renal tubular adenoma</td><td></td><td></td></tr><tr><td>M</td><td>0/50</td><td>3/50 (6%)</td></tr><tr><td>F</td><td>0/50</td><td>0/50</td></tr><tr><td>Alveolar/bronchiolar adenoma and carcinoma</td><td></td><td></td></tr><tr><td>M</td><td>0/50</td><td>4/50 (8%)</td></tr><tr><td>F</td><td>0/50</td><td>3/50 (6%)</td></tr></table>		0	129/158.9	Mononuclear cell leukemia			M	24/50 (48%)	21/50 (42%)	F	8/50 (16%)	17/50 (34%)*	Renal tubular adenoma			M	0/50	3/50 (6%)	F	0/50	0/50	Alveolar/bronchiolar adenoma and carcinoma			M	0/50	4/50 (8%)	F	0/50	3/50 (6%)	4																						
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	CD-1 mice	0,66, 245, 750	<table><tr><td>0</td><td>66</td><td>245</td><td>750</td></tr><tr><td colspan="4">Mammary gland tumors</td></tr><tr><td>F</td><td>1/50 (2%)</td><td>2/50 (4%)</td><td>0/50</td></tr><tr><td></td><td></td><td></td><td>8/50 (16%)</td></tr></table>	0	66	245	750	Mammary gland tumors				F	1/50 (2%)	2/50 (4%)	0/50				8/50 (16%)	5
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Mammary gland tumors																				
F	1/50 (2%)	2/50 (4%)	0/50																	
			8/50 (16%)																	
DCA ^a	rats, mice		liver tumors	6																

a/ Ref: 1. Batham et al., 1984; 2. IRDC, 1984; 3. Chan, 1989; 4. Christenson, 1990 5. Hayes, 1988; 6. DeAngelo et al., 1991 and 1996. DCA=dichloroacetic acid.

b/ += statistically significant at p <0.05 level based on the trend test. *= statistically significant at p <0.05 level when compared with control values.

References:

- Batham, P., B.E. Osborne, C. Bier, P. Araujo, B. Broxup, and B.G. Procter (Bio-Research Laboratories Ltd.), 1984. Dibrom chronic oral toxicity/carcinogenicity study in rats. Chevron Chemical Company. DPR Vol. 215-064 to 071 #37591.
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Winston H. Hickox
Secretary for
Environmental
Protection

Department of Pesticide Regulation

James W. Wells, Director
830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov



Gray Davis
Governor

MEMORANDUM

TO: John S. Sanders, Chief
Worker Health and Safety Branch

FROM: Michael H. Dong, Staff Toxicologist
Worker Health and Safety Branch

DATE: January 26, 1999

SUBJECT: RESPONSE TO OEHHA'S COMMENTS ON NALED

Submitted for your consideration of its placement, is our response to OEHHA's comments on the exposure assessment portion of the naled RCD. OEHHA's comments were made available to WH&S staff last August. One reason for the delay of drafting this response, as you may already know, is the issue on the determination of the SADD (seasonal average daily dosage) values.

A. General

1. *Seasonal Occupation Exposures (bottom, p.4 of, herein, OEHHA's comments unless otherwise noted).* The annualized dosages for workers were presented in various tables in the exposure assessment document. Their calculations were based on annual exposure frequencies of 40 days (for cotton scouts) or greater (for other workers). Since most pesticide applications are seasonal by nature, seasonal exposures are certainly there for naled workers. However, meaningful and useful SADD should be calculated from the average daily dose amortized over the dosing time required to induce the subchronic effect in question. This time-to-effect, or at least the study duration used for the investigation of the subchronic effect, is yet to be provided by the Medical Toxicology Branch.
2. *DDVP in Occupational Exposure (bottom, p.5).* The higher acute and subchronic toxicity of DDVP is not crucial here in terms of the risk (and hence the exposure) assessment for naled, at least not based upon the data on hand. Although metabolic data showed that naled initially converts to DDVP in animals, the toxicity as well as the potency of DDVP (or of any other metabolites of naled) would manifest in the animal data used to determine



adverse effects. For example, if there were no (increased) tumors observed when certain doses of naled were administered in a group of rats for two years, but this were not the case when certain doses of DDVP were given, then the only logical interpretation is that DDVP as an *in vivo* metabolite of naled is not in the form or shape that can cause tumors in rats. On the other hand, if DDVP as an *in vivo* metabolite could cause different acute and subchronic effects or result in higher toxicity of the same effects caused by naled, such should manifest in the health effects data for *naled* and hence would be picked up during the hazard identification process.

We might argue that *in vitro* DDVP residues that enter into the body could behave differently compared to those available *in vivo*. However, as indicated in Table 7 of the exposure assessment document, exposure to the airborne DDVP residues of 0.005 µg/kg/hour at day 1 after treatment was minimal for grape harvesters or other field workers. (This amount of worker exposure is equivalent to an absorbed dosage of < 0.05 µg/kg/day.) Table 7 also shows that the ratio of naled residues on grape foliage to those of DDVP was 4:1 or higher. However, this ratio is actually 19:1 in terms of *absorbed* dosage, since the default dermal absorption of 50% was used in the assessment when the dermal absorption for DDVP was in fact 11%.

If we must be concerned with the exposure to *in vitro* DDVP residues that are available from a naled application, then the absorbed dosages for the various field worker groups from this type of DDVP exposure would be one-twentieth of those presented in Table 5. The dosages in Table 5 were calculated for naled and DDVP combined, under the presumption that *some* time (at least a few hours) would have to lapse before some 15% naled residues could be transformed to DDVP in the atmosphere. It is based on this understanding that *handlers* and *users* were not expected to be exposed to any significant amount of *in vitro* DDVP residues (immediately) following an application of naled.

For completeness, however, a summary table will be appended to the exposure assessment document to list the acute and chronic dosages calculated for *field* workers exposed to *in vitro* DDVP residues available in the atmosphere.

B. Specific

1. *Pesticide Usage (p.8)*. The revised document will incorporate OEHHA's comments on this issue.
2. *Title of Table 3 (p.8)*. The revised document will incorporate the comments on this issue.
3. *Use of Default Dermal Absorption (p.8)*. Concurred (without changes).
4. *Estimate of Total Exposure of Human Volunteers (p.8)*. Although the outcome would still be the same, a statement justifying the use of a two-hour exposure for the entire day's exposure was inadvertently left out in the last paragraph on p.11 of the original exposure assessment document. That statement, along with further elaboration, will be included in the revision. Basically, that last paragraph pointed out that 99% of the study subjects had a DMP level of well below 0.009 ppm, which was used in the calculation for the daily dosage. The use of that conservative value should be enough to offset any underestimation from using exposures monitored for the first two hours, during which dermal and inhalation exposures to aerial type application are supposed to be at their peak.
5. *Based on Experiments in Grapes (p.9)*. Initial depositions of pesticide foliar dislodgeables are primarily based on application rate, and should not be crop- or task-specific. Also see response to General Comment #2 above for DDVP in occupational exposure.
6. *Of the 20% Naled Collar Powder Released (p.9)*. The release of naled powder is triggered primarily through hand contact with the collar. Although we recognize that not all (of the 20% released) that is dislodgeable from the collar will become transferable onto the human hand or skin, at this time no (non-proprietary) empirical data are available to quantify that lower transfer rate.
7. *Use of Backpack Data (p.9)*. The main reason is that exposure estimates from backpack sprayers would over, rather than under, predict those from treatment of sewage system via injections. This point for justification will be included in the revision.

8. *Evaluation of Maximum Likely Exposures (p.9)*. The range of likely exposures rests not only on exposure rates, but also on other, sometimes even more crucial, exposure-related factors. Despite the fact that measured exposures could vary over 100- or 1,000-fold, such as from 1 to 1,000, by the time we use the average or midpoint, the difference between the highest (possible) and the average is merely two-fold. The PHED exposure rates used were expressed as per lb AI handled. If the total amount of AI handled per day is at its upper extreme, then the *actual* daily exposure is likely to be overestimated even if an *average* exposure *rate* is used.

The PHED subsets appended to the exposure document clearly showed that the 95% confidence limits (C.I.) on the arithmetic mean for dermal exposure included negative values. Therefore, to use the upper 95% C.I. from such a statistical interval is meaningless. To have a negative value for the mean exposure rate (even though physically impossible), the sample set must contain two clusters of exposure rates representing two extremes that are very far apart, with the *lower* extreme group dominating. Arithmetic means calculated from lognormal distributions are often seen to be at the 75th percentile or thereabouts. For the type of lognormal distribution that has the lower extreme group so dominating as described above, the arithmetic mean would be at a higher percentile, like around 85th or above. On the other hand, the mean plus the upper 90% or 95% C.I. from this type of distribution would yield an upper extreme that is materially unreal.

9. *Irreversible Adverse Effects (p.9)*. The statement "*Adverse effects occur only when plasma levels in the target organ exceed a critical level.*" also refers to a chemical that acts in an *irreversible* manner. Whether they were originated from dermal or oral exposure, plasma levels reflect how much a chemical under study is available (or circulating) in the body system. To simplify the points made, the discussion presented in the exposure appraisal section may be summarized in quantitative terms as follows:

$$[{}^8\{1 \text{ unit (dermal)}\}] \leq [8 \text{ units (dermal)}] < [8 \text{ units (oral)}].$$

Where an *irreversible* damage is involved, the 8-hour effect from the first term or condition is likely to be equal to, and not less than, the bolus effect from the

second term. However, the *reversible* effect from the first term certainly would be less than that from the second term, given the reasons stated in the exposure appraisal section. The third term typically would yield a much higher peak plasma level or a much greater effect, whether irreversible or not, than would any of the first two terms.

The study by Auton *et al.* (1993), which was cited in the exposure appraisal section, showed that the peak plasma level from oral dosing of fluazifop-butyl, after normalization for the amount absorbed, could be as high as 8 times the peak level from dermal dosing. (The smaller amount of dermal dose absorbed, the greater the difference was seen.) The study by Carmichael *et al.* on triclopyr (*Human Toxicol.* 8:431-437, 1989) and that by Nolan *et al.* on chlorpyrifos (*Toxicol. Appl. Pharmacol.* 73:8-15, 1984), which were not but will be cited in the exposure appraisal, are two additional cases among several others supporting such a finding.

In the study by Nolan *et al.*, for example, peak blood concentrations of the 3,5,6-TCP metabolite were, respectively, 0.93 and 0.063 µg/ml following a 0.5 mg/kg po and later a 5.0 mg/kg dermal administration of chlorpyrifos in human volunteers. *Even if* the oral to dermal absorption had a 100:1 margin for chlorpyrifos in humans, the observed peak blood level of 3,5,6-TCP from the oral absorbed dose would still be 50% higher than the peak level from the dermal absorbed dose. If the margin for oral to dermal absorption of chlorpyrifos were lowered to 50:1, then the observed peak blood level of 3,5,6-TCP from the oral absorbed dose would be twice (200% of) the peak level from the dermal absorbed dose. Using the margin of 50:1 for oral to dermal absorption, the study by Carmichael *et al.* showed that the human peak plasma level of triclopyr from oral dosing was 1.5 times the level from dermal dosing.

Attachments: OEHHA's comments

cc: John H. Ross

NALED

HUMAN PESTICIDE EXPOSURE ASSESSMENT

Volume II

Worker Health and Safety Branch
Department of Pesticide Regulation
California Environmental Protection Agency

June 30, 1999

HUMAN PESTICIDE EXPOSURE ASSESSMENT

NALED

(An Organophosphate Insecticide for a Variety of Agricultural and Non-Agricultural Uses)

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Worker Health and Safety Branch
Department of Pesticide Regulation
California Environmental Protection Agency

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ABSTRACT

This exposure assessment is written to be an integral part of the Department's risk characterization document prepared for the active ingredient naled, which is an organophosphate used for control of a great variety of insects and mites. A total of 15 naled products are currently registered in California, with over 70% of the total (reported) annual usage being on cotton, fruits, nuts, vegetables, and other agricultural commodities. The non-agricultural uses include applications in aquatic areas, forests, dwellings, and indoor environments. The toxicological endpoints of primary concern are acute and (sub)chronic cholinergic signs observed in animal studies, which included dyspnea, inactivity, oral exudate, tremors, salivation, and death. Dichlorvos (DDVP), which is the initial metabolite of naled in the biotransformation process and an insecticide itself, is listed under California's Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause cancer. During the 15-year period between 1982 and 1996, there were a total of 145 illnesses or injuries reported in California as having an association with naled alone, or in combination with other pesticides. The symptoms involved in these cases were either eye and skin irritation only, or systemic and respiratory in nature, or all of the above. There were no studies available on dermal or truly on inhalation absorption for naled. Available animal metabolism studies showed that naled was completely biotransformed to various metabolites while being distributed to all tissues, with about 40% and 10% excreted in the urine and the feces, respectively, within 48 hours after dosing. In this exposure assessment, the potential exposures to naled for the various activities were calculated for six major subpopulations which included residents, bystanders, applicators, mixer/loaders, flaggers, and field workers. Actual data on human exposure to naled were very limited. The daily exposures to naled for these individuals hence were calculated primarily from surrogate data, such as those available in PHED (Pesticide Handlers Exposure Database). The highest calculated absorbed daily dosage was 1.3 mg per kilogram of body weight. This was the dosage calculated for agricultural workers applying naled with backpack sprayers while wearing chemical-resistant gloves and coveralls over normal work clothing (i.e., long pants, shoes, socks, and a long-sleeved shirt). There were no exposure data available that could be used to calculate the dosages for applicators spraying naled with a thermal/cold fogger or a flit/hydro-gun, or for greenhouse workers painting naled on hot pipes/plates.

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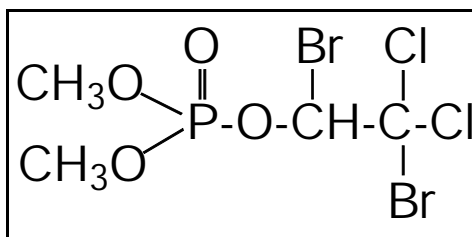
I. INTRODUCTION

Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) is an organophosphate which has been used in California for control of insects and mites in a great variety of agricultural and non-agricultural settings. The primary biological activity of this insecticide is, like those of many other organophosphates, through its inhibition of cholinesterase (ChE) enzymes. Naled has been used on fruits, cotton, nuts, greenhouse ornamentals, and vegetables. Its non-production agricultural uses include applications in aquatic areas (e.g., marinas and swamps), forests, dwellings (e.g., hotels), and indoor environments (e.g., animal buildings, hospitals, factories, restaurants, warehouses, feedlots, and meat packing establishments,). The assessment of occupational and non-occupational exposures for this active ingredient (AI) necessitated the construction of numerous use scenarios, some of which were considered for the first time in pesticide exposure assessment. This exposure assessment by the Worker Health and Safety Branch (WH&S) is written to be an integral part of the risk characterization document (RCD) prepared by the Department of Pesticide Regulation (DPR) for all uses of naled in California. The Department's risk characterization for naled is performed in part because of the insecticide's adverse effects observed in acute, (sub)chronic, and reproductive studies. The major adverse effects observed were cholinergic symptoms, which included dyspnea, inactivity, exudate, tremors, salivation, and death. Dichlorvos (DDVP), which is the initial metabolite of naled in the biotransformation process and an insecticide itself, is listed under California's Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause cancer. The potential exposure to DDVP as an active ingredient is addressed only briefly toward the end of this exposure assessment document, since a separate exposure assessment document (Fong and Formoli, 1993) has been completed for this metabolite.

II. PHYSICAL AND CHEMICAL PROPERTIES

Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate, CAS Registry No. 300-76-5, molecular weight 380.89, molecular formula $C_4H_7Br_2Cl_2O_4P$) is an organophosphate insecticide. This chemical is commercially available as a yellow liquid (with a pungent odor). Although naled has low

water solubility (2 g/L at 22°C), it can be completely hydrolyzed in water within 48 hours at room temperature. It is only sparingly soluble in petroleum solvents but is freely soluble in aromatic and chlorinated hydrocarbons, ketones, and alcohols. Its solubility in heptane at 20°C is 82 g/L. The vapor pressure of naled is 2×10^{-3} mm Torr at 20°C, with a boiling point of 110°C at 0.5 mm Hg and a melting point of 26.5 to 27.5°C. Its specific gravity, Henry's Law constant, and octanol-water coefficient are, respectively, 1.971 at 27.5°C, 5.014×10^{-8} atm m³g·mol⁻¹, and log P = 2.18 at 500 ppm (all above properties as reported by Chevron Chemical Company, 1980, 1983a, 1983b, 1983c, 1983d, 1983e, 1987; Farm Chemicals Handbook, 1996). The following is the chemical structure of naled:



III. FORMULATION/INTENDED USE PATTERN

Technical naled available in the United States is manufactured by Valent USA Corporation, under the trade name Valent Naled Technical. This technical is intended only for use in the formulation of other naled insecticide products. The other naled products that are currently registered in California, together with the technical naled, are summarized in Table 1 below.

Of the 15 currently-registered naled products, Valent Dibrom 8 Emulsive appears to have the broadest use. Its product label covers essentially all uses included in the other naled products listed in Table 1 except Naled Technical, Dibrom Concentrate, and those available as flea or tick collars for dogs or cats. The use of the flea and tick products involves simply placing or buckling the collar around the animal's neck. Unlike the technical, Dibrom Concentrate cannot be diluted with water but can be diluted with diesel oil and applied with ultra low volume equipment. This concentrate is a special formulation designed for control of mosquitoes, houseflies, and certain other nuisance insects.

As shown in Table 1, Valent Dibrom 8 Emulsive contains 62% of naled by weight, or 7.5 lb naled per gallon of the emulsive. To facilitate the discussion of the present exposure assessment, the agricultural commodities to which this emulsive product can be applied may be divided into 6 crop groups: (1) vines (e.g., grapes, *typically by airblast or over-the-vine boom*); (2) vegetable or row crops (e.g., broccoli, cabbage, celery, eggplant, strawberries, summer squash, etc., *by air or groundboom*); (3) field crops (e.g., cotton, cantaloupes, muskmelons, melons, safflower, sugar beets, beans, etc., *by air or groundboom*); (4) orchards (e.g., almonds, walnuts, oranges, lemons, grapefruit, peaches, etc., *by air or airblast*); (5) forestry (e.g., shade trees, ornamental shrubs, flowering plants, etc., *by hand-held type*); and (6) greenhouse crops (e.g., roses and other ornamental plants, *by vapor from hot pipes or pans*).

Uses of Valent Dibrom 8 Emulsive other than the above are likewise numerous; they can be further subdivided into residential and predominantly non-residential. These residential and non-residential sites include shade trees, shrubs in lawns, swamps, livestock pastures, feedlots, holding pens, woodlands, cull piles, refuse areas, food processing plants, and loading docks. Valent Dibrom 8 Emulsive is used at these sites mainly to control flies or mosquitoes, in addition to clover mites, roaches, earwigs, leafhoppers, or other insects and mites. In or around food processing plants, this emulsive is applied to walls, doorways, windows, and cull piles using a coarse sprayer or by injection; otherwise, for control of flies and mosquitoes in open fields, mist or cold fog by aircraft is typically used. Applications at other (non-production agricultural) sites usually can be made with either ground or hand-held equipment.

Table 1. Naled Products Currently Registered in California			
EPA Reg. No.	Product Name	Company Name	%AI/Net Contents ^a
2517-44-AA	Bansect Flea & Tick for Cats	ConAgra Pet Products	10.0%/14 g in 1 collar
2517-43-AA	Bansect Flea & Tick for Dogs	ConAgra Pet Products	15.0%/25 g in 1 collar
2517-46-ZA	Sergeant's Dual Action Flea & Tick Collar for Cats	ConAgra Pet Products	7.0%/14 g in 1 collar
2517-45-ZA	Sergeant's Dual Action Flea & Tick Collar for Dogs	ConAgra Pet Products	15.0%/25 g in 1 collar
2517-46-ZB	Sergeant's Flea-Brites Flea & Tick Collar for Cats	ConAgra Pet Products	7.0%/14 g in 1 collar
2517-45-ZB	Sergeant's Flea-Brites Flea & Tick Collar for Dogs	ConAgra Pet Products	15.0%/25 g in 1 collar
59639-18-AA-2393	Hopkins Fly Killer D	HACO, Inc.	36.0%/1 gal
34704-351-AA	Clean Crop Dibrom 8 Miscible Naled Insecticide	Platte Chemical Co.	58.0%/1 gal
59639-21-AA	Dibrom Fly & Mosquito	Valent USA	1.0%/1 gal; RTU
59639-15-AA	Valent Dibrom 8 Emulsive	Valent USA	62.0%/5 gal
59639-18-AA	Valent Fly Killer D	Valent USA	36.0%/1 gal
59639-19-ZA	Dibrom Concentrate	Valent USA	87.4%/(not given)
59639-15-ZA	Legion Insecticide	Valent USA	58.0%/5 gal
59639-43-AA	Valent Naled Technical	Valent USA	90.0%/30 gal
59639-90-AA	Trumpet EC Insecticide	Valent USA	78.0%
^a AI ≡ active ingredient; RTU ≡ ready-to-use.			

IV. REGULATORY HISTORY/STATUS

Naled was introduced in 1956 by Chevron Chemical Company (Gallo and Lawryk, 1991), with Orthocide Dibrom 10-4 Dust in 1966 being the first end-use product registered in California (now no longer available in the State). In response to the petition by Chevron Chemical Company in 1989, the U. S. Environmental Protection Agency (USEPA) established residue tolerances of 1.0 ppm (parts per million) and 5.0 ppm, respectively, for naled present in/on alfalfa hay and in/on alfalfa forage (Federal Register, 1989).

In 1990, the U. S. Department of Agriculture was granted a quarantine exemption for the use of naled baits as a means to eradicate the oriental fruit fly *Dacus dorsalis* and other *Dacus* spp. in California (Pesticide & Toxic Chemical News, 1990). The following conditions were specified for the quarantine exemption use: At least 600 bait spots per square mile; no applications to food or feed crops; a reapplication interval of 2 weeks or longer; and an expiration date of December 2, 1992.

USEPA (1995a) established a reference dose (RfD) of 0.002 mg/kg/day for chronic exposure to naled. This RfD was based on ChE inhibition observed in rat brain in a two-year dietary study, in which a NOEL (no observed effect level) of 0.2 mg/kg/day was found. According to the California Code of Regulations (1991), the PEL (Permissible Exposure Limit) of naled in the workplace is 3 mg/m³, or 0.19 ppm, at 25°C and 760 mm Hg. A Reregistration Eligibility Decision review for naled was issued by USEPA (1995a) on July 13, 1995.

V. USAGE IN CALIFORNIA

Naled is not a restricted pesticide in California. As such, only licensed pest control operators were required to report its usage prior to 1990. Now with a few exceptions, commercial users must report pesticide use. According to the latest (available) annual pesticide use reports (DPR, 1994, 1995, 1996a, 1996b, 1999), from 1992 through 1996 more than 70% of the total reported annual usage was for production agricultural uses. In 1995, 79% of the total reported annual usage was on cotton alone. (Note that there was a data entry error in listing the annual usage for cotton in the original 1994 annual pesticide use report.) Table 2 below lists the 1992 through 1996 annual usage of naled in California by pounds and by number of applications.

The raw agricultural commodities with the 8 highest *percent* pound usage (as determined for the majority of the earlier years) are listed in Table 3 below. As indicated in Table 3, since 1994 annual usage on cotton continued to be the highest among all crops and sites. For non-production agricultural sites, animal husbandry premises topped the 1996 list, taking up approximately 3% of the reported total annual naled usage in California. In 1996, the use of naled on almonds also reached 6% of the reported total annual usage.

The annual pesticide use reports do not cover pesticides used as flea/tick killers or fly killers. To some extent, the annual usage for these unreported sites can be approximated from the mill assessment (sales) data which showed that, for the past several years, less than 5% of the annual sales have been for flea/tick and fly killer products. Of these minor sales, the market share of flea/tick naled collar products has been 1% or less.

Table 2. Annual Usage of Naled in California From 1992 Through 1996,
by Pounds and by Number of Applications^a

	Pounds	Number of Applications
1992	164,905	6,731
1993	180,041	5,368
1994	460,222	9,992
1995	711,519	11,944
1996	351,266	6,607

^abased on the Department's pesticide use reports (DPR, 1994, 1995, 1996a, 1996b, 1999).

Table 3. Raw Agricultural Commodities With the 8 Highest Percent Usage in Pounds
(Based on the Earlier Years) From 1992 Through 1996^a

Commodity	1992	1993	1994	1995	1996 ^b
fresh market grape	14	7	5	1	1
processed grape (wine)	6	4	2	1	1
orange	14	12	4	2	3
safflower	7	14	4	2	6
strawberry	9	7	2	2	3
cotton	11	15	65	79	58
broccoli	3	2	4	2	4
sugarbeet	4	5	2	1	2

^afor actual (absolute) usage in pounds, simply multiply the year's total pounds listed in Table 2 by the percentage listed in this table.

^bin 1996, the use of naled on almonds also reached 6% of the reported annual usage.

VI. LABEL PRECAUTIONS

All of the naled products listed in Table 1, except those of the ready-to-use (RTU) type and those with limited usage, are labeled as toxicity Category I pesticides with the signal word DANGER. The

exceptions are the Dibrom Fly & Mosquito Spray by Valent USA and the flea collar products, all of which are classified as having Category III (CAUTION) toxicity. According to the labels as well as the newly-adopted worker protection standard (WPS), workers are required to wear chemical-resistant gloves, long-legged pants, shoes plus socks, protective eyewear, chemical-resistant headgear (for overhead exposure), and a long-sleeved shirt when handling naled products having Category I toxicity. The toxicity Category I products are labeled as corrosive to eyes and the skin. In California, a closed system must be used when mixing/loading pesticides having Category I toxicity if their usage per application exceeds 1 gallon.

The labels for the toxicity Category I products advise that large amounts of water be given to the victim if he or she accidentally swallows the product. For eye and dermal contact, the labels recommend flushing the affected areas with large quantities of running water for at least 15 minutes. If poisoning is through inhalation, the victim should be immediately removed from the contaminated atmosphere. In all cases, medical attention should be sought as soon as possible. For the toxicity Category III products, clothing requirements for users are not specified but the labels reflect similar precautionary statements, especially on the part pertaining to eye and skin contact.

Technical grade naled has caused mild skin sensitization in guinea pigs (USEPA, 1995b; Knaak, 1984). Despite these findings, the labels for *some* of the naled products listed in Table 1, primarily those having Category III toxicity, do not contain a precautionary statement warning that the insecticide may cause allergic skin reaction in humans.

VII. WORKER ILLNESSES AND INJURIES

Annual cases of illness and injury that have been reported by California physicians or health authorities as related to pesticide exposure have been compiled for 1982 through 1996. During this 15-year period, a total of 145 cases were reported as having an association with naled alone, or in combination with other pesticides (Mehler, 1999).

In 1995, a drift episode occurred in Kern County, in which 22 employees working in a potato packing house developed symptoms after odors were produced from misapplications of naled and two disinfectants (Verder-Carlos, 1999). Many of their symptoms were systemic and respiratory in nature. The pesticides were misused (i.e., contrary to label instructions) to control infestation of stagnant water kept in an unused tank in the packing house. In addition to this drift episode, four other cases were also reported in 1995 to have been related to the use of naled.

A review of all 145 cases by the WH&S staff in the Pesticide Illness Surveillance Program (Verder-Carlos and Mehler, 1999) indicated that more than half of these illnesses and injuries were due to accidental applications of the organophosphate onto the patients' face, to their contact with (foliar) dislodgeable residues, or to spray drifts. The symptoms for 59 of these 145 cases (i.e., slightly over 40%) were eye and skin irritation only. For the 86 cases reported as having systemic symptoms, 56 cases were tested for cholinesterase levels. Of the 56 cases tested, 11 cases had no results available, 6 cases had levels below the baseline, 5 cases had levels below the normal range, and another 2 cases had levels below the midpoint of the normal range. Of the remaining 32 cases whose levels were reported to be within the normal range, 28 cases furnished test reports.

VIII. ACUTE DERMAL AND RELATED TOXICITY

According to USEPA (1995b) and the Medical Toxicology Branch (Berliner *et al.*, 1985), the acute dermal LD₅₀ for technical naled was 360 mg/kg in female rabbits and 390 mg/kg in male rabbits (Category II). The acute inhalation LC₅₀ for 4 hours of exposure to technical naled were 0.19 and 0.20 mg/L (Category II) in female and male rats, respectively. In addition, USEPA considered the eye and dermal irritation observed in rabbits to be severe (Category I). Their reported acute oral LD₅₀ ranged from 92 mg/kg (Category II) in female rats to 325 mg/kg in male rats. As mentioned in Section VI, technical grade naled was noted to have caused mild skin sensitization in guinea pigs.

IX. DERMAL AND INHALATION ABSORPTION

There does not appear to be any dermal absorption study available for naled. Valent USA, which is the sole manufacturer of naled technical and the major registrant of the non-technical naled products, suggested that an absorption rate of 20% be used for calculation of dermal exposure to naled (Valent USA, 1995a). Their suggestion was based on the argument that USEPA had used a dermal penetration of 11% for DDVP, which has a chemical structure similar to naled (as the former is the initial metabolite of the latter). As reflected in Section VIII, there does not appear to be any compatible dermal and oral LD₅₀ available in the same species *and* sex to give an approximation of the dermal absorption of naled (technical or emulsive) by taking the ratio of the LD₅₀ from the two routes. Neither are there any acceptable data available on inhalation uptake or intake for naled.

The Department cannot make use of the DDVP surrogate because the technique or method of using structure activity relationships to predict dermal absorption has not been well validated. The default adopted recently by WH&S for dermal absorption without any data is 50% (Donahue, 1996). For inhalation uptake and intake for many chemicals, the default values used by WH&S are 50% and 100%, respectively (Thongsinthusak *et al.*, 1993a). These absorption defaults were used here for calculating the dermal and inhalation exposures to naled.

X. ANIMAL AND HUMAN METABOLISM

No metabolism studies were submitted by Valent USA or by other registrants for evaluation of naled's biotransformation observed directly in humans, as such human studies apparently had never been conducted or reported. Valent USA did provide four animal metabolism studies on naled. Rats (Cheng, 1981a, 1981b), goats (Chen, 1982), and chickens (Cheng, 1983) were the three species used separately in the four animal studies. Valent USA also provided a short summary report on the results of these studies (Abell, 1985). The use of dogs and cows as test species for metabolism study was mentioned, but without much detail.

In all the species tested, naled was found completely biotransformed to various metabolites while being distributed to all tissues. The metabolic pathways proposed by the investigators for these species were similar. For simplicity, only the major metabolic pathways for rats alone are depicted in Figure 1 on the next page. As shown in this figure, initially naled is metabolized to DDVP, which is then hydrolyzed to dichloroacetaldehyde (DCA).

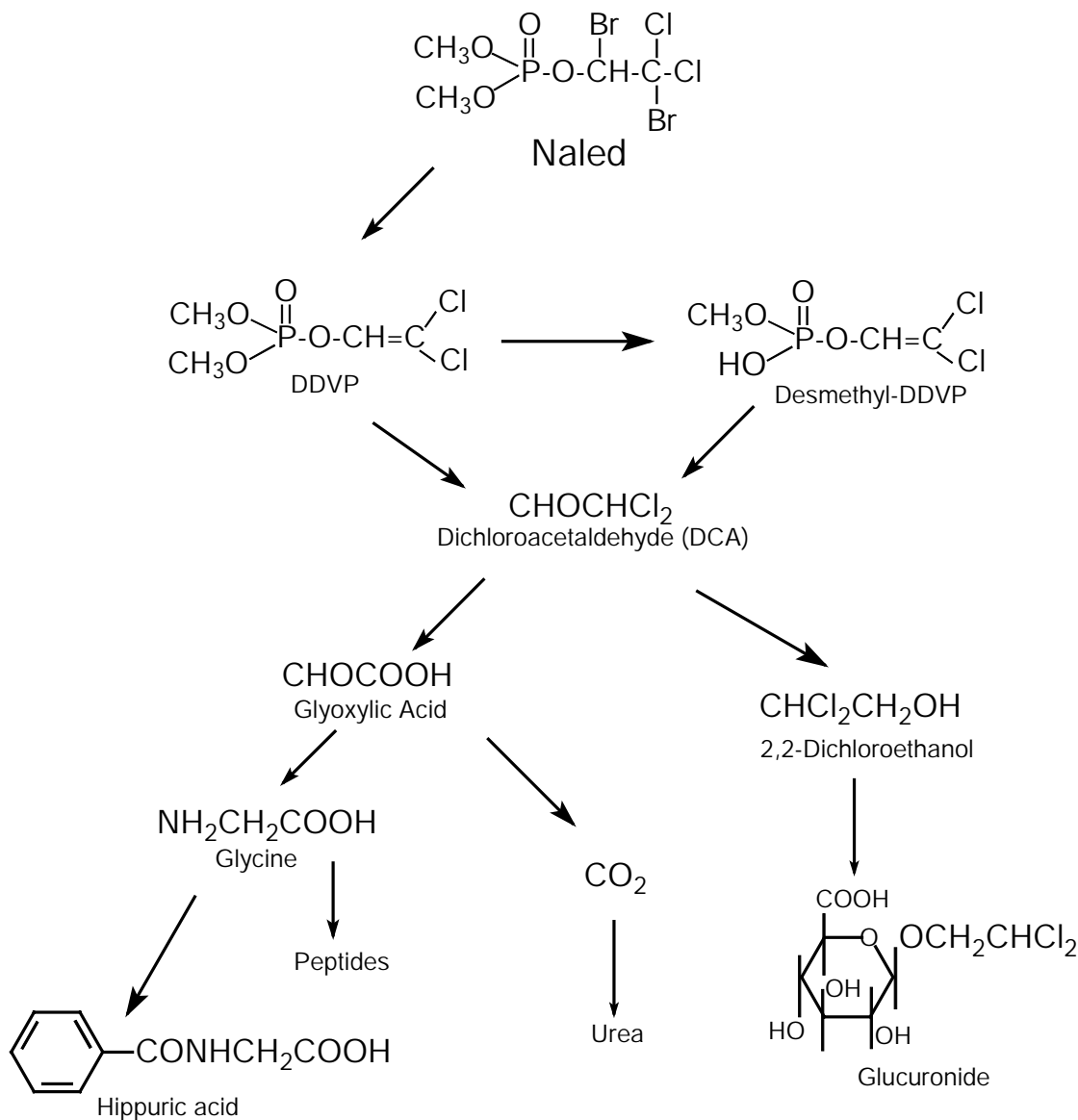


Figure 1. Major Metabolic Pathways of Naled in Rats as Proposed by Valent USA (Cheng, 1981a; Abell, 1985)

In the first (Cheng, 1981a) of the two rat studies cited above, the test animals were orally treated with [Ethyl-¹⁴C]naled at 28 and 50 mg/kg for the excretion pattern. Two days after dosing, approximately 40% of the radioactivity was reportedly excreted in the urine, 10% in the feces, 20 to 30% in the expired air, and 20 to 30% remained in the carcass. According to the investigator, approximately 90% of the amount excreted in urine was characterized as a conjugate of 2,2-dichloroethanol, probably of a glucuronide type. Similar findings on the 48-hour recovery of radioactivity in the urine

were observed in the second rat study (Cheng, 1981b), in which the animals treated with a single oral dose at approximately 25 mg/kg were sacrificed at 2, 6, 24, and 96 hours after dosing. In this second, more extensive metabolism study, 5.3% of the applied radioactivity was found in the urine at 2 hours after dosing.

XI. EXPOSURE ASSESSMENT

XI-1. Ambient Air

In mid 1991, Air Resources Board (ARB) contracted out a monitoring study (Royce *et al.*, 1993) in which ambient naled air levels were measured at five sampling sites located in central Tulare County. The *highest* naled level and DDVP level measured over a 24-hour period in this 1991 study were, respectively, 0.08 and 0.06 $\mu\text{g}/\text{m}^3$. The 1991 usage of naled in Tulare was the second highest by county, over 80% of the annual amount (38,000 lb) used in Fresno County. Although between 1994 and 1996 the annual naled usage in Tulare dropped slightly in rank, in 1996 the total amount of naled applied in Tulare was approximately 40% of the county's total naled applied in 1991 (based on the Department's annual pesticide use *electronic* database).

In terms of inhalation exposure to naled, a maximum air level of 0.08 $\mu\text{g}/\text{m}^3$ suggests that a *six-year-old child* would receive at most an absorbed daily dosage (ADD) of 0.03 μg per kilogram of body weight. This dosage estimation was based upon a 24-hour average inhalation rate of 16.7 m^3/day (USEPA, 1997), an average body weight of 21.7 kg (USEPA, 1997), and an inhalation uptake of 50% (see Section IX). This dosage estimation was calculated as follows:

$$\text{ADD} = 0.03 \mu\text{g}/\text{kg}/\text{day} = [(0.08 \mu\text{g}/\text{m}^3) \times (16.7 \text{ m}^3/\text{day})] \times (50\%) \times (21.7 \text{ kg})^{-1}.$$

For *adults*, the ADD derived from the above maximum naled air level was 0.01 $\mu\text{g}/\text{kg}$. This three-fold difference in absorbed naled dosage was strictly a result of using the smaller ratio of the default average inhalation rate (16.0 m^3/day) to average body weight (70 kg) assumed for adults. It was due to this type of rate-to-weight ratio that a six-year-old was used to represent the children population.

XI-2. Residents/Bystanders

Table 4 below is presented for quick reference summarizing the potential exposures to naled estimated for bystanders and non-user residents staying at or around the treatment site. Some of the assumptions used in the estimations are consistent with common practice and hence are mentioned as table footnotes only. Others that require clarification or appear to be unique to this population subgroup or to naled are discussed below, along with a brief description of the exposure estimations involved.

Children. Naled is commercially available as a flea and tick collar for cats and dogs. There is thus a potential for young children to be exposed to naled dust impregnated in the collars, provided that they are allowed to pet animals wearing these collars. Surrogate data are not available for this type of exposure assessment for any pesticide. It is anticipated, however, that such exposure would be insignificant if occurring at all. For one thing, parents are not supposed to let their children near or share pillows or the like with pets whose body is found to have fleas or ticks (and have the collar on). The effect of collar treatment is not meant to be instantaneous since, as stated on the naled product

labels, the collar should be used continuously to attain maximum efficacy. It is also a known fact to many people that unlike fleas, ticks are relatively harder to kill and die more slowly. In addition, the product labels specify explicitly that children are not allowed to play with these collars.

Table 4. Daily Exposure to and Absorbed Daily Dosage of Naled Estimated for Bystanders and Non-User Residents at or Near Treatment Sites

Subgroup	No. of Days ^a Exposed per Year	Daily Exposure ^b (mg/kg BW/day)	Absorbed Daily Dosage ^c (µg/kg BW/day)	Seasonal Daily Dosage ^d (µg/kg BW/day)
Adult Residents	4	< 0.04	< 20	< 4.0
Children ^e	4	< 0.04	< 20	< 4.0
Non-User farmers ^f	4	< 0.04	< 20	< 4.0
Bystanders ^g	4	< 0.04	< 20	< 4.0

^a based on the expectation that at most 2 to 3 applications will be made per season and that the naled airborne or surface residues will dissipate substantially after 2 days post application (see discussion in this section).

^b back calculated from absorbed dosage, based on a dermal absorption and an inhalation uptake of 50% (see Section IX).

^c estimated primarily from the biomonitoring data presented in the Delaware study (Kutz and Strassman, 1977), as discussed in this section for adult residents.

^d presented for completeness only, since the seasonal frequency of 4 days is generally not considered to be adequate to induce the subchronic effect of concern when this effect was in fact observed in a 21-day rat study (per e-mail from Lori Lim of the Medical Toxicology Branch dated 02/10/99; for annualized average daily dosage, the estimates would be < 0.22 µg/kg BW/day, or 18 times (i.e., per 20 days vs. per 365 days) lower than those calculated here for the seasonal dosage.

^e included for this group were exposures from soil ingestion and from hugging animals with treated collars on.

^f including non-user growers whose crops are treated by commercial applicators.

^g including chefs, cooks, waiters, bus boys, and food service personnel, whose restaurants or food plants are treated for control of flies, mosquitoes, and other pests.

Inhalation of airborne naled residues could also be a possible route of exposure for children playing in treated areas. Naled is considered as a volatile chemical (see Section II), which suggests that its residues on soil could act as a source of potential inhalation exposure. There are no data available on airborne or soil residues present on residential properties treated with naled. However, exposure of children to naled via inhalation can be alleviated to a great extent if certain reentry procedures and sound application practices are followed.

There was indication that the airborne residues did not dissipate rapidly enough during the first 48 hours after naled was applied to an orange grove (ARB, 1995). It is important to note that in addition to their dissipation pattern, the level of airborne pesticide residues is a function of application *rate* and *usage*. The orange grove data showed that following application the naled air levels ranged from

0.02 $\mu\text{g}/\text{m}^3$ to a maximum of 6.30 $\mu\text{g}/\text{m}^3$. The application rate (0.94 lb per acre) used for the orange grove treatment was nearly 10 times that typically used for residential treatments. The average air level from a typical treatment made in residential areas is thus expected to be less than 0.63 $\mu\text{g}/\text{m}^3$. Based on the algorithm presented in Subsection XI-1, the ADD would be less than 0.25 $\mu\text{g}/\text{kg}/\text{day}$.

In addition to the control for houseflies and mosquitoes, naled can be applied directly to turf and soil surfaces around flowers, shrubs, and trees in residential areas for eradication of other general pests, such as clover mites and earwigs. Due to naled's high vapor pressure (see Section II), its residues present in or on soil and turf from this type of residential treatments are expected to be transient, if in any significant quantity at all.

Although data on naled soil residues were not available to WH&S, the maximum naled concentration in residential soil was expected to be less than 1 mg/kg, or 1 ppm. This expectation was based on the label specification that naled is applied in residential areas at a rate normally not to exceed 0.1 lb AI per acre, or approximately 1 mg per sq ft. Since the density of soil of most any type is around 1.6, 1 square foot of soil with a depth of 0.25 inch would weigh about 1,000 g (i.e., $1,000 \text{ g} \approx [12 \times 12 \times 0.25 \text{ cu in}] \times [\text{cu cm}/0.06 \text{ cu in}] \times 1.6 \text{ g/cu cm}$). This suggests that the initial deposition of naled in residential soil normally would not exceed 1 mg/kg, or 1 ppm. At this maximum soil concentration and the mean soil ingestion rate of 200 mg/day (USEPA, 1997; Dong *et al.*, 1994), the oral ADD of naled through soil ingestion by a six-year-old child would be less than 0.01 $\mu\text{g}/\text{kg}/\text{day}$. Even at a much higher daily soil ingestion rate of 10,000 mg for pica problem (i.e., abnormal mouthing behavior), the daily soil intake of naled by this child would still be less than 1 $\mu\text{g}/\text{kg}/\text{day}$.

Adult Residents. In a biomonitoring study by Kutz and Strassman (1977), the mean urinary level of dimethyl phosphate (DMP) was found to have increased from 0.005 to 0.014 ppm (i.e., a net gain of 0.009 ppm) in 56 volunteers after an aerial application of naled for mosquito control near Dover, Delaware. These volunteers stayed outside of their houses within the treatment area. The maximum net increase among this subgroup was 0.44 ppm, or 440 μg per liter of urine. There was no noticeable increase (as a group) observed in the DMP levels in other volunteers who either stayed outside of the treatment area or remained indoors (but within the treatment area).

Altogether two groups of volunteers whose ages ranged from 4 to 83 years old were included in the above Delaware study, in which naled was applied at approximately 0.05 lb AI/acre, along with a trace amount ($< 0.002 \text{ lb/acre}$) of temephos. There were 107 volunteers staying inside the actual spray target area and 100 others staying in a 1 mile margin outside the treatment zone. Two urine specimens were collected from each of these 207 volunteers, with one collected at several hours prior to application and the other collected at within 3 hours after the application. Of six metabolites detected in the study, DMP and DMTP (dimethyl phosphorothionate) were specifically used as indicators of exposure to naled and temephos, respectively. As shown in Figure 1 in Section X, naled cannot be converted to DMTP since the former lacks the thiol group. For this reason, the average increase of 0.009 ppm in DMP noted in 56 of the 107 volunteers (i.e., of all those in the first group that stayed outdoors but inside the spray target area) is thought to be due more to their exposure to naled than to temephos, especially when the latter insecticide was applied only in trace amount. Even under this worst case assumption (that *all* of the DMP came from naled), the exposure to naled from aerial sprays applied at 0.05 lb/acre would be at most 13.5 μg per day based on a maximum daily urine output of 1.5 liter for adults (i.e., $13.5 \mu\text{g}/\text{day} = 9 \mu\text{g}/\text{L} \times 1.5 \text{ L}/\text{day}$). This is

equivalent to an absorbed dose of 40.5 µg naled per adult since the molecular weight (380.0) of naled is 3 times that (125) of DMP.

From the estimate of 40.5 µg/adult calculated above, the absorbed daily dosage (ADD) of naled is expected to be about 20 µg per kilogram of body weight (BW). This expectation is based on the fact that for mosquito control in California, the product label allows up to 0.1 lb of Dibrom Concentrate (which contains 87.4% of the naled active ingredient) to be applied per acre of area. It is also based on the observation in animal studies, as stated in Section X, that 5% of the absorbed dose would be excreted in the urine at 2 hours after dosing. (That is, $ADD \leq 20.0 \mu\text{g/kg BW} [= 40.5 \mu\text{g} \times (0.1 \text{ lb}/0.05 \text{ lb}) \times (87.4\%) \times (5\% \text{ for incomplete urine collection})^{-1} \times (70 \text{ kg})^{-1}]$). *Note that this absorbed daily dosage of 20 µg/kg BW is applicable to young children as well.* The DMP levels measured in the 56 volunteers in the Delaware study were not given by age. However, it is expected that few, if any, of the young children would be among those who remained outdoors during the aerial application. Also, young children's daily urine output is about 3 times less than the maximum amount assumed above for adults. This difference in daily urine output, together with young children's usual limited duration of outdoor activities, is sufficient to offset much of the disparity in body weight between young children and male or female adults.

It was mentioned earlier that the maximum level of DMP observed among the 56 volunteers was 0.44 ppm (after adjustment for baseline value). A more conservative value for the daily absorbed dosage hence would be 1 mg/kg BW (i.e., $\approx 977.8 \mu\text{g/kg BW} [= (20.0 \mu\text{g/kg BW}) \times (0.44 \text{ ppm}/0.009 \text{ ppm})]$). However, this value is considered highly unrealistic in that there was apparently only one individual receiving such high exposure. Even though there were no individual data given, it is intuitive that the DMP levels from the other 55 volunteers (plus the remaining 51 = 107 - 56 volunteers in the same group) were *well* below their average of 0.009 ppm (after adjustment for their baseline values). Otherwise, their arithmetic mean could not have been this low since the total from the 56 volunteers altogether was only 0.50 ppm (= 0.009 ppm x 56). Despite this statistical implication, the rather conservative DMP average of 0.009 ppm was used here because if not used, the daily dosage could have been underestimated since the urine samples were collected within the first couple of hours, though during which time dermal and inhalation exposures to aerial type application are supposed to be at their peak (partly due to residue fall-out and partly due to rapid residue dissipation).

When formulated as a ready-to-use (RTU) spray for control of flies and mosquitoes, naled is suitable for use with a variety of handgun (e.g., flit guns, hydro-guns, etc.) or fogger (e.g., microsol, heat generating foggers, dairy barn foggers, etc.) application equipment. This RTU formulation contains 1% of the naled active ingredient (*see* Table 1 in Section III), or 0.15 lb AI per gallon of the spray product. The product label for this formulation specifies that fog applications not be made if treatment sites are inside dwellings or restaurants. On that basis, it is expected that the airborne and surface residues of naled from this type of application would not be any greater than those from aerial sprays for mosquito control.

There is no restriction for the amount of the RTU spray used per application, whereas the maximum labeled rate for aerial application with the Dibrom Concentrate is 0.0874 lb AI/acre (equivalent to 0.002 lb AI/1,000 sq ft). According to the product label, Dibrom Fly & Mosquito Spray should be used at the rate of 1 fl oz of the product per 3,000 cubic feet of space if used as a dairy barn fogger. The label also recommends that all doors and windows of the barn be closed where possible before

fogging. Such use apparently will not involve much, if any, exposure of residents or bystanders to naled. The label specification suggests that 1 fl oz (= 1/128 gallon) of the spray product, which contains 1% (i.e., 0.0012 lb) of the active ingredient, is sufficient to cover a 15 ft x 15 ft (= 225 sq ft) area. That is, for a surface area of 1,000 sq ft, the usage with the RTU spray is expected to be around 0.005 lb AI (equivalent to 0.035 gallon of the spray product). Although this usage is 2 to 3 times greater than that (0.09 lb AI/acre) specified for mosquito control by aerial application (using the Dibrom concentrate), the amount of airborne residues of naled or its fall-out from RTU sprays is likely to be similar and not twice as much. This is because about half of the usage is applied at or below the breathing level.

The maximum daily exposure should be trivial for children and adult residents when the RTU formulation is applied as a coarse spray to areas infested by roaches and the like. These cracks, crevices, and hiding places usually are located below the breathing zone and are not openly accessible to children or adult residents. For this reason, the post application exposure received by non-user residents from this type of application should be minimal when compared to that from aerial sprays for mosquito control.

Non-User Farmers/Growers. Naled formulated as emulsive can also be applied to reduce livestock pests in corrals, holding pens, feedlots, and rangelands that contain dairy and beef cattle, hogs, sheep, or horses. Even though the maximum label rates for these sites are nearly 3 times that allowed for mosquito control in residential areas, the maximum daily exposure to naled received by farmers who themselves are not applicators is expected not to exceed the dosage of 20 µg/kg BW calculated above for non-user residents. This expectation is based on the presumption that these bystander farmers have a greater opportunity (or are better advised as through one-on-one instructions) to stay away from the sprays during the first few hours of (livestock) treatment. This argument also holds true for growers whose crops are treated by commercial applicators.

Other Bystanders. Potentially, chefs, cooks, waiters, waitresses, bus boys, food service workers, and the like can be exposed to naled when they return to restaurants or to food processing plants treated with naled. However, daily exposure to naled for these other bystanders is not expected to be as much as that received by adult residents staying in an area that has been treated for mosquito control. This is because normally it will be many hours after treatment before these individuals return to work. Reentry restrictions have been proposed by USEPA (1995c) for homeowner and non-WPS (i.e., non-worker protection standard, implying non-agricultural) occupational uses of naled products. These include labeling language that restricts people from touching treated livestock, plants, soil, or other surfaces until the sprays have dried.

XI-3. Field Workers

Several groups of field workers are subject to occupational exposure from contact with dislodgeable naled residues present on treated foliage. These include harvesters, cotton scouts, and those who perform cane or shoot turning, leaf pulling, cane thinning, or girdling especially in vineyards. Data on reentry exposure to naled for these field workers were not available to WH&S, except for grape harvesters. For other field workers, it is thus necessary to extrapolate the dermal exposure from available dislodgeable foliar residue (DFR) data. This extrapolation was accomplished by means of a dermal transfer rate, which is defined here simply as the ratio (or sometimes some other relation, such as linear regression) of hourly dermal exposure (µg/hr) to DFR (µg/cm²) measured more or less

Table 5. Daily Exposure to and Absorbed Dosage of Total Naled for Various Field Workers, by Crop Type or Cultural Operation^a

Field Workers	Daily Exposure		Absorbed Daily Dosage ^d	Seasonal Dosage ^e	Annualized Dosage ^f
	Dermal ^b	Inhalation ^c			
Grape Girdler/Thinners ^g	1,240	13.4	9.0	3.87	0.74
Grape Harvesters ^h	115	4.5	0.9	0.39	0.19
Cotton Scouts ⁱ	372	10.1	2.7	1.16	0.15
Vegetable Crop Harvesters ^j	1,984	13.4	14.3	6.15	5.09
Greenhouse Harvesters ^k	44,800	13.4	320.1	137.6	65.8

^a for workers wearing long-pants, shoes, socks, and a *short*-sleeved shirt without gloves; except perhaps for *greenhouse* plants, naled residues at 3 DAT (days after treatment) and thereafter are expected to be negligible or not detectable.

^b in µg/person per 8-hour workday except for cotton scouts, whose workday was assumed to be 6 hours (*see* Dong *et al.*, 1991; Dong, 1993, 1994).

^c in µg per person per 8-hour workday except for cotton scouts (*see* footnote *b* above); calculated from total hourly inhalation exposures at 1 DAT (or at 3 DAT for grape harvesters) presented in Table 7 below.

^d in µg/kg BW/day; based on a default dermal absorption and a default inhalation uptake of 50% (*see* Section IX), on an adult male/female average body weight (BW) of 70 kg; and on the algorithm: Absorbed Daily Dosage (ADD) = [(Dermal Exposure + Inhalation Exposure) x (50% absorption) x (BW)⁻¹].

^e in µg/kg BW/day; based on (roughly) one-half of the residue levels observed at day 1 (or day 3 for grapes) since the reapplication interval is typically 7 days and dissipation data (other than grapes) were not available to give a more accurate estimate for the foliar residue level over the first 7 days post application; and on the amortization factor of 0.86 for working 6 out of 7 days per week, given that the annual exposure frequencies listed below (*see* footnote *f*) are 40 days or higher and that the time-to-effect for the subchronic effect at issue was 21 days (per e-mail from Lori Lim of the Medical Toxicology Branch dated 02/10/99). [Overall, seasonal dosage = (1/2) x ADD x (6/7) = 43%(ADD).]

^f in µg/kg BW/day; based on (roughly) one-half of the residue levels observed (*see* footnote *e* above) and on the amortization factor of AEF/365, where the annual exposure frequencies (AEF) are as follows: 40 days for cotton scouts (Dong, 1994); 60 days for grape girdler/thinners; 150 days for greenhouse harvesters (Dong, 1994) and grapes; and 260 days for other (i.e., mainly vegetable/row crop) workers who throughout the year may harvest *multiple* crops/fields treated with naled. [Overall, annualized dosage = (1/2) x ADD x (AEF/365) = (ADD) x (0.00137) x (AEF).]

^g based on 8 hours/day, on an average dermal transfer rate of 5,000 µg/hr per µg/cm² (*see* discussion in this section), and on total naled and DDVP foliar residues of 0.031 µg/cm² at 1 DAT (as shown in Table 6 below).

^h based on 8 hours/day and from hourly exposure to total naled and DDVP combined at 3 DAT presented in Table 7 below, as there is a PHI (pre-harvest interval) of 3 days for grapes.

ⁱ based on 6 hours/day (*see* footnote *b* above), on an average dermal transfer rate of 2,000 (*see* discussion in this section), and on total naled and DDVP foliar residues of 0.031 µg/cm² at 1 DAT (as shown in Table 6 below).

^j based on 8 hours/day, on an average dermal transfer rate of 4,000 (*see* discussion in this section), and on total naled and DDVP foliar residues of 0.062 µg/cm² at 1 DAT (which is twice that shown in Table 6 below because the maximum application rate for row crops is *twice* that for grapes; note that strawberry pickers are included in this field worker subgroup).

^k based on 8 hours/day, on an average dermal transfer rate of 7,000 (*see* discussion in this section), and on total naled and DDVP foliar residues of 0.8 µg/cm² at 0 DAT (*see* discussion in this section for use of 0 DAT even though the PHI is 24 hours).

at the same time. The term DFR is defined as the amount of pesticide residues that can be removed from *both* sides of treated leaf surfaces using aqueous surfactant. When multiplied with a proper dermal transfer rate, the DFR under study may be readily converted to hourly dermal exposure of workers entering a treated area.

Table 5 above summarizes the dermal exposures to *total* naled foliar residues that were calculated using the extrapolation method just described. Total naled residues were determined by adding the DDVP foliar residues in Table 6 to the naled foliar residues provided in that same table. The rationale for this addition is given in Subsection XI-5 (under Exposure to DDVP). The dermal transfer rates used for the various groups of field workers are justified in the subsections below. Also included in Table 5 are the various inhalation exposures estimated from air samples collected in vineyards sprayed with naled at 0.9 lb AI per acre.

To this date, there has been only one DFR study submitted for extrapolation of dermal exposure to naled. That study was conducted by Pan-Agricultural Labs, Inc. of Madera, California in the summer of 1993 (Rosenheck and Cone, 1994a), with Valent Dibrom 8 Emulsive applied to mature Thompson seedless raisin grapes at two sites in the San Joaquin Valley. Each trial site included eight rows of treated vines plus one row serving as controls. Three applications of the naled emulsive were made at 7 day intervals at each site, at the maximum label rate of 0.9 lb AI/acre. Leaf disc samples for measuring foliar dislodgeables were collected at 8 intervals through 14 days following treatment. The results from the study indicated that both naled and its first major metabolite DDVP (dichlorvos) dissipated to about the minimum quantifiable limit (2.5 ng/cm^2) by 3 DAT (days after treatment). Table 6 below lists the average levels of naled foliar residues observed for the first 6 sampling days. The timed dissipation of these dislodgeables is depicted graphically in Figure 2, in which the coefficients from the conventional log-linear regression are also given.

Table 6. Average Levels of Naled and DDVP Residues on Grape Foliage Observed at Various Sampling Intervals ^{a,b}						
Days Post- Application	Site 1		Site 2		Both Sites	
	Naled	DDVP	Naled	DDVP	Naled	DDVP
0	0.226	0.053	0.344	0.040	0.285	0.047
1	0.040	0.006	0.012	0.003	0.026	0.005
2	0.014	0.003	0.007	ND	0.011	0.003
3	ND	ND	0.009	ND	ND	ND
4	ND	ND	0.007	ND	ND	ND
5	0.003	ND	ND	ND	ND	ND

^a from a study by Rosenheck and Cone (1994a); residue levels averaged over 3 replicates (in $\mu\text{g/cm}^2$) from the third and final application (at reapplication interval of 7 days) at two sites located in the same raisin vineyard in Fresno County; adjusted for recovery (ranging from 77.8 to 100.0%); ND = not detectable (or below the minimum quantifiable limit of 2.5 ng/cm^2).

^b residue levels of DDVP, which is the initial metabolite of naled, are included here for calculation of exposure to total naled (based on the presumption, as stated in Section XI-5, that some hours would have to lapse before some naled residues could be transformed to DDVP in the atmosphere).

During the second trial, which occurred in late August, 1993, an exposure study was conducted concurrently by Pan Agricultural Labs (Rosenheck and Cone, 1994b) for harvesters entering the treated vineyard sites. A total of 10 volunteers (2 laborers from Pan Agricultural Labs and 8 local vineyard harvesters) were monitored for dermal and inhalation exposures using whole-body dosimetry (i.e., long underwear), handwashes, facial swipes, and typical personal sampling air pumps. During each replicate, the 10 volunteers all wore a clean pair of long cotton pants and a clean long-sleeved cotton/polyester shirt (over their long underwear dosimetry), plus shoes, socks, and some sort of hat. These harvesters used picking knives to cut the grape clusters from the vines. In order to reach all of the bunches from both sides of the vine, the harvesters also had to climb into and under the vines, thus necessarily coming into extensive contact with the treated foliage.

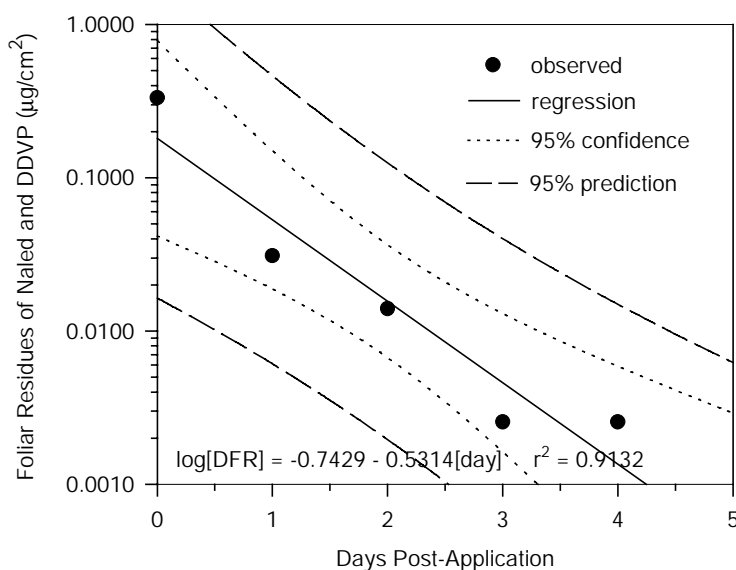


Figure 2. Dissipation of Naled and DDVP Dislodgeables on Grape Foliage (based on 0.9 lb naled/acre, after third application)

The above reentry exposure study was reviewed by Versar, Inc. (Dawson, 1995) for USEPA. According to Versar, the (actual) dermal transfer rate for the 10 workers, based on arithmetic means (of exposure rates monitored for the volunteers), was approximately 7,500 (µg/hr per µg/cm²), with a 95% upper limit of 11,000. For DDVP, the average transfer rate and the upper limit were about 10% lower. These estimates for transfer rate were found acceptable to WH&S, since they are consistent with those observed (Welsh *et al.*, 1993) for various other pesticides and by DuPont (Dong *et al.*, 1992) for methomyl. The average exposure rates calculated by WH&S for the 10 volunteers are presented in Table 7 below.

Table 7 shows that the (arithmetic) mean inhalation exposure to naled monitored for the 10 volunteers was 0.019 µg/kg BW per hour at 1 DAT (day after treatment). At this sampling interval,

the mean inhalation exposure of the 10 volunteers to DDVP was also found to be roughly 1 to 2% of their dermal exposure to DDVP. At 3 and 7 DAT, the ratios of dermal to inhalation exposure decreased noticeably for both Naled and DDVP; this is not inconceivable, however, since at these sampling intervals the residues are down to the detection limit which often yields a relatively unstable relation between dermal and inhalation exposure.

Table 7. Hourly Dermal and Inhalation Exposures to Naled and DDVP for Grape Harvesters

Reentry Interval ^d	Dermal ^a		Inhalation ^b		Total ^c	
	Naled	DDVP	Naled	DDVP	Naled	DDVP
1	1.619	0.283	0.019	0.005	1.638	0.288
3	0.174	0.031	0.004	0.004	0.178	0.035
7	0.050	0.019	0.004	0.004	0.054	0.023

^a arithmetic mean in $\mu\text{g/kg BW/hour}$, calculated from data in the reentry exposure study by Rosenheck and Cone (1994b) and adjusted for analytical recovery.

^b arithmetic mean in $\mu\text{g/kg BW/hour}$, calculated from data in the reentry exposure study by Rosenheck and Cone (1994b) using a default respiration rate of 14 L/min (Thongsinthusak *et al.*, 1993a) and adjusted for analytical recovery.

^c in $\mu\text{g/kg BW/hour}$; representing (mean) value for both dermal and inhalation exposures combined.

^d also referred to as days after treatment (DAT).

The reentry exposure rates listed in Table 7 and the resultant transfer rate were determined primarily for harvesters picking raisin (or wine) grapes. The rate values for table grape harvesters are expected to be lower, due to differences in canopy management of the vine involved. Unlike raisin or wine grape harvesters, table grape harvesters typically do not need to climb into and under the vines to pick grapes.

Available data (Dong *et al.*, 1992; Welsh *et al.*, 1993) to WH&S showed that the potential transfer rate and daily exposure would be higher, by about 2- to 10-fold, if the worker performed cane girdling, cane turning, or similar tasks, instead of picking and handling raisin or wine grapes. According to DuPont (Dong *et al.*, 1992), the *potential* dermal transfer rate for grape girdling operation ranged from 18,000 to 93,000 $\mu\text{g/hr per } \mu\text{g/cm}^2$. In this reentry exposure assessment, the midrange of 50,000 was used instead. This slightly-rounded down midrange was preferred over the upper observed extreme, even for acute or short-term exposure, because there were certain sampling limitations (e.g., sensitivity issues as discussed above regarding the data presented in Table 7) inherent in the DFR data that generated those extreme transfer rates. Using a default clothing protection factor of 10, the actual dermal transfer rate for this work group was reduced to 5,000.

In addition to grapes, Naled is used on numerous other crops for which certain cultural operations by field workers are likewise needed. For ease of reentry exposure assessment, these other crops were

loosely divided into the following crop groups: vegetable/row crops (including strawberries and field crops), tree fruit crops, greenhouse ornamentals, and cotton.

Naled is applied to tree crops during their dormant or delayed dormant period. Reentry exposure to naled thus need not be considered here for tree fruit harvesters. By nature of their work, the actual contact with foliage is expected to be very minimal for those field workers who, if any, must reenter treated orchards to verify treatment efficacy or perform similar activities.

For row and field crops such as beans, broccoli, strawberries, and the kind, the dermal transfer rate observed or used previously by WH&S were much lower than that for raisin or wine grapes noted above. WH&S used a dermal transfer rate of 3,500 – 4,000 previously to determine the reentry exposure to fenpropathrin for tomato and strawberry harvesters not wearing gloves (Dong, 1995). Based on this rate range, the dermal exposure to naled for vegetable or row crop harvesters at 1 DAT would be around 217 to 248 $\mu\text{g}/\text{hour}$. In this exposure extrapolation, the total naled and DDVP residues used for 1 DAT was 0.062 $\mu\text{g}/\text{cm}^2$, which is *twice* the sum of naled and DDVP presented in Table 6 because the maximum application rates for row or field crops are roughly *twice* that used for grapes in the two trials. For this vegetable harvester work group, the actual dermal transfer rate was considered to be close to the potential dermal transfer rate, in that much of the exposure is from the hands and the forearms.

WH&S previously also used a *potential* dermal transfer rate of approximately 11,000 for workers scouting in cotton fields treated with pesticides (Dong *et al.*, 1991; Dong, 1993, 1994). Using a default clothing protection factor of 10, the actual dermal transfer rate was reduced to 2,000. Since the maximum label rate for cotton is the same as that for grapes, the dermal exposure for cotton scouts at 1 DAT was estimated to be 62 $\mu\text{g}/\text{hour}$ ($= 2,000 \times 0.031 \mu\text{g}/\text{cm}^2$). There should be no significant reentry exposure to naled for cotton *harvesters* since the insecticide is not recommended for use on cotton after its first bolls have opened.

Since the *dissipation* kinetics for foliar dislodgeables observed on grapes are mainly a chemical- (rather than a crop-) specific phenomenon, these foliar residues were used here as surrogate for row crops, field crops, and cotton. In general, initial depositions of pesticide foliar dislodgeables are primarily based on application rate, since application methods are often carefully selected to cope with foliage density with the goal of producing an efficacious uniform concentration on leaf surfaces. Nonetheless, the naled (and DDVP) dislodgeables on greenhouse ornamental plants are expected to behave differently, *except initially*, in that they are constantly housed in an enclosed structure under regulated temperature. The initial deposition of total naled and DDVP on greenhouse crops was estimated to be as high as 0.8 $\mu\text{g}/\text{cm}^2$, or about 2.5 times the total naled and DDVP presented in Table 6 above, since the maximum label rate for greenhouse crops is 1 fl oz per 10,000 cu ft, or 1 fl oz per 1,000 sq ft (of floor surface). This estimation was based on the assumption that much of the initial airborne residues inside the greenhouse would settle quickly on its floor. The 2- to 3-fold increase in initial deposition for greenhouse crops was due to the fact that the maximum label rate used for grapes in the two trials was 1 pt of naled AI per acre, which is equivalent to 0.37 fl oz per 1,000 sq ft (or about 2.5 times *less* than that for greenhouse ornamentals, based on floor surface).

WH&S previously used a dermal transfer rate of 7,000 for greenhouse harvesters not wearing gloves (Dong, 1994, 1996). This transfer rate, together with the initial deposition of 0.8 $\mu\text{g}/\text{cm}^2$, would

yield an hourly dermal exposure of 5,600 µg per greenhouse worker. This hourly dermal exposure is considered to be applicable for greenhouse harvesters working at 1 DAT, since the dissipation of naled (and DDVP) dislodgeables may be slower in a confined area. As mentioned earlier, much of the airborne residues (from fogging or fumigation with hot plates, etc.) were assumed to settle quickly on the treated greenhouse floor. Without any empirical data, it is not certain how much, if any, of the initial foliar residues in a greenhouse would dissipate by 1 DAT.

No consideration was made for residue build-up from previous application, since the reapplication interval for naled is typically 7 days or longer and the dissipation of naled DFR is very rapid. The initial deposition and the DFR levels at 1 DAT or thereafter were based on *observed* values, as those presented in Table 6. They were not calculated from the log-linear regression statistics presented in Figure 2, since the data points involved were considered to be statistically too few to constitute a powerful regression. Although there appears to be a high degree of correlation, the DFR for day 3 and day 4 that are presented in Figure 2 are artificial values assuming half of the detection limit. (Figure 2 was constructed and is presented here only for further reference as well as for completeness. Note that because of the relatively rapid dissipation of naled dislodgeables, more data points could result only if the foliar samples were collected more than once per day.)

XI-4. Agricultural Handlers and Other Users

For assessment of handler or user exposure, WH&S followed closely the scheme used by USEPA (1995a) in constructing the potential use scenarios. Based on the currently-registered labels, a total of 12 major exposure scenarios were identified for naled handlers or users. These use scenarios included: (1) mixing/loading naled liquid for aerial application, for groundboom application, for backpack spray, or for airblast spray; (2) applying the naled liquid mixture with aerial equipment; (3) applying with groundboom equipment; (4) applying with backpack equipment; (5) applying with airblast equipment (including using over-the-vine booms); (6) applying with thermal fog generators; (7) applying with ultra low volume cold fog generators; (8) applying by painting on heating or steam pipes in greenhouses; (9) applying by evaporating liquid with a hot plate or pan; (10) flagging during aerial sprays; (11) mixing/loading/applying with low pressure hand wands; (12) mixing/loading/applying with backpack sprayers; and (13) applying dog/cat collars.

Tables 8 and 9 below *summarize* the expected daily exposures to and the absorbed daily dosages of naled for the above agricultural handlers and non-production agricultural users, respectively. (In this exposure assessment document, the term production agricultural uses is synonymous with uses on agricultural crops.) Except where otherwise noted, such as for homeowners or non-production agricultural users, it was assumed that naled handlers would wear coveralls over long pants and a long-sleeved shirt, shoes plus socks, chemical-resistant gloves, goggles, head gear, and an approved respirator (as all of these were required by label). In California, a closed system is required for mixing/loading more than 1 gallon of liquid product per application that has Category I toxicity.

A full-face respirator is also specifically required for applicators painting naled on *hot* pipes or plates in greenhouses. Further assumptions used in the exposure calculation are footnoted in these two tables. Other than for mosquito control, no chemical-specific measurements of handler exposure to naled were available to WH&S. Accordingly, the exposures to naled calculated in the subsections below were necessarily based on surrogate data. For the most part, the surrogate data used were extracted from PHED (Pesticide Handlers Exposure Database, 1995).

Table 8. Expected Daily Exposures and Dosages for Production Agricultural Uses of Naled^a

Work Group/Task	Application Rate (lb AI/acre) ^b	Acres Treated ^c	Dermal Exposure ^d	Inhalation Exposure ^e	Total Exposure ^f	Absorbed Dosage ^g	Seasonal Dosage ^h	Annualized Dosage ⁱ
Mixer/Loaders - Aerial Spray	1.875	600	23.5	0.08	23.6	189.6	108.3	20.8
Mixer/Loaders - Groundboom ^j	1.875	100	23.5	0.08	23.6	31.6	18.1	3.5
Flaggers - Aerial Application	1.875	600	18.4	0.01	18.4	147.9	84.5	16.2
Applicators - Aerial Spray	1.875	600	1.5	0.02	1.5	12.1	6.9	1.3
Applicators - Airblast	3.750	40	89.9	0.63	90.5	97.0	55.4	10.6
Applicators - Groundboom	1.875	100	9.5	0.02	9.5	12.7	7.3	1.4
Applicators - Backpack	0.047 ^k	40 ^l	96,070 ^m	26.47	96,096.5	1,290.4	737.3	141.4
Applicators - Painting Hot Pipes	0.047 ^k	—	no data	no data	—	—	—	—
Applicators - Hot Plate/Pan	0.047 ^k	—	no data	no data	—	—	—	—

^aassuming that workers wear coveralls over long pants, a long-sleeved shirt, shoes, socks, chemical-resistant gloves, goggles, and a respirator, and that for mixing/loading, they would use a closed system in lieu of wearing a half-face respirator.

^bmaximum label rate in lb AI/acre, except otherwise noted.

^cmaximum acres treated per workday (*see* discussion in this section), except otherwise noted.

^din µg/lb AI handled; (arithmetic) mean exposure rate from PHED (*see* appendices) for total body surface with the specified clothing on, after adjustment for the default 90% protection from wearing coveralls and head gear (Thongsinthusak *et al.*, 1993a) and for the default (rounded-down) 95% protection from using both a closed system and an apron during mixing/loading (Thongsinthusak and Ross, 1994).

^ein µg/lb AI handled; (arithmetic) mean exposure rate from PHED (*see* appendices), based on a respiration rate of 14 L/min (Thongsinthusak *et al.*, 1993a) and after adjustment for the 20-fold reduction from using a closed system or for the 10-fold reduction from wearing a (half-face) respirator, where applicable.

^fcumulative rate of dermal and inhalation exposures, in µg/lb AI handled.

^gabsorbed daily dosage (ADD), in µg/kg BW/day; based on an average adult male/female body weight (BW) of 70 kg and on the default dermal absorption and inhalation uptake of 50% (*see* Section IX): $ADD = [(total\ exposure\ rate) \times (application\ rate) \times (acreage\ or\ gallonage) \times (absorption\ or\ uptake) \times BW^{-1}]$.

^hbased on the use of two-thirds of the maximum acres treated or gallons used as a conservative usage average; and on the amortization factor of 0.86 for working 6 out of 7 days per week given that the time-to-effect for the subchronic effect at issue was 21 days (per e-mail from Lori Lim of the Medical Toxicology Branch dated 02/10/99) and that the annual exposure frequencies were all assumed to be 60 days (*see* footnote *i* below); seasonal dosage (µg/kg BW/day) = (2/3) x ADD x (6/7) = 57.14%(ADD).

ⁱbased on the use of two-thirds of the maximum acres treated or gallons used as a conservative usage average; and assuming an annual exposure frequency (AEF) of 60 days, which is noticeably more frequent than the default of 40 to 50 days used earlier (Dong *et al.*, 1991; Dong, 1993, 1994) because of the relatively broader use for naled (on multiple crops); annualized dosage (µg/kg BW/day) = (2/3) x ADD x (AEF/365) = (0.001826) x (ADD) x (60) = 10.96%(ADD).

^jincluding those mixing/loading naled liquid for groundboom, backpack, or airblast sprays, since in general the task of mixing and loading is not specific to the (ground) application method used.

^kin lb AI per gallon of spray dilution (*see* discussion in this section).

^lmaximum gallons of naled dilution to be sprayed per day (due to limited areas for treatment).

^mdue to lack of acceptable data, the PHED subset for this work group included only measurements that reflect total deposition (i.e., on workers without clothes); therefore, *additional* adjustment was made for applicators wearing normal work clothes (with a default protection factor of 90%).

Table 9. Expected Daily Exposures and Dosages for Non-Production Agricultural Uses of Naled^a

Work Group/Task	Application Rate (lb AI/gallon) ^b	Gallons Used ^c	Dermal Exposure ^d	Inhalation Exposure ^e	Total Exposure ^f	Absorbed Dosage ^g	Seasonal Dosage ^h	Annualized Dosage ⁱ
<u>Homeowner Users</u>								
Dog/Cat Collar ^j	—	—	—	—	—	317.5	31.8	1.74
Low Pressure Hand Wand	0.047	4	1,564.5	19.1	1,583.6	2.1	0.21	0.01
Backpack Sprayer	0.047	10	22,174.0	14.7	22,188.7	74.5	7.45	0.41
Pump Sprayer/Hydro-Gun	0.059 ^k	—	<i>no data</i>	<i>no data</i>	—	—	—	—
<u>Occupational Users</u>								
Dog/Cat Collar (Veterinarians) ^j	—	—	—	—	—	63.5	36.3	6.96
Low Pressure Hand Wand	0.047	10	973.5	19.1	992.6	3.3	1.88	0.36
Backpack Sprayer	0.047	40	3,735.8	14.7	3,750.5	50.4	28.8	5.52
Sewage System Injection ^l	0.047	40	3,735.8	14.7	3,750.5	50.4	28.8	5.52
Thermal/Cold Fog Generator	0.047	—	<i>no data</i>	<i>no data</i>	—	—	—	—
Pump Sprayer/Hydro-Gun	0.059 ^k	—	<i>no data</i>	<i>no data</i>	—	—	—	—
Mosquito Control (Aerial) ^m	—	—	—	—	—	< 60.0	34.2	< 6.58

^a assuming that homeowner users wear long pants, a long-sleeved shirt, shoes, and socks; and that occupational users wear normal work clothes *plus* coveralls and chemical-resistant gloves; both the homeowner user and occupational user groups were considered as mixer/loader/applicators (except when using the ready-to-use products or dog/cat collars).

^b maximum label rate in lb AI per gallon of spray solution, except otherwise noted.

^c maximum gallonage per workday (see discussion in this section), except otherwise noted.

^d in µg/lb AI handled; (arithmetic) mean rate from PHED (see appendices) for total body surface with the specified clothing on (after adjustment for the 10-fold reduction from wearing coveralls or gloves, where applicable).

^e in µg/lb AI handled; (arithmetic) mean rate from PHED (see appendices), based on a respiration rate of 14 L/min (Thongsinthusak *et al.*, 1993a).

^f cumulative rate of dermal and inhalation exposures, in µg/lb AI handled.

^g absorbed daily dosage (ADD), in µg/kg BW/day; based on an average adult male/female body weight (BW) of 70 kg and on the default dermal absorption and inhalation uptake of 50% (see Section IX): $ADD = [(total\ exposure\ rate) \times (application\ rate) \times (gallonage\ or\ poundage) \times (absorption\ or\ uptake) \times BW^{-1}]$.

^h where applicable (e.g., for workers but not for homeowners), based on the use of two-thirds of the maximum gallons or poundage used as a conservative usage average; and on the amortization factor of 0.86 for working 6 out of 7 days per week (as justified in footnote *h*, Table 8); seasonal dosage (µg/kg BW/day) = $(2/3) \times ADD \times (6/7)$ for workers, and = $(2/20) \times (ADD)$ for homeowner users due to difference in the annual exposure frequencies assumed in footnote *i* below).

ⁱ where applicable (e.g., for workers but not for homeowners), based on the use of two-thirds of the maximum gallons or pounds used as a conservative usage average; and assuming that workers would be handling the insecticide 60 days per year as would agricultural use applicators; and that for homeowners, the exposure frequency would be 2 days (from 2 applications) per year; annualized dosage (µg/kg BW/day) = $(2/3) \times ADD \times (60/365)$ for workers, and = $(2/365) \times (ADD)$ for homeowners [for completeness only, otherwise not likely to be of concern due to the very low exposure frequency involved].

^j based on the release rate estimated by Haskell (1995); veterinarians (*with* gloves) and homeowners (*without* gloves and hence receiving comparatively higher exposure) are expected to treat (up to) 10 and 5 animals per day, respectively (see text discussion).

^k in lb AI per 3,000 cubic feet (note that 0.059 lb AI is equivalent to 1 fl oz of the ready-to-use spray).

^l based on the dermal and inhalation rates estimated for applying with backpack sprayers (see text discussion for justification).

^m based on the Delaware study by Kutz and Strassman (1977), as discussed in the text in this section.

All PHED subsets used in this exposure assessment contained grade A and B data with handlers all (except otherwise noted) wearing long pants, gloves, and a long-sleeved shirt. For agricultural applicators and flaggers, the dermal exposure rates calculated from these PHED subsets were adjusted for the 10-fold reduction from wearing coveralls and head gear/goggles (as required by label), which together cover over 80% of the total body surface. The rates of inhalation exposure for these agricultural applicators (except pilots) and (aerial) flaggers were also adjusted for the 10-fold reduction from wearing a respirator which is part of the required additional personal protective equipment (PPE). For mixer/loaders, the dermal exposure rates were further adjusted for the (rounded-down) 20-fold reduction from using both an apron and a closed system (as required by California regulations). The rates of inhalation exposure calculated from the PHED subsets for mixer/loaders were adjusted for the 20-fold reduction from using a closed system, but not for the 10-fold reduction from using a respirator (as such is not required to be worn by mixer/loaders using a closed system).

Mixer/Loaders. Mixing/loading naled liquid as a separate task was considered to be for production agricultural uses only. Otherwise, it was treated as part of the routine performed by the same individual (i.e., by an applicator) using hand-held equipment. The dermal exposure rate for total body surface from mixing/loading liquids, based on the arithmetic mean calculated from a PHED subset, was 23.5 $\mu\text{g/lb AI}$ handled (after adjustment for using a closed system, etc., as noted earlier). The arithmetic mean inhalation exposure from PHED for mixing/loading liquid was much lower, only 0.08 $\mu\text{g/lb AI}$ (after adjustment for using a closed system). For further reference, the exposure statistics from the two PHED subsets are attached to the end of this document as Appendices 1A and 1B. The maximum acres treated per day for aerial and ground applications were assumed to be, respectively, 600 and 100. The maximum usage was assumed to be the equivalent of 100 acres for a worker mixing/loading naled liquid for (multiple) backpack or airblast type application(s), the same maximum usage as assumed for groundboom mixer/loaders. For backpack and airblast applicators, however, the maximum usage was assumed to be, respectively, 40 gallons (due to limited areas for treatment) and 40 acres per person per day.

The above usage defaults, while comparable to the maximum values adopted by USEPA (1995a) and the upper extremes observed by Valent USA (1995b), are not unrealistic. It was found that 15 of the 97 aerial applicators (replicates) in PHED treated more than 600 acres per monitoring duration (presumably per application or per workday); the highest (total daily) usage observed in this group of applicators in PHED was 1,061 acres. Of the 200 groundboom applicators (replicates) included in PHED, 8 individuals treated more than 100 acres per monitoring duration; the highest usage observed in this group in PHED was 348 acres. Among the 123 airblast applicators (or replicates) in PHED, 8 individuals treated more than 20 acres per monitoring duration; the highest usage observed in this group in PHED was 37 acres.

In addition, the PUR (pesticide use report) data showed that in Kings County during the single month of June, 1995, naled was sprayed to an average of 448 acres of cotton per aerial application. In Fresno in May, 1995 alone, naled was sprayed to an average of 476 acres of safflower per aerial application. And in Kings County again, naled was reportedly sprayed to an average of 111 acres of cotton per ground application during July, 1995 alone. The data also showed that for oranges that are usually sprayed using airblast equipment, an average of 44 acres in Kern County was treated per application during the month of May, 1996. Although these pesticide use data reflect greatly the

maximum acres treated per application, the daily maximum acreage treated also depends on the number of applicators involved per application and the number of applications that can be made in a workday (of 6 or 7 actual application hours). With groundboom application equipment, an operator typically can treat no more than 10 to 15 acres of crop per hour. An aircraft pilot (i.e., an aerial applicator), on the other hand, can typically treat up to 100 acres of crop per hour.

The maximum label rates for aerial or ground application and for airblast spray are 1.875 and 3.75 lb AI per acre, respectively. That for backpack or other hand held spray is 4.69×10^{-2} lb AI per gallon of water or spray dilution. The expected daily exposures (and hence the absorbed daily dosages as well) calculated from these assumed usages and rates are summarized in Table 8.

Flaggers. The dermal exposure rate for total body surface of a flagger during aerial sprays was calculated to be 18.4 $\mu\text{g/lb AI}$ handled (after adjustment for the required additional PPE protection). This exposure rate again was an arithmetic mean calculated from a subset extracted from PHED, which is attached as Appendix 2A. The arithmetic mean rate of inhalation exposure calculated from the same sample group, which is attached as Appendix 2B, was 0.01 $\mu\text{g/lb AI}$ (after adjustment for additional PPE protection). The maximum acres treated per day were also assumed to be 600 for aerial sprays.

Applicators. As expected, the daily exposure of applicators to naled varies greatly depending upon the application method or equipment used. For production agricultural uses, the rates of dermal and inhalation exposures of naled applicators were based on the arithmetic means calculated from PHED for use with various application methods or equipment. The daily exposures and absorbed dosages calculated for these applicators are summarized in Table 8 above. Also included in Table 8 are rates of dermal and inhalation exposures that were obtained from various subsets extracted from PHED. These subsets are appended to this assessment document for further reference (as Appendices 3A through 6A for dermal exposure, and 3B through 6B for inhalation exposure).

As shown in Table 8, the highest average dermal and inhalation exposures are, respectively, 96.1 and 0.03 mg per pound of naled AI applied with a backpack sprayer (after adjustment for required work clothing and PPE). These findings are not surprising, in that backpack operators tend to walk towards where they are directing their spray and walk past foliage that has been treated (Matthews, 1992). USEPA also included this task group in their calculation of occupational exposure to naled (1995a). However, according to Valent USA (1995b), backpack type equipment is seldom used during treatment of agricultural crops. And if used, normally it would be used by a grower who would mix, load, and apply the pesticide himself (or herself). Treatments of cotton, row crops, or field crops are made primarily with aerial or groundboom equipment. Grapes and fruit or nut trees, on the other hand, are typically treated via airblast.

No PHED or other types of data are available for use to estimate the exposure of applicators painting naled on hot plates/pans or on heat/steam pipes in greenhouses. There are data from PHED on application with a paint brush that which even though were all of grade C quality, were used by USEPA (1995a) as surrogate for painting naled on heat/steam pipes. According to the label for Valent Dibrom 8 Emulsive, applicators are required to wear goggles and approved respirator when painting naled on *hot* pipes. Workers in the PHED paint brush surrogate studies did not apply volatile pesticides on heated surfaces. The surrogate data used by USEPA thus would *underestimate*

the dermal exposure considerably, and the inhalation exposure somewhat (even if a very effective full-face respirator were used). It was for this argument that WH&S did not follow suit.

Non-Production Agricultural Use Operators. For this group of users, the daily exposures and absorbed dosages that could be estimated from available rates are summarized in Table 9 above. As expected, there are no exposure data available for many of these operators. The exposure rates that are available and were used in the exposure calculations are discussed below. In most cases, non-production agricultural use operators were further subdivided into homeowners and commercial applicators. In accordance with USEPA (1995a), homeowner users in this exposure assessment were assumed to wear long pants and a *long*-sleeved shirt (plus shoes and socks) *without* gloves *nor* coveralls while handling or applying the insecticide. (WH&S concurred that homeowner users would wear a long-sleeved shirt in that naled is not as common a pesticide product as, e.g., diazinon.) As footnoted in Table 9, commercial operators and homeowner users were assumed to handle the insecticide 60 days and 2 days per year, respectively. The exposure duration of homeowner users was also expected to be less, compared to that of commercial operators who were supposed to be clothed additionally with coveralls and gloves (as per label requirements).

Flea/Tick Collars. Naled is available in the form of an impregnated collar for use by homeowners and veterinarians to control ticks and fleas present on dogs or cats. This pet collar typically weighs less than 1 oz and contains between 7% and 15% naled AI (by weight). Exposure to naled from placing the collar around the neck of the animal is expected to be minimal due in part to the small dose of AI (< 4 gm) being handled. There are also data showing that a maximum release rate of an AI *over a 90-day period* is likely not to exceed 20% of the chemical initially present in a collar (Haskell, 1995). If the pet handler experienced the maximum released dose of naled available while placing the collar on the animal with *bare* hands, and treated 10 pets per day, then the absorbed daily dosage (ADD) that he or she would receive, prior to adjustment for glove protection, would be 634.9 µg/kg BW/day [= (4 gm/animal) x (20% as amount released) x (10 animals/day) x (90 days)⁻¹ x (50% dermal absorption) x (70 kg BW)⁻¹] for a veterinarian with an average body weight (BW) of 70 kg. For homeowners (without gloves), the ADD would be 2 times *less*, or 317.5µg/kg BW/day, since even those who love pets very much are not expected to treat more than 5 animals per day.

Mosquito Control Crew. The Delaware study by Kutz and Strassman (1977), which was discussed earlier regarding the exposure for non-user residents, also monitored the urinary levels of DMP for workers of the mosquito control crew and the aircraft pilot. The results of the urine analysis indicated that the arithmetic mean of the DMP level from this work group was approximately 3 times the mean level seen in the 56 residents who stayed outdoors at the time of application. The maximum ADD for these workers hence is expected to be less than 60 µg/kg BW, or not to exceed 3 times that estimated for the residents.

Thermal Fog Generator. When used with a thermal fog generator, pesticides like the Dibrom concentrate usually will be dissolved in a petroleum solvent and injected into a hot gas to be vaporized. A dense fog is hence formed by condensation of the petroleum when the pesticide vapor is discharged into the atmosphere. Fogging is particularly useful for the control of flying insects not only through their contact with the droplets, but also by the fumigant effect of the volatile pesticide involved. Adequate engineering controls and PPE must be provided to avoid inhalation of the fog, since the smallest droplets are not trapped in the nasal area but may be carried into the lungs.

There were no PHED or other data available to WH&S for estimation of the exposure to naled from application with thermal fog generators, mist blowers, or ultra low volume cold fog generators in *wide* areas. A review of the literature indicated that there was one related study available by Giles *et al.* (1995), in which fogger application of pesticide in *greenhouses* was investigated. In that greenhouse study, the air concentration of permethrin was monitored for 16 hours immediately following the spray by a *fully*-clothed (from head and face down) applicator using a thermal fogger. Dermal exposure was not monitored.

Low-Pressure Hand Wand. Users who mix/load and apply naled at non-agricultural (production) sites with low pressure hand wands are typically commercial applicators. The two PHED subsets in Appendices 7A and 7B show that the dermal and inhalation exposures for these workers are 973.5 (after adjustment for wearing coveralls and gloves, which homeowners were not expected to wear) and 19.1 µg/lb AI handled, respectively. In accordance with USEPA's scenario scheme (1995a), in this exposure assessment individuals are not expected to spray naled with a high-pressure hand wand since other specific application methods, such as via thermal fog generator, pump sprayer/hydro-gun, and hot plate/pan, are suggested as an alternative.

Pump Sprayer/Hydro-Gun. According to the label, Dibrom Fly & Mosquito Spray is to be applied (as a RTU product) with microsol foggers, flit guns, heat generating foggers, dairy barn foggers, hydro-guns, or some suitable automatic atomizing equipment. No PHED or other data were available for estimation of the exposure to naled from spraying with these types of application equipment.

Backpack/Sewage System Injection. Exposure from applying with backpack sprayers was derived from PHED and used as a surrogate for exposure received from treatment of sewage system via injection. These surrogate data are summarized in Appendices 8A and 8B (after adjustment for wearing coveralls and gloves, which homeowners were expected not to wear). There were no data on exposure for applicators treating sewage systems with injection type equipment. Exposure for backpack (mixer/loader) applicators was used as a surrogate here partly because such would over, rather than under, predict the doses received from treatment of sewage system via injection, and partly due to the fact that sewage injection equipment can also be considered loosely as the hand-held or backpack type. The exposure for sewage injection applicators is likely to be overestimated with this backpack surrogate because as mentioned earlier, backpack operators tend to walk towards where they are directing their spray and walk past foliage that has been treated (Matthews, 1992). Another justification, though not as direct, for the lower exposure expected from sewer injection treatment was given earlier by WH&S (Donahue, 1993) when it commented on the use of metam-sodium for treating sewer systems. As pointed out by Valent USA (1995b), the uses/sites where backpack spraying is important for naled include: (1) ornamental shade trees and shrubs (not for use by homeowners); and (2) fruit fly control in and around food processing plants, cull piles, refuse areas, and cider mills. It is important to note that here the exposure rate from backpack spraying is supposed to be lower for non-production agricultural uses than for production agricultural uses. This expectation was based on the assumption that for non-production agricultural uses, the operator is not expected to work within a confined area as much, or to walk past *dense* foliage that has been treated.

XI-5. Exposure Appraisal

In using the absorbed dosages calculated in this exposure assessment, it is important to note that there were uncertainties built into the process that might not be immediately apparent to the risk

assessor or the risk manager. Many of these uncertainties tend to overestimate the exposures involved, but are typically hidden and therefore seldom acknowledged. Below is a brief account of the uncertainties associated with the factors used here that tend to have a critical impact on the exposures calculated.

Data on Inhalation/Dermal Exposures. As presented earlier (*see* Section XI-1), only the *highest* air level of naled measured over a 24-hour period in the 1991 Tulare study was used to calculate the daily inhalation exposure to naled from ambient air. The calculated daily inhalation exposure from ambient air would be much lower if the (outdoor) ambient air levels used were averaged over the 16 daily samples (from each monitoring station), and not based on the highest observed over the 16 sampling days. It is of note that the value of the collocated duplicate of the highest observed (0.08 $\mu\text{g}/\text{m}^3$) for naled (for that same day at the same monitoring station) was only 0.04 $\mu\text{g}/\text{m}^3$. Airborne naled and DDVP residues were found to be below the LOQ (limit of quantitation) in over 70% of the 16 daily samples (collected from May 9 through June 6, 1991). Yet despite its overrepresentation (especially in reference to subchronic or chronic exposures), the use of the highest ambient air level was not considered to be totally inappropriate in that the 1991 usage of naled in Tulare was only the second highest by county (*see* Section XI-1). Nor was the 1991 naled usage in all counties the highest by year, as evident from the usage data presented in Table 2.

The dermal exposure rates derived from surrogate studies included in PHED were based on passive patch dosimetry data. Less accurate estimates could result from extrapolating the patch residues observed in limited areas to a much greater body surface area, since this approach would magnify any errors inherent or introduced in the measurement. These passive patch data in theory would hence likely over- or under-estimate the actual dermal dose substantially when compared to whole body dosimetry data. However, in practice patch data tend to overestimate, rather than underestimate, the actual dermal dose (e.g., Maddy *et al.*, 1989). One likely explanation for this overestimation tendency is that the areas under the arms and between the legs are shielded by the appendage and hence would have lower exposure than the unshielded areas that were monitored with a patch.

The exposure rates presented in Tables 8 and 9 were, for the most part, based on arithmetic means calculated by PHED or directly from observed values. Upper-end values were not used for the exposure rates in question partly because the values assumed for the application rate and for the daily usage were already at their (practical) maximum. Because of the great variability inherent in the PHED data, the upper-end values would be unrealistically high to use if they were to be derived from the confidence limits provided on the arithmetic mean. Similarly, the biomonitoring data in the Delaware study (Kutz and Strassman, 1977) would not allow the calculation of a distribution that can be used to estimate the upper percentiles.

The PHED subsets appended to this document clearly showed that the 95% confidence limits (C.I.) on the arithmetic mean for dermal exposure included negative values. Therefore, to use the upper 95% C.I. from such a statistical interval is meaningless. To have a negative value for the mean exposure rate (even though physically impossible), the sample set must contain two clusters of exposure rates representing two extremes that are very far apart, with the lower extreme group dominating. Arithmetic means calculated from lognormal distributions are often seen to be at the 75th percentile or thereabouts. For the type of lognormal distribution that has the lower extreme group so dominating as described above, the arithmetic mean would be at a higher percentile, like

around the 85th or above. On the other hand, the mean plus the upper 90% or 95% C.I. from this type of distribution would yield an upper extreme that is materially unreal.

Although PHED could not provide realistic upper-end values for the exposure rates, it is important to note that these rates were expressed as per lb AI handled. If the total amount of AI handled per day is at its upper extreme, as in the case here where reasonable maximum usage defaults were used (see Section XI-4 for daily acreages and application rates), then the actual daily exposure is likely to be overestimated even if an average exposure *rate* is used. Also, despite the fact that measured exposures could vary over 100- or 1,000-fold, by the time the average or midpoint is used, the difference between the highest and the midpoint is merely two-fold.

Dermal vs. Oral Plasma Levels. Dosage is expressed as a single *static* value both in worker exposure and animal toxicology studies. The rate of dermal absorption is often seen or expected to be lower than the rate of oral absorption in animals used for toxicology testing. It is very likely the case that adverse effects occur only when plasma levels in the target organ exceed a critical level (see Ross *et al.*, in press); yet dermal acquisition takes place over the entire workday. Since dermal acquisition is slower and less than that by the oral route, plasma levels for the same total absorbed dosage thus will not be nearly as high from a dermal versus oral exposure. In other words, a dermal dose acquired over the entire workday produces peak plasma levels much lower than those from the bolus oral feeding dosage acquired by animals in minutes to less than an hour. Because the adverse effect used for risk assessment is dependent on the concentration at the site(s) of action (which generally correlates with plasma level), treating an 8-hour dermal acquisition as though it were a bolus (i.e., summing the entire dermal dose) is so conservative that it outweighs any perceived source of dose underestimation.

The above argument applies to naled as well, even though its adverse effects might in fact be considered (totally) irreversible by some (e.g., regulatory) standards. First, there is some indication that reactivation of inhibited dimethyl phosphate cholinesterase would occur spontaneously, at approximately 1% per hour (Fan, 1998). Second, it is important to note that whether originated from dermal or oral exposure, plasma level reflects how much a chemical under study is available (or circulating) in the body system and is a function of dose. To simplify the points made, the argument may be summarized in quantitative terms as follows:

$$[\Sigma^8 \{1 \text{ unit (dermal)}\}] \leq [8 \text{ units (dermal)}] < [8 \text{ units (oral)}].$$

Where an *irreversible* effect is involved, the 8-hour incremental effect from the first term or exposure scenario is likely to be close to, and not less than, the bolus effect from the second term. However, the *reversible* effect from the first term certainly would be less than that from the second term, given the reasons stated above regarding the slower absorption and acquisition of dermal dose. On the other hand, the third term (the oral exposure scenario) typically would yield a much higher peak plasma level or a much greater effect, whether irreversible or not, than would either of the first two dermal exposure scenarios.

The study by Auton *et al.* (1993) showed that the peak plasma level from oral dosing of fluazifop-butyl, after normalization for the amount absorbed, could be as high as 8 times the peak level from dermal dosing. It was found that the lower the absorbed dose, the more pronounced the difference

became. This difference is particularly pertinent when comparing the doses used in a toxicology study versus those to which a human would be exposed. Lower urinary metabolite concentrations (i.e., an indication of lower peak plasma concentration) have been seen with dermally applied pesticides when compared with the urinary metabolite concentrations observed following oral dosing (Krieger *et al.*, 1991). The study by Carmichael *et al.* (1989) on triclopyr and that by Nolan *et al.* (1984) on chlorpyrifos are two additional cases among several others supporting the findings by Auton *et al.*

In the study by Nolan *et al.*, for example, peak blood concentrations of the 3,5,6-TCP metabolite were 0.93 and 0.063 µg/ml following, respectively, a 0.5 mg/kg oral and later a 5.0 mg/kg dermal administration of chlorpyrifos in the same group of human volunteers. Oral absorption (especially in humans) is not available for most pesticides (including fluazifop-butyl, chlorpyrifos, and triclopyr). In this example, even if the oral to dermal absorption of chlorpyrifos had a 100:1 margin in humans, the normalized observed peak blood level of 3,5,6-TCP from the oral absorbed dose would still be 50% higher than the normalized observed peak level from the dermal absorbed dose. If the margin for oral to dermal absorption of chlorpyrifos were lowered to 50:1, then the normalized observed peak blood level of 3,5,6-TCP from the oral absorbed dose would be three times the normalized peak level from the dermal absorbed dose. If the margin were lowered further to 25:1, then the difference in the normalized peak blood level would be increased (from three-) to six-fold. Using the margin of 25:1 for oral to dermal absorption, the above study by Carmichael *et al.* showed that the normalized human peak plasma level of triclopyr from oral dosing was 5 times the normalized level from dermal dosing. There is good indication (Haskell *et al.*, 1998; Thongsinthusak 1996) that the ratio of oral to dermal absorption is well below 25:1 for both compounds. Further discussion and illustration on these numerical comparisons can be found in the work by Ross *et al.* (in press).

Partial vs. Full Workday Exposure Monitoring. Ross *et al.* (in press) also suggested that another source of dose overestimation could come from monitoring worker exposure for less than a full day's work. There is evidence (Spencer *et al.* 1995) showing that if an estimate of full day exposure (12 bins picked) were extrapolated from 1/3 day (4 bins picked), the exposure would be overestimated by more than 50 to 80% and if from 1/2 day (6 bins picked), 20 to 40%. Shorter monitoring periods are often encouraged for economic reasons in that they allow an investigator to obtain two or more observations per handler per day of monitoring. There is evidence that hand residues remain virtually constant after exposure for the first couple of hours, indicating that they reach the saturation point rather quickly. Thus, summing hand washes taken throughout the work (or exposure) day may grossly overestimate actual dose. This same principle is operative for studies involving exposure to pesticide handlers. The overestimation from partial day monitoring is not limited to data from serial hand washes, but also extended to those from passive patches, including those in PHED, from which the data were used to calculate many of the absorbed daily dosages presented in Tables 8 and 9.

Dermal Absorption. The default dermal absorption value of 50% used throughout this exposure assessment was likely to have overestimated the actual dermal doses by as much as 2- to 3-fold. The mean human dermal absorption for 13 pesticides from several different chemical classes, as compiled by Thongsinthusak *et al.* (1993b), was 19%. When the pesticides in this 1993 compilation were limited to organophosphates (n = 6, not including DDVP), the mean and the highest were 10% and 16%, respectively. It is of note here that in many cases, a substantial difference would still occur even if chemical-specific data from animal studies were available and used. According to a review

on a handful compounds tested and available, the rat was found to overestimate human dermal absorption by two- to ten-fold (Wester and Maibach, 1993; Ross *et al.*, in press).

Exposure To DDVP. The concern (Fan, 1998) over the apparently higher acute and (sub)chronic toxicity and effects of DDVP (dichlorvos) is not warranted here in terms of the risk (and hence the exposure) assessment for naled, at least not based upon the data on hand. Although metabolic data showed that naled initially converts to DDVP in animals (*see* Section X), the toxicity as well as the potency of DDVP (or of any other metabolites of naled) would manifest in the animal data used to determine the adverse effects for naled. For example, if there were no (increased) tumors observed when certain doses of naled were administered in a group of rats for two years, but this were not the case when certain doses of DDVP were given, then the only logical interpretation is that DDVP as an *in vivo* metabolite of naled is not in the form that can cause tumors in rats. On the other hand, if DDVP as an *in vivo* metabolite could cause different acute and (sub)chronic effects or result in higher toxicity of the same effects caused by naled, such should manifest in the health effects data for *naled* and hence would be picked up accordingly during the hazard identification process.

One might argue that the airborne or surface DDVP *residues* that enter into the human body could behave differently compared to those available *in vivo*, as some adverse effects are indeed highly tissue- or route-specific. However, as indicated in Table 7, exposure to the airborne DDVP residues of 0.005 µg/kg/hour at day 1 (post application) was minimal (equivalent to an ADD of 0.04 to 0.05 µg/kg/day) for grape harvesters or other field workers. Table 7 also shows that the ratio of naled residues on grape foliage to those of DDVP was greater than 4:1. However, this ratio is actually greater than 19:1 in terms of *absorbed* dosage, since the default dermal absorption of 50% was used in this exposure assessment when the percutaneous absorption for DDVP was in fact 13% (*see* Fong and Formoli, 1993).

In terms of the exposure to DDVP residues in the atmosphere or on foliage that are available directly from a naled application, the absorbed dosages for the various field worker groups hence would be one-twentieth (i.e., 5%) of those presented in Table 5. On the other hand, to err on the side of overestimation, the dosages in Table 5 were calculated for naled and DDVP combined. While naled is easily degraded by sunlight, it will lose its bromide to form DDVP normally only in the presence of metals and reducing agents. Also, it takes time for this debromination process to initiate or to complete. Thus, potential exposure to airborne or foliar residues of DDVP (from conversion of naled) is expected to be very minimal for applicators and homeowner users. Commercial handlers are expected to leave the site shortly once application has been made. For homeowner users, like for commercial handlers, the daily exposures were in one form or another *already* based on the *total* amount of naled applied. When DDVP residues were added to naled to calculate the dosages for field workers, it was based on the premise that a field worker could be exposed to the naled residues before the foliar residues had time to lose their bromide molecules to form DDVP. That is, it was based on the very conservative presumption that, if the foliar samples were collected an hour or so earlier, some of the DDVP residues could still be in the parent form (i.e., naled). Another good reason for adding naled and DDVP residues together for field workers is when both compounds would or could induce the same adverse effects. It is important to note here that although DDVP is said to be 5 times potent or toxic (Fan, 1998), its dermal absorption is 4 or 5 times less than that of naled. Because at most only a fraction of the (observed) DDVP residues is expected still to be in the parent form, the addition of DDVP to naled was not adjusted for their difference in molar weight.

The daily dosages from ambient air calculated for children and adults in Section XI-1 were for inhalation exposure to naled alone. There was no evidence that the airborne DDVP residues as measured and reported were totally a breakdown product of the naled residues at issue. Otherwise, for children and adult residents exposed to *total* naled in ambient air, the daily dosages at most would be 1.3 times those calculated in Section XI-1. In this exposure assessment, such a small (uncertain or unlikely) increase was considered insignificant and hence an adjustment was not made in the final calculations in Section XI-1, especially in light of the fact that the highest air level of naled was used already. The above suggestion of using a factor of 1.3 was based on the observation that the 24-hour air level of DDVP measured on the same day at the same site (where the highest naled level of 0.082 $\mu\text{g}/\text{m}^3$ was observed) was 0.025 $\mu\text{g}/\text{m}^3$. As indicated in Table 7, a similar residue ratio was observed at the site on day 1 following a naled application to grapes. This ratio suggests that where the dosages and adverse effects of DDVP must be dealt with separately, one-third of the naled dosages calculated in Section XI-1 could be used as the daily dosages expected for exposure of children and residents to DDVP in ambient air.

As shown in Table 4, for bystanders and non-user residents directly subject to aerial sprays (and release from pet collars or the like), their *un*absorbed daily doses of naled back-calculated from the biomonitoring data were less than 40 $\mu\text{g}/\text{person}$. According to Table 7, no more than 20% of the airborne and surface naled residues would be transformed to DDVP in the atmosphere (vs. *in vivo*). That is, if the dosages and toxicity of DDVP must be dealt with separately, then one-fifth of the dosages presented in Table 4 could be used as the dosages of DDVP for bystanders and non-user residents following a naled application.

In short, if the dosages and adverse effects of DDVP from a naled application must be dealt with separately, then the absorbed dosages of DDVP for the various exposure scenarios can be estimated as follows:

For ambient air, use one-third of the dosages calculated for naled in Section XI-1.

For bystanders and non-user residents directly subject to aerial sprays, release from pet collars, and the like, use 20% of the dosages listed in Table 4.

For field workers, use 5% of those listed in Table 5.

Handlers/users are not expected to be exposed to DDVP as a breakdown product in the atmosphere following a naled application.

Other Factors. In calculating the absorbed dosage in this exposure assessment, the average body weight assumed for workers was 70 kg. The use of this default value might have overestimated slightly the naled dosages for several work groups whose exposure rates were calculated from PHED. The exposure rates calculated from PHED were based on studies in which the volunteers were primarily male workers. The average body weight for male adults is approximately 10% higher than the average of 70 kg assumed here for male/female adults (USEPA, 1997; Thongsinthusak *et al*, 1993a). Also, the total body surface area used for the PHED rate estimates was 21,760 cm^2 , which is about 15% higher than that later re-calculated by USEPA (1997) for an average male adult of 78 kg. Another conservatism made with the PHED estimates is the use of 14 L/min as the average breathing

rate for light work, when the default value is 11 L/min for average male/female adults engaged in most pesticide handling tasks. In using the higher respiration rate, it was assumed that this physiological parameter is related more to the type of activity involved than to an adult's sex or body size. Also, as noted earlier, the volunteers in the PHED studies were primarily male workers.

The use of 260 days for vegetable crop harvesters was a conservative approach, given that it is very unlikely for a worker to migrate from crop to crop or field to field, or for those crops all to be treated with naled. However, due to the lack of more specific data, such a conservative default was used, and was based on the assumption that these workers could harvest naled-treated crops 6 days a week for as many as 10 months in a year. A comparable annual exposure frequency (of 227 days) was also used by Thongsinthusak *et al.* (1996) for broccoli harvesters exposed to chlorothalonil. As indicated in Table 3, the usage of naled on broccoli remained in the top five crops between 1994 and 1996. The Department's PUR data showed that in Monterey County, naled was applied to broccoli every month between 1994 and 1996. The data also showed that in the same county, the insecticide was applied to celery nine months in 1994 and another nine months in 1995.

For flea and tick killer products, veterinarians and homeowners were assumed to be exposed to 100% of the amount (i.e., of the 20%) of naled released from the pet collar. The reality is that even if the release is triggered primarily through hand contact with the pet collar, not *all* that is dislodgeable (i.e., releasable) from the collar will become transferable onto the human hand or skin. There are, nonetheless, no empirical data available to quantify the lower transfer rate. Although transferability studies following pet application have been conducted by USEPA's Office of Research and Development, they are not currently available.

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XIII. APPENDICES

- Appendix 1A: Subset from PHED for Dermal Exposure of Agricultural Mixer/Loaders (Prior to Adjustment for Using a Closed System or Additional PPE)
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(These PHED attachments are neither photocopies nor, due to system incompatibility, from imported files; they were reproduced using an imperfect scanner and hence necessarily with some touch-up work. Nonetheless, the accuracy of their contents had been checked and assured to the extent possible.)

APPENDIX 1A
(Mixer/Loaders)

Name: NALED1A.MLOD Subset Specifications for NALED1A.MLOD

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Mixing Procedures Equal to 1 and
With Outdoor Equal to "X" and
With Dermal Grade Uncovered Equal to "A" "B"
Subset originated from MLOD.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	2.275	138.9955	475.6384	4.1048	112
NECK.FRONT	Lognormal	1.8975	25.192	347.498	1.8583	94
NECK.BACK	Lognormal	.352	17.0884	365.4479	.5605	100
UPPER ARMS	Other	.582	174.6754	859.3712	1.3153	81
CHEST	Other	3.0175	20.4569	259.5853	3.1796	80
BACK	Other	.71	11.6161	221.3109	1.6665	79
FOREARMS	Other	.484	4.7255	209.4022	.8135	75
THIGHS	Other	3.82	18.3668	191.5423	3.7869	62
LOWER LEGS	Other	.714	42.5789	781.3018	.9574	72
FEET	Lognormal	5.371	346.998	180.1404	19.5296	25
HANDS	Lognormal	4.65	39.0121	297.6143	4.325	71

TOTAL DERM: 39.7057 23.873 839.7056 42.0974

95% C.I. on Mean: Dermal: [-12917.0481, 14596.4593]

Number of Records: 128

Data File: MIXER/LOADER

Subset Name: NALED1A.MLOD

APPENDIX 1B
(Mixer/Loaders)

Name: NALED1B.MLOD Subset Specifications for NALED1B.MLOD

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
 With Mixing Procedures Equal to 1 and
 With Outdoor Equal to "X" and
 With Airborne Grade Equal to "A" "B"
 Subset originated from MLOD.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB. TYPE	Median	NANOGRAMS PER LB AI MIXED			
			Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Other	466.6667	1686.2531	283.7279	247.4691	76

95% C.I. on Geo. Mean: [3.8108, 16070.55]

Number of Records: 83

Data File: MIXER/LOADER

Subset Name: NALED1B.MLOD

APPENDIX 2A
(Aerial Flaggers)

Name: NALED2A.FLAG Subset Specifications for NALED2A.FLAG

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B"
Subset originated from FLAG.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	4.94	11.3028	127.5702	5.6188	18
NECK-FRONT	Lognormal	.5025	.9533	134.3334	.5146	18
NECK.BACK	Lognormal	.4895	1.4111	215.8529	.4931	18
UPPER ARMS	Other	.291	.388	36.3918	.3666	18
CHEST	Other	.355	.4438	35.7819	.4222	16
BACK	Other	.355	.4438	35.7819	.4222	16
FOREARMS	Other	.121	.4235	267.7214	.1803	18
THIGHS	Other	.382	.5491	71.7174	.4811	16
LOWER LEGS	Other	.238	.476	98.5084	.3586	18
FEET						0
HANDS	Lognormal	14.6516	14.6516	68.9979	12.7892	2
TOTAL DERM:		21.1577	22.3256	31.043	21.6467	

95% C.I. on Mean: Dermal: [-462.1881, 524.2741]

Number of Records: 18

Data File: FLAGGER

Subset Name: NALED2A.FLAG

APPENDIX 2B
(Aerial Flaggers)

Name: NALED2B.FLAG Subset Specifications for NALED2B.FLAG

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B"
Subset originated from FLAG.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB. TYPE	Median	NANOGRAMS PER LB AI MIXED Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Normal	129.9002	135.2485	75.5819	96.1357	18

95% C.I. on Geo. Mean: [-65.1094, 335.6064]

Number of Records: 18

Data File: FLAGGER

Subset Name: NALED2B.FLAG

APPENDIX 3A
(Aerial Applicators)

Name: NALED3A.APPL Subset Specifications for NALED3A.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B" and
With Application Method Equal to 5 or Equal to 6
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Other	.13	.4689	190.9362	.2178	28
NECK.FRONT	Other	.015	.0413	164.4068	.0239	28
NECK.BACK	Other	.011	.033	181.8182	.0169	28
UPPER ARMS	Other	.291	.3274	44.4411	.3117	16
CHEST	Other	.355	.355	0	.355	14
BACK	Other	.355	.355	0	.355	14
FOREARMS	Other	.121	.1452	35.124	.139	10
THIGHS	Other	.382	.382	0	.382	14
LOWER LEGS	Other	.238	.2975	54.6555	.273	16
FEET	Lognormal	.393	.4803	88.8195	.3311	12
HANDS	Lognormal	.7366	.7366	29.4461	.7205	2
TOTAL DERM:		2.9496	3.0276	3.6222	3.1259	

95% C.I. on Mean: Dermal: [-12.5748, 19.8192]

Number of Records: 28

Data File: APPLICATOR

Subset Name: NALED3A.APPL

APPENDIX 3B
(Aerial Applicators)

Name: NALED3B.APPL Subset Specifications for NALED3B.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Application Method Equal to 5 or Equal to 6
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.		NANOGRAMS PER LB AI MIXED			
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Lognormal	15.2466	21.0077	117.5524	8.556	15

95% C.I. on Geo. Mean: [0.3351, 218.482]

Number of Records: 15

Data File: APPLICATOR

Subset Name: NALED3B.APPL

APPENDIX 4A
(Airblast Applicators)

Name: NALED4A.APPL Subset Specifications for NALED4A.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B" and
With Application Method Equal to 1
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	18.85	388.3567	272.7476	26.9791	39
NECK.FRONT	Lognormal	1.695	15.0926	300.9117	2.7594	35
NECK.B.XCK	Lognormal	1.166	17.7159	240.8114	1.4981	39
UPPER ARMS	Other	.582	.7134	95.8649	.5366	31
CHEST	Other	.71	7.7463	344.1282	1.1881	39
BACK	Other	.71	4.8426	325.8312	.9606	39
FOREARMS	Lognormal	.242	.6635	163.2404	.3398	31
THIGHS	Other	.573	33.1385	335.4283	1.4449	24
LOWER LEGS	Other	.357	2.5089	249.165	.6312	24
FEET						0
HANDS	Lognormal	10.3364	13.3257	106.1618	6.2495	31
TOTAL DERM:		40.7579	35.2214	484.1041	42.5873	

95% C.I. on Mean: Dermal: (-10147.2995, 11115.5077]

Number of Records: 39

Data File: APPLICATOR

Subset Name: NALED4A.APPL

APPENDIX 4B
(Airblast Applicators)

Name: NALED4B.APPL Subset Specifications for NALED4B.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Application Method Equal to 1
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.		NANOGRAMS PER LB AI MIXED			
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Lognormal	2870.717	6277.758	204.742	2682.656	27

95% C.I. on Geo. Mean: [266.8431, 26969.5845]

Number of Records: 27

Data File: APPLICATOR

Subset Name: NALED4B.APPL

APPENDIX 5A
(Groundboom Applicators)

Name: NALED5A.APPL Subset Specifications for NALED5A.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B" and
With Application Method Equal to 2 or Equal to 3
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	.26	1.4602	185.1938	.4689	43
NECX.FRONT	Lognormal	.06	.2283	144.5905	.0794	36
NECK.BACK	Other	.033	.1921	208.4852	.0507	39
UPPER ARMS	Other	.291	.8366	128.2572	.5337	32
CHEST	Other	.355	1.1928	125.6455	.7049	25
BACK	Other	.355	1.2354	125.0121	.7164	25
FOREARMS	Other	.121	2.4162	475.627	.2849	32
THIGHS	Lognormal	1.146	1.4065	101.4077	.9699	22
LOWER LEGS	Lognormal	.714	1.3982	180.4892	.7148	32
FEET	Lognormal	4.323	4.1629	45.8935	3.66	9
HANDS	Lognormal	3.9648	3.9648	125.2068	1.8435	2
TOTAL DERM:		8.8915	11.6228	18.494	10.0271	

95% C.I. on Mean: Dermal: [-240.8942, 277.8822]

Number of Records: 44

Data File: APPLICATOR

Subset Name: NALED5A.APPL

APPENDIX 5B
(Groundboom Applicators)

Name: NALED5B.APPL Subset Specifications for NALED5B.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Application Method Equal to 2 or Equal to 3
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.		NANOGRAMS PER LB AI MIXED			
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Lognormal	51.7178	165.4924	157.4362	50.6591	26

95% C.I. on Geo. Mean: [1.9802, 1296.002]

Number of Records: 26

Data File: APPLICATOR

Subset Name: NALED5B.APPL

APPENDIX 6A
(Backpack Applicators)

Name: NALED6A.APPL Subset Specifications for NALED6A.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B" and
With Application Method Equal to 9
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Total Deposition

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	9626.24	58902.7595	171.62	13741.5982	60
NECK.FRONT	Lognormal	2024.25	7242.2773	157.8308	2643.6795	60
NECK.BACK	Lognormal	1484.45	5311.0033	157.8308	1938.6983	60
UPPER ARMS	Lognormal	39270.45	140500.1787	157.8308	51287.3815	60
CHEST	Lognormal	47907.25	171400.5616	157.8308	62567.0806	60
BACK	Lognormal	47907.25	171400.5616	157.8308	62567.0806	60
FOREARMS	Lognormal	16328.95	58421.0365	157.8308	21325.681	60
THIGHS	Lognormal	225044.2	619291.403	145.116	236362.9993	60
LOWER LEGS	Lognormal	140210.7	385841.240	145.116	147262.8111	60
FEET	Other	227219.5	227278.45	28.787	214339.6995	20
HANDS	Other	275924.6	394292.836	80.5735	288008.9015	60

TOTAL DERM: 1102841.2 1032948.1 2239882.308 1102045.611

95% C.I. on Mean: Dermal: [-7390270.493, 11870035.109]

Number of Records: 60

Data File: APPLICATOR

Subset Name: NALED6A.APPL

APPENDIX 6B
(Backpack Applicators)

Name: NALED6B.APPL Subset Specifications for NALED6B.APPL

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Application Method Equal to 9
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.	NANOGRAMS PER LB AI MIXED				
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Other	184410.0698	264662.9895	119.4529	128768.951	40

95% C.I. on Geo. Mean: [3193.7091, 5191907.5933]

Number of Records: 40

Data File: APPLICATOR

Subset Name: NALED6B.APPL

APPENDIX 7A

(Low-Pressure Hand Wand Mixer/Loader/Applicators)

Name: NALED7A.MLAP Subset Specifications for NALED7A.MLAP

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
 With Dermal Grade Uncovered Equal to "A" "B" and
 With Mixing Procedures Equal to 1 and
 With Application Method Equal to 7
 Subset originated from MLAP.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, no gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	24.375	124.293	137.9493	47.2773	10
NECK.FRONT	Lognormal	6.0975	453.432	311.0744	8.6612	10
NECK.BACK	Lognormal	1.144	330.0869	313.6188	4.0327	10
UPPER ARMS	Lognormal	15.132	111.8313	232.934	32.6211	10
CHEST	Other	18.46	235.1875	185.929	48.9756	10
BACK	Other	18.46	163.797	202.4421	41.5723	10
FOREARMS	Other	6.292	40.9585	267.6492	9.412	10
THIGHS	Other	19.864	37.9878	115.1859	27.6737	9
LOWER LEGS	Lognormal	12.376	66.9309	164.3135	30.0241	9
FEET						0
HANDS						0

TOTAL DERM: 185.6924 122.2005 1564.5049 250.25

95% C.I. on Mean: Dermal: [-35036.7278, 38165.7376]

Number of Records: 10

Data File: MIXER/LOADER/APPLICATOR

Subset Name: NALED7A.MLAP

APPENDIX 7B

(Low-Pressure Hand Wand Mixer/Loader/Applicators)

Name: NALED7B.MLAP Subset Specifications for NALED7B.MLAP

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Mixing Procedures Equal to 1 and
With Application Method Equal to 7
Subset originated from MLAP.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.		NANOGRAMS PER LB AI MIXED			
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
EXPOSURE	Other	14583.3333	19148.8095	75.3953	16805.3069	10

95% C.I. on Geo. Mean: [6976.1648, 40483.3237]

Number of Records: 10

Data File: MIXER/LOADER/APPLICATOR

Subset Name: NALED7B.MLAP

APPENDIX 8A
(Backpack Mixer/Loader/Applicators)

Name: NALED8A.MLAP Subset Specifications for NALED8A.MLAP

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Dermal Grade Uncovered Equal to "A" "B" and
With Mixing Procedures Equal to 1 and
With Application Method Equal to 9
Subset originated from MLAP.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, no gloves

PATCH LOCATION	DISTRIB. TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	70.46	345.2564	194.899	91.4483	11
NECK.FRONT	Lognormal	43.38	178.6391	155.1078	38.2719	11
NECK.BACK	Lognormal	617.441	1163.209	108.1731	611.9794	11
UPPER ARMS	Lognormal	104.469	10116.4827	239.4633	257.2654	11
CHEST	Normal	18.46	275.4477	170.903	65.7564	11
BACK	Lognormal	477.83	8918.1809	167.9854	1044.0635	11
FOREARMS	Lognormal	6.292	153.593	184.2219	30.0425	11
THIGHS	Lognormal	19.864	597.2782	282.8189	49.147	9
LOWER LEGS	Lognormal	32.13	425.8878	230.6324	64.6874	9
FEET						0
HANDS						0

TOTAL DERM: 2462.3531 1390.326 22173.9748 2252.6618

95% C.I. on Mean: Dermal: (-512436.8583, 556784.8079]

Number of Records: 11

Data File: MIXER/LOADER/APPLICATOR

Subset Name.: NALED8A.MLAP

APPENDIX 8B
(Backpack Mixer/Loader/Applicators)

Name: NALED8B.MLAP Subset Specifications for NALED8B.MLAP

With Liquid Type Equal to 1 or Equal to 2 or Equal to 3 or Equal to 4 or Equal to 5 and
With Airborne Grade Equal to "A" "B" and
With Mixing Procedures Equal to 1 and
With Application Method Equal to 9
Subset originated from MLAP.FILE

SUMMARY STATISTICS FOR CALCULATED INHALATION EXPOSURES

	DISTRIB.		NANOGRAMS PER LB AI MIXED				
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.	
EXPOSURE	Other	14583.3333	14699.0509	4.8415	14683.9317	11	

95% C.I. on Geo. Mean: [13408.489, 16080.697]

Number of Records: 11

Data File: MIXER/LOADER/APPLICATOR

Subset Name: NALED8B.MLAP