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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

December 22, 1982

SUBJECT: Naled Registration Standard: TOXICOLOGY CHAPTER

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Special Pesticides Review Division (TS-791)

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Please find attached the TOXICOLOGY CHAPTER of the Naled
Registration Standard.

Judy Heckaman

cc: Judy Heckaman, HED. (Memo only)
Geri Werdig, SPRD (TS-791)
IM (2)
File (2)

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NALED REGISTRATION STANDARD

003289

Caswell #586
Chemical #034401

November 30, 1982

Toxicology

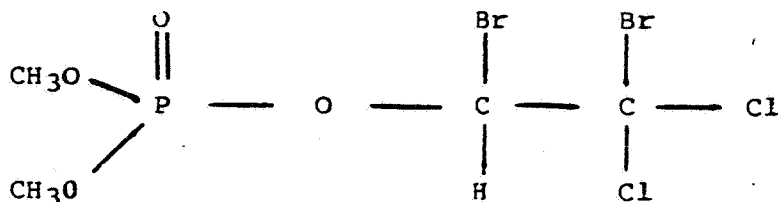
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I. Preface

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Naled (aka: bromchlophos, Dibrom*, Bromex*, Ortho RE 4355*) is a non-systemic contact and stomach insecticide and acaricide, with some short-lived, residual fumigant action. Chemically, naled is an organophosphorus compound: 1,2-dibromo-2,2-dichloroethyl dimethyl phosphate, with the following structural formula:



MW = 380.79

It shares many of the biological properties of this class of compounds, including effects on enzymatic activities, notably cholinesterase inhibition, which is the basis for its insecticidal-acaricidal efficacy, as well as contributing to mammalian toxicities.

Naled is manufactured by the addition of bromine to O,O-dimethyl-O-(2,2-dichlorovinyl) phosphate (dichlorvos, DDVP). This MUP ("technical"), normally a liquid with a pungent odor, contains 90% of the active ingredient; it is insoluble in water, slightly soluble in aliphatic, but highly soluble in aromatic, organic solvents. The results of toxicological testing incorporated into this chapter are from reports and studies with this technical chemical, unless otherwise specified. The 10% remainder of ingredients in the MUP technical comprise manufacturing impurities, stabilizers and other inerts, which are of negligible toxicological concern.

Naled technical is formulated into liquids, dusts, emulsion concentrates, and LVC's for agricultural use on numerous major crops; for fly control in livestock feedlots, small animal kennels, poultry houses, greenhouses, and food processing plants; and, for mosquito control in municipal and other large areas. It is also incorporated into flea and tick pet collars, as well as into other solid carriers (fly strips) and liquid formulations (sprays, cleaners, etc.) for household and commensal use.

*Trade Names

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II. Disciplinary Summary

A. Toxicological Profile

Following is a tabulation of animal toxicological testing, drawn from experimental studies and reports which the Agency considers valid by Toxicology Branch Core Standards. Detailed discussions of these studies are found below under the appropriate "Topical Discussion" of Subsection III B. Experimental studies performed for registrants by Industrial Bio-Test (IBT) have been declared invalid. A summary of these studies is included in the following Subsection (II B-"Data Gaps"), extending the list of data requirements which must be submitted to support the continued registration of pesticide products containing naled technical.

TOXICOLOGICAL TESTING WITH NALED

<u>Study Type</u>	<u>Route</u>	<u>Species</u>	<u>Result</u>	<u>Investigator</u>
Acute	Oral	Sherman Rat	LD ₅₀ = 250 mg/kg	Gaines (1969)
		"Albino" Rat	LD ₅₀ = 389 mg/kg	Chevron (?)
		Wistar Rat	LD ₅₀ = 281 mg/kg	Brzezicke-Bak & Bojanowski (1969)
		S-D Rat	LD ₅₀ = 222 (209-235) mg/kg	Berteau et al. (1976)
		NAMRU Mouse	LD ₅₀ = 160 (131-195) mg/kg	Berteau et al. (1976)
	(7% Pellets in feed)	Cat	LD ₅₀ > 2150 mg/kg (HDT)	Robins (1978)
	(15.5% Pellets in feed)	Dog	LD ₅₀ > 1,000 mg/kg (HDT, due to emesis)	Robins (1978)

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<u>Study Type</u>	<u>Route</u>	<u>Species</u>	<u>Result</u>	<u>Investigator</u>
	(Potenti- ation with OP's)	CD Rat	<u>POS</u> with Ciodrin, malathion and methyl-malathion (of 21 combina- tions tested)	Witherup and Schlecht (1963)
		Long-Evans Rat	<u>NEG</u> with DDVP	Narcisse (1967)
		Elias (albino) Rat	<u>NEG</u> with Abate	McNerney and Levinskas (1967)
	Intraperit- oneal	S-D Rat	LD ₅₀ = 35 (31.8- 38.5) mg/kg	Berteau et al. (1976)
	Dermal	N.Z. White Rabbit	LD ₅₀ = 390 mg/kg	Narcisse and Cavalli (1971)
		Sherman Rat	LD ₅₀ = 800 mg/kg	Gaines (1976)
		Rabbit	LD ₅₀ = 1,100 mg/kg	Elsea (1958)
Primary	Eye irritation	N.Z. White Rabbit	Corneal opacities 7 days +	Bullock & Narcisse (1974)
	Dermal irritation	N.Z. White Rabbit	PIS = 5.8	Bullock & Narcisse (1975)
		N.Z. White Rabbit	PIS = 5.92	Phillips et al. (1972)
		Human Volunteers	"Severe irritation"	Phillips et al. (1972)
Subchronic	Dermal irritation (7% collar)	Cat	Minor flaking only; transient plasma ChE depression.	IRDC (1977)
	Dermal irritation (15% collar)	Dog	Dry, flaky skin only; plasma ChE depression.	IRDC (1977)

<u>Study Type</u>	<u>Route</u>	<u>Species</u>	<u>Result</u>	<u>Investigator</u>
	Dermal irritation (7% cat collar; 16% dog collar)	Rabbit	PIS = 0.42 (7%) PIS = 0.67 (16%) (i.e., no irritation)	Robins (1978)
Delayed	Dermal sensitization (3% acetone solution)	Guinea Pig	"Weak sensitizer"	Rittenhouse (1978)
Acute	Inhalation	S-D Rat	LD50 = 3.1 mg/kg at MMD = 2.1 μ m	Berteau et al (1976)
		NAMRU mouse	LD50 = 12.4 mg/kg at MMD = 13-20 μ m	
Delayed	Neurotoxicity (acute intubation)	White Leghorn Hens	NEG for demyelination at LD60 (117 mg/kg)	Schwartz et al. (1978)
		White Leghorn Hens	NEG to 118.5 mg/kg (5/5 hens died)	Ives et al. (1962)
	(20 day feeding)	White Leghorn Hens	NEG at 5 ppm	Ives et al. (1962)
Subchronic	Feed (90 days)	CR Rat	ChE NOEL = 30 ppm. Syst. NOEL >300 ppm (HDT)	Weir & Hurst (1958)
	Gavage (63 days)	Wistar Rat	At 30 mg/kg (ODT), 4/10 died; brain-ChE = 25.6% of control.	Brzezicke-Bak & Bojanowska (1969)
	Gavage	Rat	ChE NOEL = 1 mg/kg/day. Syst. NOEL < 10 mg/kg/day	Lough et al. (1981)
	Gavage (Capsule, 90 days)	"Mongrel" Dog	ChE NOEL = 0.25 mg/kg day. Syst. NOEL >7.5 mg/kg (HDT)	Weir (1958)
Teratology	Intra-ovo injection	White Leghorn Hen Eggs	NEG at 1 mg/kg (HDT)	Proctor et al. (1976)

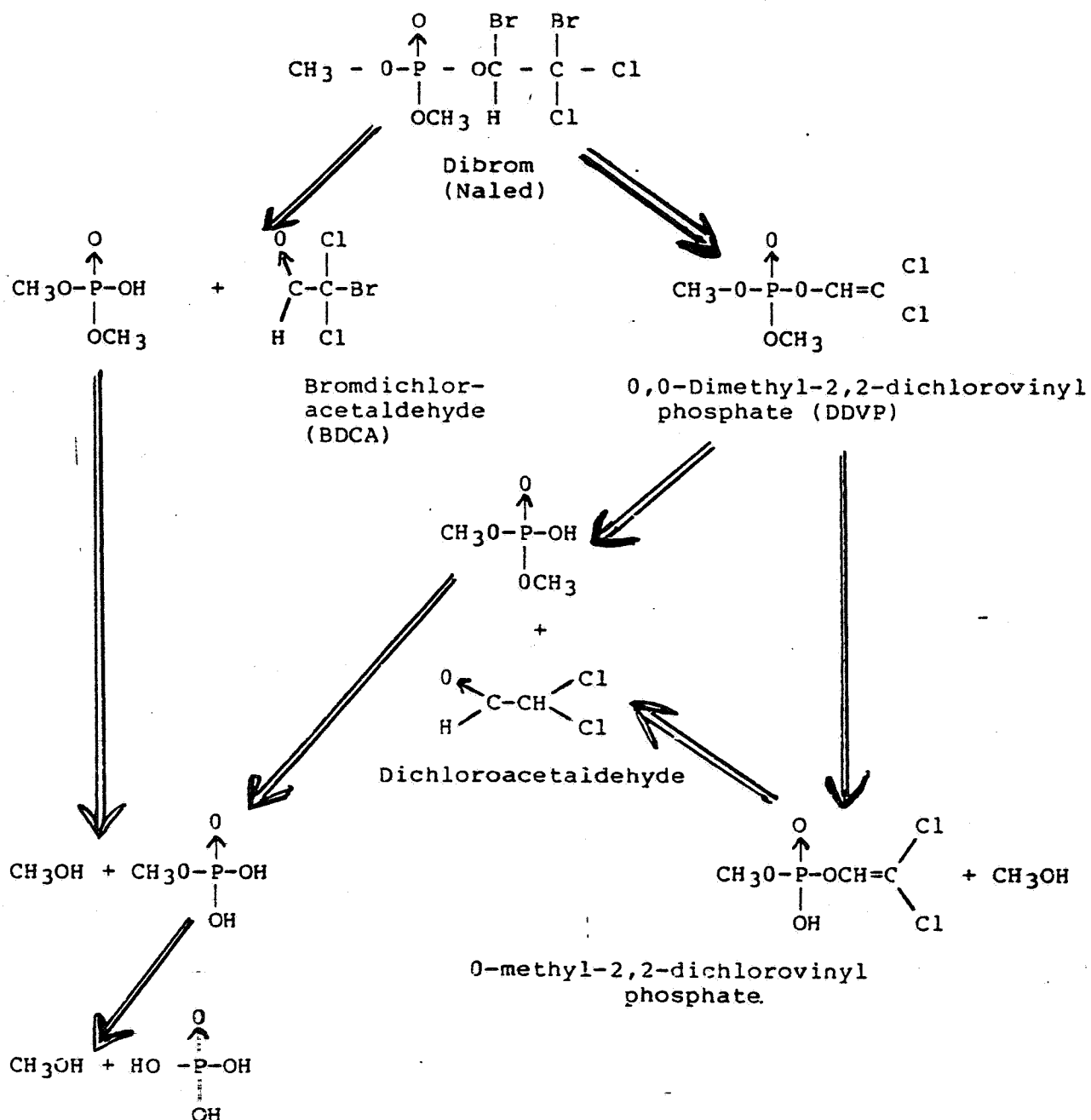
<u>Study Type</u>	<u>Route</u>	<u>Species</u>	<u>Result</u>	<u>Investigator</u>
Teratology	Intubation ("Fly Killer-D," 36% tech.)	Wistar Rat	NOEL > 100 mg/kg (HDT)	Khera et al. (1979)
Mutagenicity	Bacterial mutation	<u>S. typhi.</u> , <u>B. sub.</u> strains	<u>POS</u> only in one <u>B. sub.</u> strain w/out activation	Shiau et al. (1981)
		<u>S. typhi.</u>	<u>POS</u> only in TA 1535 w/out activation (of 21 strains tested)	Hanna & Dyer (1975)
		<u>S. typhi.</u>	<u>NEG</u> in TA 100.	Byeon et al. (1976)
	Chromosome aberration	"White" Mouse	<u>NEG</u> at 10 mg/kg (ODT)	Kurinnyi (1975)

POS = Positive result
 NEG = Negative result
 NOEL = No observable effect level
 HDT = Highest dose tested
 ODT = Only dose tested
 CHE = Cholinesterase (inhibition)
 Syst. = Systemic (NOEL)

B. Metabolism

A suggested scheme for the metabolism of naled in mammals is found on the following page. The studies contributing to this metabolic flow-chart are discussed in Section III C ("Metabolism").

METABOLISM OF NALED



Adapted from : Menzie (1969)

C. Data Gaps

Following is a listing of toxicological testing not represented in the profile tabulation above (Subsection II A), but which would be required for the continued registration of pesticidal products containing named technical:

- Acute inhalation in the rat (NOEL).
- Subchronic inhalation in the rat (NOEL).
- Two-year oral in the rat (*).
- One-year oral in the dog (*).
- Two-generation reproduction in the rat.
- Teratology in the rat.
- Teratology in the rabbit.
- Metabolism in the rat.
- Mutagenicity: Gene mutation in mammalian cells
- Mutagenicity: Chromosome aberrations in mammalian systems.
- Mutagenicity: DNA damage/repair in mammalian systems.

Many of these data gaps have been generated by studies performed at Industrial Bio-Test (IBT), and which have been declared invalid by the Agency. Some of these have previously been submitted to the Agency in support of registrations, e.g., as reported in summary by one registrant (Chevron, 1966).

The status on their replacement or alternates, as of August, 1982, is tabulated on the following pages.

III. Topical Discussions

A. Background

Discussions on validated and/or useful studies contributing to the toxicological profile tabulated above (Subsection II A) follow below (Subsection III B). As well, case reports on human toxicities and epidemiological surveys of persons exposed to naled (as well as other pesticides in combination with naled) are reviewed (Subsection III D). Tolerances on food and/or raw agricultural commodities, and other issues pertinent to toxicological considerations (exposures, usage pattern, residues, etc.) are also outlined below (Subsection III E). Finally, inferences about the metabolic disposition of absorbed active ingredient (from dermal, inhalation or ingested exposures) are considered in a cursory review (Subsection III C).

(*) Assessment of carcinogenicity may be included.

VALIDATION SUMMARY

(RATING: I-II)

<u>IBT STUDY NO.</u>	<u>STUDY TYPE</u>	<u>SPECIES</u>	<u>AUDIT RESULTS</u>	<u>REPLACEMENTS/ALTERNATES</u>
B 2948	2-Year oral	Rat	Invalid	Replacement expected.
C 1446	2-Year oral	Dog	Invalid (no raw data)	Replacement (12-month study) expected.
B 2804	3-Generation reproduction	Rat	Invalid	Replacement expected.
8580-08991	Teratology	Rabbit	Invalid	Replacement (rat study) expected.
B 1445	13-Month oral	Rat	Invalid (no raw data)	Replacement (2-year study) expected.
H 3705	90-Day oral	Rat	Invalid	Replacement (2-year study) expected.
C 1240	90-Day oral	Dog	Invalid (no raw data)	Replacement (1-year study) expected.
C 1012	90-Day oral	Dog	Invalid	Replacement (1-year study) expected.
C 1010	12-Week oral	Rat	Invalid (no raw data)	Replacement (2-year study) expected.

VALIDATION SUMMARY (Continued)

<u>IBT STUDY NO.</u>	<u>STUDY TYPE</u>	<u>SPECIES</u>	<u>AUDIT RESULTS</u>	<u>REPLACEMENTS/ALTERNATES</u>
D 2797	Metabolism	Rat	Invalid (no raw data)	Replacement expected.
E 1022 (M 2325)	Mutagenicity (dominant lethal-male)	Mouse	Invalid	Replacement expected.
1332	Residue	Chicken	Invalid (no raw data)	Replacement expected.
A 3738	Antidote	Rat	Invalid	Replacement expected.
C 1012	90-Day oral cholinesterase	Dog	Invalid (no raw data)	Replacement (1-year study) expected.
D 2203	12-Week oral cholinesterase	Rat	Invalid (no raw data)	Replacement (2-year study) expected.
B 1568	28-Day oral	Rat	Invalid (no raw data)	<u>Replacement submitted.*</u>
-	Delayed neuro- toxicity (21- day)	Chicken	Invalid (no raw data)	<u>Replacement submitted.*</u>
-	Delayed neuro- toxicity (76- day)	Chicken	Invalid (no raw data)	<u>Replacement submitted.*</u>

*See Toxicological Profile (Subsection II A, above)

<u>IBT STUDY NO.</u>	<u>STUDY TYPE</u>	<u>SPECIES</u>	<u>AUDIT RESULTS</u>	<u>REPLACEMENTS/ALTERNATES</u>
D 2203	21-Day oral	Cow	Invalid	<u>Alternate available.*</u>
965	Primary dermal irritation and sensitization	Human	Invalid (no raw data)	<u>Alternate available.*</u>
A 3284	Oral LD ₅₀	Dog Guinea pig	Invalid	<u>Alternate available.*</u>
A 4132	4-Day LC ₅₀	Rainbow trout	Invalid	<u>Alternate available.*</u>
C 1012	Demyelination	Dog	Invalid (no raw data)	Replacement not required.
1010	Demyelination	Rat	Invalid (no raw data)	Replacement not required.
C 1511	Metabolism	Dog	Invalid	No alternate or replacement available.
A 4629	Acute potentiation	Rat	Invalid	No alternate or replacement available.
A 3878	Acute potentiation w/ethyl alcohol	Rat	Invalid	No alternate or replacement available.
965	21-Day dermal	Rabbit	Invalid (no raw data)	<u>Alternate or replacement available.*</u>
965	35-Day (aerosol) inhalation	Guinea pig	Invalid (no raw data)	<u>Alternate or replacement available.*</u>

* See Toxicological Profile (Subsection II A, above)

VALIDATION SUMMARY (Cont Inued)

<u>IST STUDY NO.</u>	<u>STUDY TYPE</u>	<u>SPECIES</u>	<u>AUDIT RESULTS</u>	<u>REPLACEMENTS/ALTERNATIVES</u>
965	Acute potenti- ation	Rat	Invalid (no raw data)	No alternate or replacement available.
965	35-Day (aerosol) Rat inhalation	Rat	Invalid (no raw data)	No alternate or replacement available.
C 1240	90-Day oral (potentiation with malathion)	Dog	Invalid (no raw data)	<u>Alternate or replacement available.*</u>
A 2484	Primary dermal irritation	Rabbit	Invalid (no raw data)	<u>Alternate or replacement available.*</u>

* See Toxicological Profile (Subsection II A, above)

These topical discussions were developed from Data Evaluation Records (DER) of all studies, registrants' submission records and published articles in the Agency files as of January 1, 1982. Individual DER's of each study are not included in this document, but are available on request. 003289

B. Toxicology

1. Experimental Acute Studies

Determinations of acute toxicities (LD₅₀'s) for various routes of administration (Subsection II A) confirm that naled technical and its formulations appear to be less toxic than many other insecticides in widespread usage, including organophosphates (OP's) such as DDVP (dichlorvos, considered to be a principal mammalian metabolite), diazinon, bidrin, coumaphos, phorate, parathion, demeton (Systox), ethion, azinphosmethyl (Guthion), etc. (Henderson, 1964; Bierlein, 1971). A toxicity category of II or III (moderate to slight) has thus been assigned to the technical grade (90% a.i. usually), based upon validated experimental studies to date. Only malathion, abate, and ronnel among the OP insecticides and most of the popular organochlorines are less toxic on an acute basis (higher LD₅₀'s, ibid.)

Naled was tested for possible potentiation of toxic effects in various combinations with other insecticides in three studies (Witherup & Schlecht, 1963; Narcisse, 1967; McNerney & Levinskas, 1967). Employing a 2³ factorial design, Witherup and Schlecht (1963) treated female CD rats orally with either the LD₀₁ of the technical grade of 23 insecticides, or various binary and ternary combinations of the LD₀₁ dose of chemicals suspended dissolved in peanut oil. The number of observed deaths was compared to the number of expected deaths by X²-analysis. The toxic effects of naled were potentiated by co-administration of Ciodrin, malathion, and methyl parathion.

Following the determination of LD₅₀'s, Narcisse (1967) intubated male Long-Evans rats with a mixture of naled plus Vapona (DDVP), each at 103 mg/kg naled plus 48 mg/kg Vapona). Since the mixture of naled plus Vapona killed only 2/10 animals, it can be concluded that potentiation of toxic effects did not occur. However, although this investigation was designed to examine potentiation of oral toxic effects by two pesticides, the design did include legitimate oral LD₅₀ data. Further, data were available for males only, and the methods and materials were not described in sufficient detail.

The possible potentiation of toxic effects of naled co-administered with Abate in young, male rats of the Elias

strain was tested by McNerney and Levinskas (1967). Preliminary experiments determined the LD₅₀ for the technical grades of naled (90%) and Abate (94%) in the authors' laboratory (177 mg/kg and 770 mg/kg, respectively). In subsequent experiments, animals were treated with a mixture of naled plus Abate (in the ratio of 20:80). The LD₅₀ of the mixture was determined and compared to an "expected" LD₅₀ which was equal to the inverse of the sum of the weighted reciprocals of the LD₅₀'s of naled and Abate. Since the observed LD₅₀ of mixture (620 mg/kg) was greater than the expected value (460 mg/kg), it can be concluded that the acute toxicity of naled is not potentiated by Abate.

Dermal irritation studies employing a modified Draize procedure and scoring (Bullock and Marcisse 1975; Phillips *et al.*, 1972) have revealed naled to produce moderate to severe irritation on both intact and abraded skin of New Zealand White rabbits (PIS = 5.8 to 5.92).

Rittenhouse (1978) compared the skin sensitization properties of naled technical to those of 1-chloro-2,4-dinitrobenzene (DNCB), a strong sensitizer, using male Hartley (albino) guinea pigs. Three initiating applications a week (10 in total) were made to the right flank of each animal during a 22-day span. Two weeks after the last initiating application, a challenge dose was applied to the left flank of each animal. At doses of 0.5 ml of a 3% solution in nanograde acetone, naled produced much less sensitization than DNCB at 0.5 ml of a 0.03% solution. Naled was observed to be a slight irritant upon single application but a strong irritant upon repeated applications to the same skin areas. It was concluded that naled was a weak skin sensitizer.

In acute inhalation studies, the effects of particle size on the acute toxicity of naled and three other pesticides in female Sprague-Dawley rats (250-300 g) and female NAMRU mice (20-30 g) were evaluated (Berteau *et al.*, 1976). Naled aerosols were generated using the technical concentrate (Dibrom 14.86.2%-87% w/w in [redacted] or 10%-20% dilutions of this concentrate in soya-bean oil (w/v). Only two particle size aerosols were achieved, one with a 2.1 micrometer mass median diameter (MMD), the other with 13-20 micrometer MMD. In the rats, the lowest LD₅₀ for naled was for the 2.1 micrometer MMD aerosol of undiluted naled, calculated to be 3.1 (2.5-4.0) mg/kg. In mice exposed to diluted naled with a 2.1 micrometer MMD, the LD₅₀ was 156 (141-174) mg/kg. Because of limitations in the experimental facilities, the authors did not calculate an LC₅₀ for naled, however, the 4-hour LC₅₀ for naled can be estimated employing Haber's law to be 0.08 mg/l for female rats. This value would place naled in Toxicity Category I. Ancillary studies investigated the

acute toxicity of naled administered via oral gavage and via intraperitoneal injection (see Subsection II A). Biochemical studies in rats and mice exposed to naled by inhalation included the determination of plasma cholinesterase activity, whole blood serotonin concentration and whole blood glutathione concentration, with the following results:

<u>SPECIES</u>	<u>DOSE</u>	<u>EFFECT</u>
Rat	2.36 mg/kg	Plasma cholinesterase <70% of control values
Mouse	4.0 mg/kg	Plasma cholinesterase <70% of control values
Rat	6.9 mg/kg	Transient (2 hr) decrease followed by a prolonged (4 day) increase in whole blood serotonin
Mouse	(? dose)	Equivocal serotonin results due to extreme variation in pre- exposure levels
Rat	4.76 mg/kg	Slightly significant ($p < 0.02$) decrease in whole blood glutathione
Mouse	56.0 mg/kg	No change in glutathione levels

This study, however, can only be classified as supplementary, because: 1) Only female rats and mice were used; 2) onset, severity and duration of pharmacotoxic reactions were not given; 3) body weights were not reported; 4) no individual exposure data were given; 5) LC₅₀'s were not reported; and 6) certain standard operating procedures for inhalation toxicology and aerosol technology were not followed.

The in vitro anticholinesterase activity of naled was studied using fly head acetylcholinesterase (AChE) (Smith, 1968), and bovine erythrocyte cholinesterase (ChE) (Johnston, 1958). The I₅₀ value (defined as the amount of test chemical required to inhibit AChE activity to 50% of control values) of naled in the fly-head enzyme system was determined by Smith (1968) to be 7.5×10^{-7} M. Johnston (1958) conducted two in vitro experiments to evaluate anticholinesterase activity of naled. In Experiment 1, the incubation times required to

obtain an I₅₀ value were found to be 78, 48, and 34 min. at 37°C for naled solutions containing 3.6×10^{-9} M, 7.2×10^{-9} M and 1.07×10^{-8} M, respectively. In Experiment 2, the author reported that naled appeared to behave as a reversible ChE inhibitor. (More extensive studies, however, would be required to support this statement.) A third study by Johnston was conducted to detect any degradation of naled following incubation with rat liver. Comparison of the anticholinesterase potency of naled and rat liver-incubated naled showed there was a slight decrease in the anticholinesterase potency of rat liver-incubated naled. The author reported that this finding provides only indirect evidence of degradation of naled by rat liver. Although these studies contain information on the potency of naled as a AChE inhibitor, their usefulness is limited.

Delayed neurotoxicity has been evaluated in standardized 21-day tests using White Leghorn hens, and with tri-ortho-cresyl-phosphate (TOCP) as a positive control (Ives et al., 1962; Schwartz et al., 1978). In both studies, no evidence of neurotoxicity or microscopic demyelination was observed following acute oral administration of LD₅₀ doses (117-118 mg/kg). Ives et al. (1962) also fed naled at 5 ppm for 20 days, or 5 to 1000 ppm for periods up to 76 days, both reportedly without any signs or symptoms of neurotoxicity.

2. Experimental Sub-Chronic Studies

Groups of 25 male and 25 female Charles River albino rats (approximately 105 g) were fed a diet containing 0, 10, 30, 100, or 300 ppm (w/w) naled (as "RE-4355") for ninety days (Weir and Hurst, 1958). No significant differences between test and control animals were noted for mortality, body weights, food consumption, or gross and histopathology. The liver weights of female rats fed 30 ppm naled were significantly lower than controls but this finding did not appear to be treatment-related. Marked reduction (to <70% of control values) in plasma, erythrocyte, and brain cholinesterase activities were noted throughout the study, with 30 ppm being the cholinesterase NOEL and 100 ppm being the LEL. The NOEL for clinical health or pathological findings was not established. This study must be considered of limited value ("Supplementary") because of experimental design deficiencies. For example, no hematological or serum chemistry data were scheduled, the histopathology reported was incomplete, test material was not identified, and no diet analyses were reported, making it impossible to determine what doses the animals received.

In two additional oral rat studies, Wistar females were gavaged for 63 days at a dose of 30 mg/kg/day (the only dose tested) by Brzezic-Bak and Bojanowska (1969), or for 4

weeks at daily doses of 0.25, 1.0, 10 and 100 mg/kg by Lough et al. (1981). In the first of these gavage studies, four of the animals died during the study period, manifesting neuromuscular signs and symptoms of severe cholinesterase inhibition. Brain cholinesterase levels in the survivors were an average of 25.6% of controls, but plasma levels were only slightly depressed (70% of controls). The second study (Lough et al. 1981), reported severe muscular tremors, salivation and deaths at the 100 mg/kg dose level, but only slight-to-moderate muscular effects at 10 mg/kg, and no clinical signs below that dose level. Serial biochemical determinations established a cholinesterase NOEL of 1 mg/kg/day (>70% activity compared to control).

Sixteen adult mongrel dogs were given naled ("RE-4355") in a capsule containing corn oil 6 days per week for 13 weeks at doses of 0.25, 0.75, 2.5, or 7.5 mg/kg/day (Weir, 1958). No treatment-related changes in clinical health were noted. Cholinesterase activity was monitored 5 times prior to treatment to establish a control mean value for plasma and red cell cholinesterase activities for each dog. Based on unreported standard deviations, the author concluded that 0.25 mg/kg/day was the cholinesterase LEL. Using 70% of control values as the cut-off for significant cholinesterase inhibition, however, the reported data can support a cholinesterase NOEL of 0.25 mg/kg/day and an LEL of 0.75 mg/kg/day. A NOEL for clinical health and gross or histopathology was not determined. This study was adjudged valid but inadequate to meet core guidelines for subchronic oral studies for the following reasons: (1) A control group was not reported; (2) gross necropsies were not performed; (3) no tissues or organs were collected for histopathology; and (4) neither hematological nor serum chemistry determinations were conducted.

3. Experimental Chronic Studies

There are no validated chronic studies, as explained above in Subsection II C ("Data Gaps").

4. Experimental Teratological Studies

The only study providing some information on the teratologic potential of naled is the published article by Khera et al. (1979). In this report, naled (as "Fly Killer D", a 36% w/v formulation with 64% unreported ingredients) was suspended in corn oil and administered to mated Wistar rats by intubation at doses of 25, 50, or 100 mg/kg on gestational days 6-15. Control dams received corn oil only. No adverse effects on maternal health were noted, and no ill effects

observed in fetal viability or weights, nor were any gross or visceral anomalies found. Minor skeletal anomalies (delayed ossification of sternebrae) were observed in the treated groups, but the incidences (2.1%-2.9%) fell within the range of incidences for control groups of animals (0-3.8%) reported in the same study. Based on these data the formulation of naled tested was not considered teratogenic at any of the doses tested; thus, the NOEL for this formulation of naled may be estimated at >100 mg/kg (highest dose tested). However, although well designed and apparently properly executed, this teratology study does not meet the criteria for minimum data guidelines and thus must be judged invalid due to the following deficiencies:

- 1) A NOEL was not established.
- 2) A 36% w/v formulation of naled was used instead of the technical material (the remaining 64% of the ingredients were unspecified).
- 3) Twenty mated females were assigned to each group instead of 20 pregnant females.
- 4) The source of the animals was not reported.
- 5) Ages, weights, and strains of male breeders were not reported.
- 6) The period of acclimation and caging conditions were not described.
- 7) Maternal weights during gestation were not reported (neither summarized nor individual data were available).
- 8) Fetal crown/rump measurements were apparently not made (unreported).
- 9) Diagrams of gravid uteri were not supplied.

Although not included as data requirements for registration, a published teratological study with naled in chick embryos is summarized here because of the possible interrelationship between teratological potential of both organophosphate and methylcarbamate insecticides and their ability to depress embryonic nucleotide adenodiphosphate (NAD) levels. Briefly, Proctor and associates (1976) injected 30 ul of a methoxytriglycol solution containing samples of 36 organophosphates, including 1 mg naled ("Analytical Reference Standard"), or 12 methylcarbamates, into the yolk sac of fertile White Leghorn eggs on day 4 of incubation and measured embryonic NAD

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levels on day 12. Insecticide-treated embryos were examined for gross teratological defects on day 19. Treatment of fertile eggs with naled on day 4 of incubation caused no gross anomalies in chicks; naled-treated chicks were reported to exhibit 90% of the body weights, body lengths, and leg lengths relative to controls. (Raw data, however, were not supplied to substantiate these claims.) Embryonic NAD levels on day 12 of incubation were reported to be 93% of controls, although again the raw data were not reported. A number of other inadequacies impair this otherwise interesting report. For example, the data in this study were underreported, the purity of naled used was not specified, some points in the materials and methods were not fully reported (e.g., which phosphate buffer was used in the neutralizing solution), and the summarized experimental data concerning naled were contained in a footnote to a table. This study is useful, however, since it suggests that naled is not teratogenic to chicken embryos at 1 mg/egg; the apparent absence of effect on embryonic NAD levels further bolsters that suggestion.

5. Experimental Mutagenicity Studies

A limited number of mutagenicity studies (all published articles) were available for review. Of the four listed in Subsection II A, only one is acceptable according to established criteria, although the others provide some useful information.

Thus, Shiao et al. (1981) tested four pesticides including naled (Chevron's Dibrom) for gene mutation in spot and quantitative bacterial assays employing six TA Ames strains of Salmonella typhimurium, as well as strains TKJ6321 and TKJ5211 of Bacillus subtilis. Positive results (increased reversion to histidine prototrophy) were reported for all four pesticides (naled, captan, folpet, triallate), in the B. subtilis TKJ6321 strain in the absence of mammalian activation (rat liver S-9). Naled was negative in activation assays with TKJ6321, as well as in all other bacterial strains tested (with/without activation).

Naled of unspecified purity and characterization was one of 140 organophosphate pesticides tested by Hanna and Dyer (1975) in bacterial spot test mutagenicity systems employing Salmonella typhimurium strains his C117, his G46, TA1530 and TA1535, as well as Escherichia coli strains WP2, WP2, uvrA, CM561, CM571, CM611, WP67, and WPI2. Although naled was reported to have induced a positive response only with S. typhimurium strain TA1535 when tested with 5-10 ul of a saturated solution, no numerical data were given to support this observation, hence the results of this study cannot be verified.

Naled was also tested by Byeon et al. (1976) in the Salmonella/microsome mutagenicity test system employing S.

typhimurium strains TA1535, TA1538, TA98, and TA100. Presumably due to the toxicity of naled in the Salmonella system, data were presented only for strain TA100. These showed a dose response of revertant mutant colony formation ranging from 17-75 colonies per plate when naled was tested at 0.02 to 0.1 ul per plate without metabolic activation. However, since the spontaneous rate for TA100 was reported to be 90-120 revertants per plate, naled must be considered non-mutagenic. The report, however, is not acceptable as an adequate assay because of underreporting. For example, data for the other strains tested were not reported, and the purity, source and characterization of the test material were not given.

In an inadequate study, Kurinnyi (1975) reported that naled (described only as "dibrom," of unspecified purity and source) did not induce significant increases in chromosomal aberrations in bone marrow cells of male "non-linear" [?] albino mice treated (by an unspecified route) with 10 mg/kg [type of schedule, acute vs repeat, not specified]. This report is judged unacceptable because of the many obvious inadequacies in reporting.

C. Metabolism

There are no definitive studies available to support the suggested metabolic scheme above (Subsection II B). Some limited information has been provided, however, by three groups of investigators.

Casida, et al. (1962) studied the metabolism of naled (and DDVP) in cows and rats. ³²P-labeled naled was administered orally to a single Guernsey cow (at 20 mg/kg) and urine, feces, blood and milk analyzed for naled and its metabolites. The total recovered radioactivity in urine and feces was 9% and 34% of the dose, respectively, 6 days after administration. However, the remaining portion (up to 57%) of the administered dose was not accounted for by the authors. Column chromatography of urine revealed three tentative metabolites (based on Rfs): methyl phosphates (mono- and di-), O-methyl 2,2-dichlorovinyl phosphate (desmethyl-DDVP), and inorganic phosphate. The presence of these metabolites suggests that hydrolysis was the predominant metabolic pathway of naled in the cow. Distribution studies showed that a peak level of ³²P (10.5 ppm) in blood was found two hours after treatment; this level declined to 1 ppm 2 days after dosing. The peak level of ³²P (7.5 to 7.8 ppm) in milk was observed in the period 8-24 hours after dosing, and slowly declined to 2.1 ppm by 4 days. An in vitro study of naled in rumen fluid showed 30% hydrolysis of naled in 4 hours; however, this statement was not substantiated by reported data.

Two metabolism studies of naled in rats (tissue distribution and fat analysis of ^{32}P -naled) in the same report (Casida *et al.*, 1962) were so severely underreported that no useful information could be obtained.

Pack and his associates (Pack *et al.*, 1962) investigated the metabolic fate of naled (designated as "Dibrom," percent naled unspecified) in four Beagle dogs (2 male, 2 female). The test substance was administered (method of administration not specified) in corn oil at 30 mg/kg, and urine and feces collected at 24-hour intervals for a period of 5 days. At the end of this test period, the dogs were sacrificed and 5 tissues (liver, kidney, muscle, subcutaneous fat, and skin) were obtained. Analyses of naled and three of its possible metabolites: 0,0-Dimethyl-2,2-dichlorovinyl phosphate (DDVP), bromodichloroacetaldehyde (BDCA), and dichloroacetaldehyde (DCA) in urine, feces, and tissues revealed the following: 1) Neither naled nor DDVP were found in any of the urine samples analyzed, and no BDCA in any of the urine or feces samples analyzed. 2) Naled was found in 1 of 17 and DDVP was found in 2 of 17 fecal samples taken after dosing, whereas DCA was found in 2 of 19 urine samples analyzed. (However, in view of the negative results in most of the samples, it is not certain whether naled or DDVP in feces, and DCA in urine samples represent actual residue.) 3) DCA (to a maximum of 0.7 ppm) was found in 4 of 8 fecal samples analyzed. 4) No storage of naled or any of its possible metabolites in the selected animal tissues was indicated at the 5th day after the administration of naled.

In vitro metabolism of naled was studied using a rat liver homogenate by the Chevron group (Chevron, 1965). Incubation of 100 ppm naled with rat liver homogenate produced three metabolites, 0,0-dimethyl 0-(2,2-dichlorovinyl) phosphate (DDVP), dichloroacetaldehyde (DCA), and bromodichloroacetaldehyde (BDCA). Analysis for naled and these 3 metabolites 5, 14, 30, 60, and 120 minutes after addition of the chemical gave the following results: 1) Naled was metabolized very rapidly (the amount of naled remaining at 30 minutes was 0.09% of the original concentration); 2) the amount of both DDVP and DCA peaked at 5 minutes; 3) amounts of DDVP and DCA at 30 minutes incubation were 0.04% and 0.03% of the original concentration of naled, respectively; and 4) the amount of BDCA was near or below the detection limit of 2 ppm (0.02% of the original concentration of naled) throughout the 120 minute incubation period. In a second experiment to evaluate the extraction efficiency of naled and the three metabolites from a liver homogenate fortified with a mixture of naled and these metabolites, recovery ranged from 69% to 110% of the original amount for both naled and the metabolites.

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D. Human Studies and Toxicity

Reliable reports of toxicities resulting from human exposure to specific organophosphate pesticides are rare. The clinical experience with naled is no exception. Most reported incidents of "naled poisoning" consist of anecdotal case reports, some with therapeutic management, but the majority of such accounts prove to have resulted from mixed exposure and were unconfirmed by laboratory analysis, as has been found, for example, with the voluntary reporting system maintained by the Health Effects Branch of the Agency, Office of Pesticide Programs, known as PIMS. During the eleven-year period, 4/17/70 through 9/7/81, 40 incidents involving purported human exposure to naled were reported through EPA's PIMS, but only 11 cases were fully documented in reporting the circumstances (e.g., household, mixing-loading, application, etc.) and route (dermal, oral, etc.) of exposure, the outcome (treatment, hospitalization, fatal, etc.), and laboratory analytical test confirmation.

Clinical effects specific to naled exposure, however, have occurred. For the most part, these were consequent to the well-known anti-cholinesterase activity common to all organophosphate pesticides, the vast majority involving neurological and behavioral problems following acute occupational exposures in agricultural practice (due to accidental or abused application), or low-level chronic exposure in factory workers. Symptoms include one or more of the following, depending upon the intensity, periodicity and duration of exposure, as well as age, sex and state of health of the individual exposed: Headache and/or dizziness; wheezing and/or chest discomfort; miosis and/or blurred vision; irritability and/or weakness; nausea and/or cramps; and diarrhea. Clinically objective findings may include excessive tearing, sweating and/or respiratory secretion, as well as twitching ("tic syndrome") convulsions, coma and cyanosis progressing to death due to respiratory paralysis, especially with massive overexposure in sensitive individuals (Lewis and Brody, 1969).

Subject to verified diagnosis by knowledgeable professionals, the recommended treatment in severe cases includes (from Lewis and Brody, 1969):

- (1) Intravenous atropine (2 to 4 mg) every 5 to 10 minutes, until dry mouth, flushing and tachycardia are achieved.
- (2) Pralidoxime (2-PAM, 1g iv) to reverse peripheral neuromuscular paralysis [NB: Morphine, aminophylline and tranquilizers are contraindicated.]
- (3) Further exposure (and consequent clinical risk) to be absolutely avoided, until both serum and erythrocyte cholinesterase levels return to normal.

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By far the largest, most recent reporting of pesticide-related work injuries in the U.S. was the evaluation of physicians' reports by the California Department of Health in 1974 (Cal. Dep. Hlth, 1974; see also related report: Uniroyal Chemical, 1976), summarized by Swift (1976). Although comprising a total of 1,157 incidents, some accidents apparently did not involve pesticides (or complete reporting), or were the result of mixed exposures. Of 734 cases relating to specific pesticide exposure, only five involved the use of naled, and only mild and transient eye and/or skin effects were reported.

Other incidents involving acute dermal and respiratory effects have been reported. Thus, a male aerial certified pesticide operator in urban mosquito control who came into contact with "Dibrom" (presumably a formulation) during ground operations necessary for spray-plane maintenance required treatment for erythema and edematous blistering (Mick et al., 1970). Response to inunction with a cortisone cream was complete three weeks after exposure.

Symptoms limited to mild, transient irritation of nasal passages and eyes were reported by operators of ULV ground application equipment during field trials of a formulation containing Dibrom-14 concentrate for mosquito control (Chevron, 1970). A total of 495 person-hours of exposure involving 75 workers were recorded, exposure time ranging from 5 minutes to 16 hours.

Evidence of sensitization was recorded by Rycroft (1977), who summarized cases of allergic dermatitis in female nursery workers occurring within 2 hours of spraying with naled (60% in xylene). Three of 4 women previously exposed to naled had positive reactions to patch-testing with the test material, whereas 7 of 8 women not previously exposed to naled were negative; the eighth worker reacted to the vehicle alone.

Cross-sensitization involving naled and other pesticides (not necessarily other OP's) may also occur. Patch-test data have been published by Matsushita and Aoyama (1979) suggesting a mild degree of cross-sensitization to benomyl (a fungicide) in agricultural workers exposed to naled (unspecified product).

Hyporeflexia has been proposed as a sensitive indicator of low-level chronic exposure. Rayner and associates (1972) measured the isometric force generated by the Achilles tendon reflex of male Japanese orchid farmers exposed to high levels of pesticide spray usage (more than 4 hours per day for 2 or more days per week throughout the year), and reported highly significant decrease in mean reflex force in such exposed subjects ($= 0.61 \pm 0.21$, arbitrary units), compared to that predicted from control subjects ($= 1.61 \pm 0.13$) matched for age, sex and race ($P < 0.005$). This type of hyporeflexia was

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apparently not a consequence of depressed neuromuscular transmission, since no differences were found in nerve-conduction velocity between the two groups (60.6 ± 1.3 m/sec in exposed, and 58.6 ± 2.3 m/sec in control). The usefulness of these data and the attendant clinical effect, however, are minimal since these agricultural workers were exposed to a number of different pesticides at the same time (fungicides, organochlorines, as well as OP's other than naled). Hence, it is not evident that hyporeflexia is a clinical consequence of OP usage, much less specific of naled.

There is a singular report of potential genotoxicity (mutagenicity) in humans exposed to naled. Yoder et al. (1973) examined lymphocyte cultures from 42 pesticide applicators and 16 controls for chromosomal aberrations. Although increased chromatid breaks and other damage were reported, exclusive occupational exposure to any single chemical of the 31 most commonly used pesticides could not be established. The exposed groups were categorized only as having been exposed to either insecticides or herbicides.

Skin irritancy of naled (30% and 5% Dibrom in ethanol) was compared to that caused by Hercules 9007 (a carbamate), Dowco 214 and formaldehyde in human male volunteers (Phillips et al., 1972). A dose of 0.5 ml of Dibrom induced a marked bulbous reaction on human forearm skin at a concentration of 30% (in ethanol), but only moderate irritation at a concentration of 5%. Twenty-one-day occlusive patch-testing on mens' backs also showed Dibrom and Hercules 9007 to be the most severe irritants. In a 21-day open patch test, Dibrom was the only chemical to cause significant skin irritation. However, the results cannot be regarded as conclusive, because several different chemicals were tested on a given subject, and too few test subjects were used for some tests.

Absorption of naled is often quite rapid, especially when present in formulations containing high concentrations of aromatic organic solvents. Demonstration of such absorption in man is provided by the following report, the only human metabolic study of naled available for review. Kutz and Strassman (1977) monitored the urine of individuals for the presence of 6 metabolites of OP pesticides among the general population, as well as in mosquito-control workers, following airborne spraying of 1% naled (contaminated with less than 0.04% temephus) in and around Dover, Delaware. Analyses of workers' urine determined the levels of two urinary metabolites: Dimethyl phosphate (DMP), a metabolite of either naled or temephus, and dimethyl phosphorothionate (DMPT), a metabolite of only temephus. Urinalyses from 107 people within the spray area showed increased DMP and DMPT levels only for 56 people who were outdoors during the spray period, but none for 51 people who remained inside

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their houses. No changes were noted in the pre- and post-exposure levels of DMP and DMPT in the urine from 100 people outside of the spray area. Levels of DMP and DMPT in the urine from mosquito control workers and the aircraft pilot were similar to the post-exposure levels of DMP and DMPT in urine from people who were outside during the spray period. In addition to DMP and DMPT, the analyses of urine specimens revealed the (unexplained) presence of four other organophosphate metabolites: 0,0-Diethyl phosphate, 0,0-diethyl phosphorothionate, 0,0-dimethyl phosphorodithioate, and 0,0-diethyl phosphorodithioate.

E. Tolerances

Based on disciplinary studies summarized elsewhere in this Standard (Residue Chemistry, Environmental Fate Exposure and Analysis, Usage Patterns, etc.), as well as validated animal toxicological studies considered here, tolerances on raw agricultural commodities (rac) and in processed foods have been published (CFR 180.215). They range between 0.05 ppm (e.g., for eggs, meats and meat byproducts, milk and dairy products) and 3.00 ppm (e.g., for citrus fruits, and certain green vegetables). The TMRC has been calculated as 1.1034 mg/day (based on a 1.5 kg daily diet). Since no NOEL's have been established, ADI and MPI cannot be calculated.

IV. Summary and Recommendations

In terms of human toxicity, products containing naled appear to present only slight to moderate risk to agricultural workers, manufacturing personnel, applicators and household users. (Toxicity Category III or IV). When used with appropriate protection against excessive dermal and/or inhalational exposure according to label directions, little hazard with acute exposures is to be expected, as clinical reporting over the past 15 years has attested. However, there is the possibility of sensitization (and cross-sensitization to other pesticides) with chronic exposures. Palliative treatment exists for the occasional overexposure leading to clinical consequences of cholinesterase inhibition. No fatalities associated with naled use have been reported.

There also appears to be little if any risk to the general public associated with the chronic ingestion of residues on rac or in processed foods. Such residues as have been found have been far below the tolerance levels established. Even if absorbed over an extended period of time, metabolic considerations (such as degradation to innocuous substances and rapid excretion, by a number of biochemical pathways) presumes a risk much lower than with many other OP compounds.

Despite these considerations of relatively low risk, it is recommended that the data gaps elicited in this review be filled, especially in several crucial chronic testing areas which lack valid no-effect levels for the technical grade of the chemical (see above), in order that appropriate margins of safety (and quantitative assessment of risk) can be derived with greater confidence. The minimum data set for immediate consideration from the listing of requirements (Subsection II C) should include:

- Inhalation studies to establish a NOEL.
- Teratology in a second species (rabbit preferred).
- Metabolism in at least two species.
- Battery of mutagenicity studies.

The long-term studies missing from the mandated registration requirements (reproduction, two-year orals) should be commissioned as soon as possible.

The Agency is prepared to assist in the completion of these studies.

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