INTERACTION OF ORGANOPHOSPHORUS INSECTICIDE
(CIOVAP[®]) WITH PHENOTHIAZINE ANTHELMINTIC
IN SHEEP WITH OR WITHOUT HAEMONCHUS
AND TRICHOSTRONGYLUS SPECIES INFECTION

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by
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INTERACTION OF CIOVAP[®] AND PHENOTHIAZINE IN SHEEP

The undersigned, appointed by the Dean of the
Graduate Faculty, have examined a thesis entitled:

Interaction of Organophosphorus Insecticide (Ciqvap®) with
Phenothiazine Anthelmintic in Sheep With or Without Haemonchus
and Trichostrongylus Species Infection.

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a candidate for the degree of Master of Science

and hereby certify that in their opinion it is worthy of
acceptance.

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Finally, I dedicate this thesis to my parents.

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I. INTRODUCTION

Organophosphorus pesticides are widely used in veterinary medicine as systemic and nonsystemic insecticides. Many factors may potentiate or enhance organophosphorus pesticides toxicity in mammals. The concurrent usage of more than one organophosphate (DuBois, 1961), and stress factors such as malnutrition or low dietary protein (Kahn, 1973; Gopal et al., 1976), and disease conditions (Khan, 1973) are important potentiators. Of particular interest is the iatrogenic effect of phenothiazine tranquilizers in organophosphate toxicity in several species such as man (Arterberry et al., 1962), rat (Gaines, 1962), and sheep (Gopal et al., 1976).

Based on phenothiazine tranquilizer data, the use of organophosphates in conjunction with phenothiazine anthelmintic is contraindicated in veterinary medicine because of possible potentiation of toxicity (Maddy and Riddle, 1977). This type of potentiation, if it exists, is important because it is not uncommon in veterinary medicine to use ectoparasiticides and endoparasiticides concurrently, and also because of the renewed interest in the usage and effectiveness of phenothiazine anthelmintic against sheep nematodes resistant to thiabendazole, levamisole, or morantel tartrate (Kelly et al., 1981a, b).

This study was undertaken to examine the extent of cholinesterase inhibition and clinical effects of repeated topical application of the organophosphorus insecticide (Ciovap[®]) and the oral administration of phenothiazine anthelmintic either alone or in combination in sheep with or without the added stress of clinical infection with gastrointestinal parasites Haemonchus and Trichostrongylus species.

II. LITERATURE REVIEW

A. PHENOTHIAZINE ANTHELMINTIC

1. Chemical and Physical Characteristics:

Phenothiazine is a three ring structure in which two benzene rings are linked by a sulfur and nitrogen atom as illustrated below:

Phenothiazine is known chemically as thiodiphenylamine, or 2,3,5,6-dibenzo-1,4-thiazine, or dibenzoparathiazine. Its molecular weight is 199.26 (Vikhlaev, 1958; Windholz, 1976). Substitutions at positions 2 and 10 abolish anthelmintic activity and significantly increase the action of the drug on the central nervous system (Esterada, 1956; Jones, 1972; Byck, 1975; Rivera-Calimlim, 1977; Heath, 1978). Thus the phenothiazine tranquilizers which are substituted chemical derivatives of phenothiazine are devoid of anthelmintic action.

Pure phenothiazine is a tasteless pale lemon-colored powder with very low solubility in water, petroleum ether, and chloroform. The drug is variably soluble in benzene, hot acetic acid, mineral oil and alcohol. Dry phenothiazine

is relatively stable, but under moist conditions or upon exposure to sunlight spontaneous oxidative degradation occurs to 7-(10'-phenothiazinyl)-3H-phenothiazine-3-one (Swinyard, 1975; Windholz, 1976; Roseboom and Perrin, 1977; Roberson, 1977).

2. Usage:

In 1938 phenothiazine was first used in veterinary medicine as an anthelmintic, urinary antiseptic and insecticide (Vikhlaev, 1958; Swinyard, 1975). Currently, phenothiazine is used mainly as an anthelmintic, either alone or in combination with other agents. Phenothiazine is highly efficacious against Haemonchus, Oesophagostomum, Ostertagia, and Trichostrongylus infection of ruminants (Roberson, 1977); and mature Strongylus (Gibson, 1950), Triodontophorus and Trichonema (Brander and Pugh, 1971) species in horses. Synergistic effects are observed in sheep infested with nematodes when phenothiazine is used in conjunction with some organophosphorus compounds (Kingsbury, 1961; Sloan et al., 1961), or certain other drugs such as phenzidole (Hungerford, 1975).

There are no rational indications for phenothiazine usage in dogs and cats, since both species are highly susceptible to phenothiazine poisoning (Buck et al., 1976a; Roberson, 1977). The drug is rarely used in pigs because of a similar susceptibility and limited efficacy (Thorning et al., 1942; Hungerford, 1975).

The particle size of the drug markedly influences its pharmacologic action (Arundel, 1962). The microform is mostly effective against the smaller parasites, while the larger ones are more effective against the larger species (Brander and Pugh, 1971).

Oral drenching is the preferred method of phenothiazine administration especially in animals heavily burdened with parasites (Roberson, 1977).

3. Disposition and Fate:

The principle biotransformation reactions of phenothiazine occur in the liver of animals, and include oxidative reactions (sulfoxidation, N-oxidation, and C-oxidation) followed by sulfate and glucuronic acid conjugations (Clare, 1947; Roberson, 1977; Mitchell and Waring, 1979; Mitchell, 1980). Some of the orally administered phenothiazine is converted, likely by the epithelial enzymes of the gastrointestinal tract, to the sulfoxide form (Clare, 1947; Roberson, 1977). Phenothiazine sulfoxide is absorbed together with the parent compound and biotransformed by the liver microsomal enzyme system mainly to leucophenothiazone and leucothionol which are excreted in the urine (Clare, 1947; Roberson, 1977). The highest tissue concentrations of phenothiazine and its metabolites are found in the liver and kidney (Ellison and Todd, 1957; Dobryina, 1963; Sundukov, 1963; Gyton et al., 1976).

The urinary excretion of phenothiazine and its

metabolites seems to vary slightly from species to species. Unchanged phenothiazine, phenothiazone, and phenothiazine sulfoxide are urinary excretory products in sheep (Alexander et al., 1958); and phenothiazine and/or phenothiazone occur in the urine of calves (Ellison and Todd, 1957). The urinary metabolites in guinea pigs are leucophenothiazone sulfate, phenothiazine N-glucuronide, small amounts of free phenothiazine, phenothiazine sulfoxide, and phenothiazone (Mitchell and Waring, 1979). In rabbits, only phenothiazone and some chemically unknown red solid particles are detectable metabolites (Alexander et al., 1958). Generally, the parent compound, and seven metabolites (Leucophenothiazone, potassium leucophenothiazine sulfate, phenothiazone, leucothionol, leucothionol glucuronide, thionol and phenothiazine sulfoxide) are identified as excretory products in various animal species (Foster et al., 1960).

Upon exposure to air, the urinary metabolic products (leucophenothiazone and leucothionol) undergo further oxidation to phenothiazone and thionol which impart a pink-red color to the urine (Clare, 1947). Similar discoloration may also occur in the milk (Brander and Pugh, 1971; Burrows, 1980).

The phenothiazine tranquilizers undergo more extensive biotransformation than phenothiazine (Goldenberg et al., 1964; Fishman and Goldenberg, 1965; Weir and Sanford, 1969; Weir and Sanford, 1972; Maylin, 1978).

MAJOR METABOLITES OF PHENOTHIAZINE ANTHELMINTIC IN ANIMALS

Phenothiazine Sulfoxide

Leucophenothiazine

Leucophenothiazine Sulfate

Phenothiazine N-Glucuronide

Leucothionol

Thionol

Phenothiazine

4. Toxicity and Clinical Effects:

Toxicity of phenothiazine varies with both species and individuals. Horses are most susceptible, but dogs and swine are also susceptible (Foster et al., 1960; Clarke and Clarke, 1967). Ruminants and birds are the least susceptible (Nicholson and McCulloch, 1942; Clarke and Clarke, 1967). Sheep and goats are the most resistant species of the ruminants (Clarke and Clarke, 1967; Buck et al., 1976a).

Severe stress factors enhance the toxicity of phenothiazine in animals; thus debilitation of any kind, immaturity, malnutrition, and dehydration are important clinical potentiators of iatrogenic disease (Thorning et al., 1942; Koch, 1963; Clarke and Clarke, 1967; Salisbury et al., 1969). In the case of oral administration the size of the drug particle is also important in the toxicity. The smaller the particle size, the greater the frequency of poisoning (Radeleff, 1970). It is quite possible that the smaller particles are more readily absorbed from the gastrointestinal tract (Niazi, 1979).

Photosensitization with keratitis may occur in cattle, swine, sheep, goats, and birds following phenothiazine administration (Thorning et al., 1942; Whitten and Filmer, 1947; Buck et al., 1976a). Hemolytic anemia (mainly in horses and dogs), and nervous disturbances (such as ataxia) are the most common manifestation of toxicity. Other adverse effects include abortion in ewes during late gestation (Warwick et al., 1946), and decreased egg production in

birds (Nicholson et al., 1942).

Upon exposure to sunlight, phenothiazine-photosensitized animals manifest, within 12-48 hours of drug administration, an acute dermatitis accompanied by keratitis (Thorning et al., 1942; Whitten and Filmer, 1947; Clarke and Clarke, 1967). The high level of circulating phenothiazine sulfoxide diffuses into the aqueous humor, and causes a photosensitized keratitis manifested by ulcerations of the cornea (Clare et al., 1947; Whitten and Filmer, 1947; Buck et al., 1976a). Sheep and goats are more resistant to photosensitization and keratitis than other species, because phenothiazine sulfoxide is rapidly biotransformed to the nontoxic metabolites, leucophenothiazone and leucothionol (Buck et al., 1976a; Roberson, 1977).

Hemolytic anemia, associated with phenothiazine toxicity, is observed mainly in horses and dogs (Clarke and Clarke, 1967; Buck et al., 1976a). This iatrogenic disease may be due to a metabolite or the presence of an impurity (diphenylamine) produced during drug preparation (Clarke and Clarke, 1967). In contrast to the phenothiazine anthelmintic, the phenothiazine tranquilizers apparently do not produce hemolysis of erythrocytes in vivo (Sinha and Sleight, 1968) or in vitro (Guth and Sprites, 1964).

Phenothiazine has complex effects on the nervous system. Signs of neurotoxicity in the horse are weakness and ataxia. Dyspnea, colic, constipation, and diarrhea are also seen (Clarke and Clarke, 1967; Buck et al., 1976a). In pigs

incoordination, ataxia, paralysis and recumbency are observed (Thorning et al., 1942; Burrows, 1980), while in sheep and cattle stiff gait, opisthotonus and incoordination are seen (Clarke and Clarke, 1967; Salisbury, 1969).

Both phenothiazine and phenothiazine tranquilizers affect the endocrine system. Studies have shown that phenothiazine (Jha and Iyer, 1967), and especially phenothiazine tranquilizers (De Weid, 1967; Gordon, 1967; Byck, 1975, Merlis and Carone, 1975) act on the hypopituitary axis. The phenothiazine tranquilizers inhibit (De Weid, 1967; Wakabayashi et al., 1980) as well as stimulate (De Weid, 1967) the secretion of growth hormone.

Increased weight gain and appetite are associated with the use of phenothiazine tranquilizers in man (Pfister, 1978; Mathues et al., 1959; Gordon, 1967; Byck, 1975). Similarly, the use of phenothiazine anthelmintic in lambs is reported to be associated with increased body weight (Varshney and Singh, 1976). Allen and Oldfield (1959) also reported significant weight gain and improved carcass quality in parasitized lambs treated with phenothiazine. The administration of a massive dose of phenothiazine (162.68 gm/lb) to a calf reportedly caused only transient signs of toxicity without adversely affecting body weight gain and growth of the animal (Rogers et al., 1957). In one experiment, however, moderately parasitized calves treated over 121 days with various phenothiazine formulations were reported to have gained approximately 14% less weight than

the parasitized untreated calves (Cauthen, 1957). In another experiment Cauthen (1952) fed small amounts of phenothiazine daily to parasitized cows with calves for 3 consecutive years, and observed no significant differences in weight gain between treated and untreated groups. In hens, higher doses of phenothiazine (1 gm daily for 85 days) were associated with decreased weight gain, but lower dosages had no adverse effects (Nicholson and McCulloch, 1942).

Toxic doses of phenothiazine were reported to decrease serum albumin levels in cattle, especially in animals on low protein ration (Ross et al., 1959).

5. Necropsy Findings:

Most necropsy lesions seen in phenothiazine poisoning are not pathognomic. Subcutaneous edema, keratitis in photosensitized animals (Thorning et al., 1942; Whitten and Filmer, 1947; Salisbury, 1969; Buck et al., 1976a), hemolysis or jaundice (Clarke and Clarke, 1967; Radeleff, 1970), kidney and liver hypertrophy, and noninflammatory necrotic changes with dark red colored urine (Salisbury, 1969; Radeleff, 1970), are highly suggestive of phenothiazine poisoning. Significant histopathological changes in the thyroid (hypothyroidism), and degenerative changes in the anterior pituitary, adrenal cortex, and pancreas are associated with phenothiazine poisoning in sheep and cattle (Jha and Iyer, 1967).

B. DICHLORVOS AND CROTOXYPHOS

1. Chemical and Physical Characteristics:

a. Dichlorvos: The organophosphorus compound, dichlorvos (DDVP, Vapona[®]) is a derivative of phosphoric acid, and is chemically known as 2,2-dichlorovinyl dimethyl phosphate, or 0,0,dimethyl-2,2-dichlorovinyl phosphate (WHO/FAO, 1967). It has the following structure:

Pure dichlorvos is a clear liquid with a mild pleasant aromatic odor (WHO/FAO, 1967), and the molecular weight is 220.98 (Windholz, 1976). It is less soluble in water and glycerine (approximately 1%) than in kerosene and mineral oil (approximately 3%) (WHO/FAO, 1967). It evaporates readily, and the vapor has an insecticidal activity (Van Raalte, 1970; Melnikov, 1971).

b. Crotoxyphos: The organophosphorus compound, crotoxyphos (Ciodrin[®], SD-4294) is a derivative of phosphoric and crotonic acids (Midwest Res. Inst., 1975). Chemically the compound is dimethyl 2-(α -methylbenzyloxy-carbonyl)-1-methyl-vinyl phosphate, 1-methyl-benzyloxy-1-propen-2-yl dimethyl phosphate, or α -methylbenzyl-3-(dimethoxyphosphinyl-oxy)-cis-crotonate, and has the following structure:

Pure crotoxyphos is a light straw-colored liquid, with a molecular weight of 314.28 (Beynon et al., 1973; Windholz, 1976). It is soluble in water approximately 0.1% (Melnikov, 1971; Windholz, 1976), and variably soluble in kerosene, saturated hydrocarbons, acetone, chloroform, ethanol, and highly chlorinated hydrocarbons (Windholz, 1976).

2. Usage:

a. Dichlorvos: The drug is widely used in veterinary medicine as a systemic and nonsystemic pesticide. Various dosage forms of dichlorvos, with or without other drug combinations, are used effectively to treat internal parasites in several animal species (Table 1).

Dichlorvos impregnated collars are used to control external parasites in dogs (Kibble, 1968; Walker and Stevenson, 1968), cats (Seawright and Costigan, 1975), goats (Darrow, 1973), and cattle (Harvey and Brethour, 1970; Beadles et al., 1978). It is also applied topically to control external parasitic infestation in farm animals. Its combination with crotoxyphos (Ciovap[®]) has been used to control flies on sheared lambs (Campbell and Doane, 1977).

TABLE 1

ANTHELMINTIC USAGES OF DICHLORVOS IN VARIOUS ANIMAL SPECIES		
<u>SPECIES</u>	<u>PARASITIC INFECTION</u>	<u>REFERENCE</u>
Pig	<u>Oesophagostomum</u> spp., <u>Hyoststrongylus rubidus</u> , <u>Ascaris summ</u> , <u>Trichuris suis</u> .	Batte <u>et al.</u> , 1965; Jacobs, 1968
Dog	<u>Ancylostoma caninum</u> , <u>A. tubaeforme</u> , <u>A.</u> <u>braziliense</u> , <u>A. duodenale</u> , <u>Uncinaria steno-</u> <u>cephala</u> , <u>Toxocara canis</u> , <u>T. cati</u> , <u>Toxascaris</u> <u>leonina</u> , <u>Trichuris vulpis</u> .	Batte <u>et al.</u> , 1966; Grey, 1974
Cat	<u>Ancylostoma</u> spp., <u>Toxocara cati</u> , <u>T. canis</u> .	Grey, 1974
Horse	<u>Gastrophilus intestinalis</u> , <u>G. nasalis</u> , <u>Strongylus vulgaris</u> , <u>S. equinum</u> , <u>Parascaris</u> <u>equorum</u> , <u>Oxyuris equi</u> , <u>Probstmayria vivipara</u> .	Drudge <u>et al.</u> , 1975; Roberson, 1977
Man	<u>Ascaris lumbricoides</u> , <u>Trichuris trichiura</u> , <u>Schistosomia mansoni</u> .	Chavarriá <u>et al.</u> , 1969; Katz, 1977

Dichlorvos is used in public health to control house flies and plant insects (Gillet et al., 1972; Vettorazzi, 1976; Derache, 1977).

b. Crotoxyphos: Crotoxyphos (either alone or in combination with other organophosphorous compounds) has been used widely as an external pesticide to control livestock insects (Drummond et al., 1967; Beynon et al., 1973; Kaemmerer and Buntenkötter, 1973; Midwest Res. Inst., 1975; Campbell and Doane, 1977). Direct application of crotoxyphos to inanimate places burdened with insects or their larvae, is also a means of insect control (Beynon et al., 1973; Kaemmerer and Buntenkötter, 1973).

3. Biotransformation:

a. Dichlorvos: is rapidly biotransformed principally in the liver into pharmacologically inert metabolites (Casida et al., 1962; Hodgson and Casida, 1962; Gaines et al., 1966; Derache, 1977). The following liver enzymes are involved in the metabolism of dichlorvos (Hodgson and Casida, 1962; Derache, 1977): an esterase that catalyzes hydrolysis of the drug at the P-O vinyl group to produce the principle metabolite dimethyl phosphate, which is excreted in the urine, and dichloroacetaldehyde; a glutathione dependent enzyme (S-alkyl transferase) that attacks the methyl groups to produce desmethyl dichlorvos and S-methyl glutathione; and microsomal mono-oxygenase systems that catalyze oxidative demethylation at the methyl groups

to produce desmethyl dichlorvos and formaldehyde. Desmethyl dichlorvos is further hydrolyzed to monomethyl phosphate and then to inorganic phosphate and dichloroacetaldehyde. The latter compound is finally reduced to dichloroethanol, and trace amounts of dichloroacetic acid.

Dichlorvos also undergoes extrahepatic biotransformation (Hodgson and Casida, 1962; Loeffler et al., 1971; Gillete et al., 1972; Derache, 1977). Four hours after infusion of dichlorvos into an isolated intestinal loop of the pig, dichlorvos, dimethyl dichlorvos, dichloroacetaldehyde, dichloroethanol, and dichloroacetic acid are detected in the lumen, whereas only dichloroethanol is found in the blood (Page et al., 1971). Within the body, the vinyl carbon atom is used for the synthesis of glycine, serine, and to a lesser extent glucose, cholesterol, fatty acids, and RNA (Hutson et al., 1971; Page et al., 1971). Some vinyl carbons are also expired as carbon dioxide (Hutson et al., 1971; Page et al., 1971). Dichlorvos is rapidly biodegraded in vitro by the blood of rats, rabbits and humans (Blair et al., 1975).

b. Crotoxyphos: is rapidly metabolized mainly into dimethyl phosphate and 1-phenylethyl acetoacetate (Chamberlain, 1964a, b). Following the oral administration of P^{32} -labeled crotoxyphos (66% α -isomer and 20% β -isomer) to a lactating ewe, high concentrations of dimethyl phosphoric acid appear in the blood (within 6 hours) and urine (Chamberlain, 1964a). Less than 0.5% of crotoxyphos is

unchanged. Forty-eight hours postadministration, the urine contains about 79% of the administered dose mainly as dimethyl phosphoric acid. Quantitatively, crotonic acid and its derivatives are of lesser importance. The feces contain about 7.3% of the administered dose, and very small quantities of the radioactive substances are recovered in milk.

Dermal applications of (99.2%) P^{32} -labeled crotoxyphos (106 mg α -isomer) to a lactating goat (Chamberlain, 1964b) results in maximum blood level of radioactive substances four hours posttreatment. Only 11% of the administered dose is eliminated in the urine, and 0.12% appears in the feces. Negligible amounts of the drug appear in the milk. The major urinary metabolite of crotoxyphos is dimethyl phosphoric acid. Small quantities of crotonic acid and other metabolites are minor urinary products. The urine of the goat, however, contains fewer metabolites than that of the ewe (Chamberlain, 1964b). The metabolites appear to be nontoxic (Beynon et al., 1973).

From in vitro studies (Beynon et al., 1973), it seems that crotoxyphos is extensively metabolized by the blood of cattle and pigs.

4. Toxicity and Clinical Effects:

a. General Mechanism and Signs of Organophosphorus Poisoning: The early signs of organophosphorus poisoning are caused by overstimulation of the parasympathetic

nervous system (Natoff, 1971; Solly, 1971; Gopal et al., 1976; Buck, 1978). The organophosphorus compound inhibits the cholinesterase, and allow endogenous acetylcholine to accumulate. Generally, the signs may be divided into muscarinic, nicotinic and CNS effects (Natoff, 1971; Buck, 1978). The onset of signs of poisoning may vary from minutes to hours depending on the route of exposure and the dose of the drug. Muscarinic signs generally appear first followed by the nicotinic signs, and central signs may appear in severe toxic cases (Natoff, 1971; Solly, 1971; Gopal et al., 1976).

The general signs of poisoning in horses (Jackson et al., 1960; Radeleff, 1970), cattle (Tracy et al., 1960; Radeleff, 1970; Solly, 1971), sheep (Radeleff, 1970; Solly, 1971; Gopal et al., 1976), dogs (Hazelwood et al., 1979), cats (Bell et al., 1975), and pigs (Stanton et al., 1979) are excessive salivation, miosis, dyspnea, diarrhea, urination, colic, muscular fasciculation, ataxia, general weakness progressing toward paralysis or convulsive muscular activity. Emesis may also occur in carnivores and omnivores. Dermatitis may be seen in dogs (Walker and Stevenson, 1968; Parkinson and Ketterer, 1969) and cats (Bell et al., 1975) wearing dichlorvos impregnated flea collars.

Respiratory failure is the main cause of death in animals poisoned with organophosphorus compounds (Radeleff, 1970; Natoff, 1971; Solly, 1971; Snow and Watson, 1973; Gopal et al., 1976).

b. Dichlorvos: When used rationally, dichlorvos is less toxic than most of the other organophosphorus compounds because it is rapidly metabolized and excreted from the body (Cochrane, 1963; Radeleff, 1970; Van Raatle, 1970). The estimated half-life of the drug in the blood of cattle is 1.2 hour (Kaemmerer and Buntenkötter, 1973). The tissue residue of dichlorvos is so low that it is not a toxicological problem (Casida et al., 1962; Hodgson and Casida, 1962; Gillette et al., 1972; Kaemmerer and Buntenkötter, 1973).

Dichlorvos apparently does not produce the delayed neurotoxicity (Durham et al., 1957; Stanton et al., 1979) which is associated with other organophosphorus compounds such as thiorthocresyl phosphate (Baron, 1981).

The acute LD₅₀ values, and minimal toxic doses of dichlorvos for different animal species are presented in tables 2 and 3, respectively. The tolerated nontoxic doses of dichlorvos for different animal species are presented in table 4.

It is apparent from tables 2, 3, and 4 that the technical form of dichlorvos is more toxic than the formulated one, which releases the active ingredient more slowly.

c. Crotoxyphos: Toxicological studies indicate also that crotoxyphos, when used rationally, is of low toxicity to animals (Weidenbach and Younger, 1962; Knapp et al., 1967; Radeleff, 1970). The rapid metabolism and excretion

TABLE 2

ACUTE LD₅₀ VALUES OF DICHLORVOS FOR DIFFERENT ANIMAL SPECIES

SPECIES	SEX	ROUTE OF ADMINISTRATION	LD ₅₀ mg/kg	FORMULATION	REFERENCE
MOUSE		Oral	124	36.5% emulsion	Yamashita, 1962
		S/C*	24	36.5% emulsion	
MOUSE	M	Oral	145	V-2	Wagner and Johnson, 1970
	F	Oral	135	V-2	
MOUSE	M	Oral	139		Haley <u>et al.</u> , 1975
	F	Oral	133		
RAT	M	Oral	80	Technical	Durham <u>et al.</u> , 1957; Gaines, 1960
	F	Oral	56	Technical	
	M	Dermal	107	Technical	
	F	Dermal	75	Technical	
RAT	M	Oral	97	Analytical Standard Quality	Bradway <u>et al.</u> , 1977
CHICKS	M	Oral	14.8	Technical	Sherman and Ross, 1961
PIGEON		Oral	16.79		Hattorik, 1974
DOG		Oral	100-316		Snow and Watson, 1973
DOG (puppy)		Oral	244.7	Formulated**	Grey, 1974
CAT		Oral	83.8	Formulated**	Grey, 1974
PIG		Oral	157	Unformulated	Stanton <u>et al.</u> , 1979

* Subcutaneous

** Polyvinyl chloride resin formulation

TABLE 3

MINIMAL TOXIC DOSES OF DICHLORVOS FOR DIFFERENT ANIMAL SPECIES

SPECIES	ROUTE OF ADMINISTRATION	MINIMAL TOXIC DOSE mg/kg	FORMULATION	REFERENCE
SHEEP	Oral	25		Radeleff and Woodard, 1957
CATTLE (Calf)	Oral	10		Radeleff and Woodard, 1957
CATTLE	Oral	27	Technical*	Tracy <u>et al.</u> , 1960
HORSE	Oral	25	Technical	Jackson <u>et al.</u> , 1960
PIG	Oral	320	Formulated**	Stanton <u>et al.</u> , 1979
DOG (Beagles).	Oral	148.5	Formulated**	Hazelwood <u>et al.</u> , 1979
DOG (Greyhound)	Oral	11	Technical	Snow and Watson, 1973
	I.V.***	4.4	Technical	
	I.V.***	2.2	Emulsified with 0.9% sodium chloride	

*Redistilled

**Polyvinyl chloride resin formulation

***Intravenous

TABLE 4

TOLERATED NON-TOXIC DOSES OF DICHLORVOS FOR DIFFERENT ANIMAL SPECIES

SPECIES	ROUTE OF ADMINISTRATION	TOLERATED DOSE	FORMULATION	REFERENCE
SHEEP	Oral	10 mg/kg		Radeleff and Woodard, 1957
CATTLE	Oral	0.91 mg/kg, daily for 7 days	Technical*	Tracy <u>et al.</u> , 1960
CATTLE	Dermal Dermal	1% dust (56.7 gm/animal) 2% solution (200 ml)		Radeleff, 1970
HORSE	Inhalation	0.5 mg/ft ³ daily for 22 days	Technical*	Tracy <u>et al.</u> , 1960
PIG	Oral	180 mg/kg	Formulated**	Stanton <u>et al.</u> , 1979
PIG (pregnant)	Oral	25 mg/kg, daily for last 30 days of gestation	Formulated**	Stanton <u>et al.</u> , 1979
PIG (pregnant)	Oral	66 gm	Formulated**	Jacobs, 1968
DOG (Beagles)	Oral	41.58 mg/kg	Formulated**	Ward and Glicksberg, 1971
RAT	Oral	1000 mg/kg diet, for 90 days	Technical	Durham <u>et al.</u> , 1957

*Redistilled

**Polyvinyl chloride resin formulation

of the drug may account for its low toxicity (Radeleff, 1970). Brahman cattle, however, are highly susceptible to crotoxyphos poisoning (Radeleff, 1970; Greer et al., 1973) and concentrations as low as 0.144%-0.3% produced severe toxic reactions in that species (Radeleff, 1970).

The acute LD₅₀ values and tolerated nontoxic doses of crotoxyphos for different animal species are presented in tables 5 and 6, respectively.

In animals suffering from crotoxyphos poisoning muscular weakness and diarrhea are the main signs observed (Weidenbach and Younger, 1962; Radeleff, 1970). Skin lesions may occur following dermal application of the drug in pigs (Palmer and Schlinke, 1971).

Since crotoxyphos does not cause demyelination of the peripheral nerves in chicken, it is possible that it does not produce delayed neurotoxicity in other species (Midwest Res. Inst., 1975).

5. Significance of Blood Cholinesterase Activity:

The exact significance of erythrocyte or plasma cholinesterase depression associated with exposure to organophosphorus compounds is not fully understood (Derache, 1977; Roberson, 1977). Animals exposed to organophosphates, especially in chronic cases, have been known to tolerate low blood cholinesterase levels without untoward effects (Solly, 1971; Khan, 1973; Roberson, 1977). In some cases, the erythrocyte and plasma cholinesterase levels are normal,

TABLE 5

ACUTE LD₅₀ VALUES OF CROTOXYPHOS FOR DIFFERENT ANIMAL SPECIES

SPECIES	SEX	ROUTE OF ADMINIS- TRATION	LD ₅₀ mg/kg	FORMULATION	REFERENCE
MOUSE	M	Oral	39.8		Vorob'eva and Lapchenko, 1973
MOUSE		Oral	89	Technical 83%	Midwest Res. Inst., 1975
		Oral	288	Wettable powder 25%	
		Oral	61 (0.16 ml/kg)	3.2 lb/gal solution	
RAT	M	Oral	38.4		Vorob'eva and Lapchenko, 1973
RAT		Oral	125		Kaemmerer and Buntenkötter, 1973; Wiswesser, 1976
RAT	M	Oral	110	Technical	Midwest Res. Inst., 1975
	F	Oral	74	Technical	
		Oral	74-125	Technical	
		Oral	288	Wettable powder 25%	
		Oral	21.3 (0.213 ml)	Emulsible concentrate 3.2 lb/gal	
	F	S/C	148.8		
	M	Dermal	375		
CHICKS	F	Dermal	202		Midwest Res. Inst., 1975
	M	Oral	111	Technical	
RABBIT	F	Oral	147	Technical	Kaemmerer and Buntenkötter, 1973
		Oral	384		
RABBIT		Dermal	742	Technical	Midwest Res. Inst., 1975
		Dermal	384	Technical	
		Dermal	>200	3.2 lb/gal	
	M	Dermal	338	Emulsible concentrate	
		Dermal	>1,250	Wettable powder 25%	
CAT	M	Oral	802		Vorob'eva and Lapchenko, 1973

TABLE 6

TOLERATED NON-TOXIC DOSES OF CROTOXYPHOS FOR DIFFERENT ANIMAL SPECIES

SPECIES	ROUTE OF ADMINISTRATION	TOLERATED DOSE	REFERENCE
SHEEP	Dermal	0.5% and 1% emulsion	Weidenbach and Younger, 1962
GOAT	Dermal	0.5% and 1% emulsion	Weidenbach and Younger, 1962
CATTLE	Dermal	2% emulsion	Weidenbach and Younger, 1962
CATTLE	Dermal	0.5% emulsion, 1.5 gal/animal/ week for 16 weeks	Knapp <u>et al.</u> , 1967
HORSE	Dermal	2% emulsion, 1 pt. 5 times every 3 days.	Knapp <u>et al.</u> , 1967
		2% in oil, 4 oz. daily for 7 days	Knapp <u>et al.</u> , 1967
PIG	Dermal	0.5% emulsion	Weidenbach and Younger, 1962
RAT	Oral	0.01 mg/kg	Vorob'eva and Lapchenko, 1973

while the enzyme activity of the nervous system is depressed (Solly, 1971). Erythrocyte and nervous system cholinesterases, however, have similar physiological properties (Solly, 1971). The measurement of erythrocyte cholinesterase activity rather than plasma or CNS cholinesterase is the best guide for detecting an animal's exposure to organophosphorus compounds (Natoff, 1971; Gopal et al., 1976; Derache, 1977; Purshottam and Kaveeshwar, 1979). This is especially true in ruminants because of the associated low plasma cholinesterase activity.

Following exposure to organophosphorus compounds, the recovery of the inhibited plasma cholinesterase activity occurs at a faster rate than that of the erythrocyte (Solly, 1971; Ward and Glicksberg, 1971; Snow and Watson, 1973; Gopal et al., 1976).

The normal cholinesterase values for different animal species are presented in table 7.

a. Dichlorvos Induced Anticholinesterase Effects:

Changes in the blood cholinesterase activity following exposure of different animal species to dichlorvos are presented in table 8.

Following the dermal contact with dichlorvos impregnated collars, some dogs (Walker and Stevenson, 1968) and cats (Bell et al., 1975) may exhibit depressed blood cholinesterase activity.

Inhibition of the blood cholinesterase activity by dichlorvos appeared not to be potentiated by certain

NORMAL CHOLINESTERASE VALUES FOR DIFFERENT ANIMAL SPECIES

SPECIES	ESTERASE	RESULT	METHOD	REFERENCE
SHEEP	erythrocyte ChE	0.08-0.40 Δ pH/hr	modified Michel*	Radeleff and Woodward, 1956
SHEEP	erythrocyte ChE	0.39 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.06 Δ pH/hr		
SHEEP	whole blood ChE	0.14-0.27 Δ pH/hr	modified Michel	Crookshank and Palmer, 1978
SHEEP	erythrocyte ChE	0.76 Δ pH/30 min	modified Michel	Silvestri, 1977
SHEEP	plasma ChE	268-382 mU/ml	biodynamic/bmc automated procedure	Crookshank and Palmer, 1978
SHEEP	erythrocyte ChE	59.4 μ M/4 min/ml	semiautomated method of Levine <i>et al.</i> ,	Hazelwood and Heath, 1976
	plasma ChE	7.3 μ M/4 min/ml		
	CSF ChE	1.5 μ M/4 min/ml		
SHEEP	erythrocyte ChE	105 μ M/ml/30 min	Hestrin color reaction	Anderson <i>et al.</i> , 1969
GOAT	erythrocyte ChE	0.35 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.16 Δ pH/hr		
GOAT	whole blood ChE	0.14 Δ pH/hr	modified Michel	Palmer <i>et al.</i> , 1963
GOAT	erythrocyte ChE	0.69 Δ pH/45 min	modified Michel	Silvestri, 1977
CATTLE	erythrocyte ChE	0.65 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.03 Δ pH/hr		
CATTLE	erythrocyte ChE	0.65 Δ pH/15 min	modified Michel	Silvestri, 1977
CATTLE	whole blood ChE	42.1 μ lCO ₂ /ml/min	manometric	Wills, 1972
CATTLE (dif- ferent breeds)	erythrocyte ChE	1.2 μ M	Fleisher and Pope (slightly modified)	Petty and Lovell, 1958
CATTLE	erythrocyte ChE	1.62 μ M	Fleisher and Pope (slightly modified)	Petty and Lovell, 1958
CATTLE (Aberdeen Angus)	plasma ChE	258 mU/ml	biodynamics/bmc automated procedure	Crookshank and Palmer, 1978
CATTLE	erythrocyte ChE	199.6 μ Mol/4 min/ml	semiautomated method of Levine <i>et al.</i> ,	Hazelwood and Heath, 1976
(Calf)	plasma ChE	10.1 μ Mol/4 min/ml		
	CSF ChE	2.0 μ Mol/4 min/ml	1966	
HORSE	whole blood	0.39 Δ pH/hr	modified Michel	Palmer <i>et al.</i> , 1963
HORSE	erythrocyte ChE	0.18 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.62 Δ pH/hr		
HORSE	erythrocyte ChE	0.78 Δ pH/45 min	modified Michel	Silvestri, 1977
	plasma ChE	0.66 Δ pH/20 min		
PIG	erythrocyte ChE	0.71 Δ pH/25 min	modified Michel	Silvestri, 1977
	plasma ChE	0.46 Δ pH/hr		
PIG	erythrocyte ChE	124.6 μ Mol/4 min/ml	semiautomated method of Levine <i>et al.</i> ,	Hazelwood and Heath, 1976
	plasma ChE	13.4 μ Mol/4 min/ml		
	CSF ChE	2.2 μ Mol/4 min/ml	1966	
PIG	erythrocyte ChE	0.32 μ M/min	colorimetric	Wills, 1972
	plasma ChE	0.16 μ M/min		
DOG	erythrocyte ChE	0.13 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.16 Δ pH/hr		
DOG	erythrocyte ChE	0.63 Δ pH/45 min	modified Michel	Silvestri, 1977
	plasma ChE	0.67 Δ pH/30 min		
DOG	erythrocyte ChE	48.3 μ Mol/4 min/ml	semiautomated method of Levine <i>et al.</i> ,	Hazelwood and Heath, 1976
	plasma ChE	55.1 μ Mol/4 min/ml		
	CSF ChE	2.4 μ Mol/4 min/ml	1966	
DOG (M)	erythrocyte ChE	10.5 μ Mol/3 min/ml	automated	Ward and Hess, 1971
	plasma ChE	10.3 μ Mol/3 min/ml		
DOG (F)	erythrocyte ChE	10.6 μ Mol/3 min/ml	automated	Ward and Hess, 1971
	plasma ChE	12.1 μ Mol/3 min/ml		
DOG	erythrocyte ChE	1.0 μ Mol/min/ml	Cranmer and Peoples, 1971	Cranmer and Peoples, 1973
	plasma ChE	0.9 μ Mol/min/ml		
CAT	erythrocyte ChE	0.10 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.56 Δ pH/hr		
CAT	plasma ChE	19.9 μ lCO ₂ /ml/min	manometric	Wills, 1972
GUINEA PIG	erythrocyte ChE	0.32 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.58 Δ pH/hr		
RABBIT	erythrocyte ChE	0.20 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.22 Δ pH/hr		
RABBIT	erythrocyte ChE	184.8 μ Mol/4 min/ml	semiautomated method of Levine <i>et al.</i> ,	Hazelwood and Heath, 1976
	plasma ChE	30.3 μ Mol/4 min/ml		
	CSF ChE	7.2 μ Mol/4 min/ml	1966	
RABBIT	erythrocyte ChE	2.1 μ M/ml/min	pH - stat	Wills, 1972
	plasma ChE	0.76 μ M/ml/min		
RABBIT	erythrocyte ChE	1.0 μ Mol/min/ml	Cranmer and Peoples, 1971	Cranmer and Peoples, 1973
	plasma ChE	0.9 μ Mol/min/ml		
RAT	erythrocyte ChE	0.19 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	0.21 Δ pH/hr		
RAT	erythrocyte ChE	1.4 μ Mol/min/ml	Cranmer and Peoples, 1971	Cranmer and Peoples, 1973
	plasma ChE	5.6 μ Mol/min/ml		
MOUSE	erythrocyte ChE	0.12 Δ pH/hr	modified Michel	Kruckenbergs and Vestweber, 1973
	plasma ChE	1.36 Δ pH/hr		
MOUSE	erythrocyte ChE	1.1 μ Mol/min/ml	Cranmer and Peoples, 1971	Cranmer and Peoples, 1973
	plasma ChE	19.8 μ Mol/min/ml		
CHICKEN	plasma ChE	24.1 μ M/min/ml	manometric	Wills, 1972
RHESUS	erythrocyte ChE	6.8 μ Mol/min/ml	Cranmer and Peoples, 1971	Cranmer and Peoples, 1973
MONKEY	plasma ChE	1.7 μ Mol/min/ml		
MAN (M)	erythrocyte ChE	114 μ lCO ₂ /ml/min	manometric	Wills, 1972
	plasma ChE	88.5 μ lCO ₂ /ml/min		
MAN (F)	erythrocyte ChE	107.7 μ lCO ₂ /ml/min	manometric	Wills, 1972
	plasma ChE	88.3 μ lCO ₂ /ml/min		
MAN	erythrocyte ChE	0.75 Δ pH/hr	Michel	Michel, 1949
	plasma ChE	0.70 Δ pH/hr		

*Consult the original references for procedural details of the modifications of Michel's method.

TABLE 8
EFFECTS OF DICHLORVOS ON BLOOD CHOLINESTERASE ACTIVITIES IN DIFFERENT ANIMAL SPECIES.

SPECIES	ROUTE OF ADMINISTRATION	DOSE	FORMULATION	ESTERASE	EFFECT	REFERENCE
SHEEP	Oral	25 mg/kg		EChE	↓	Radeleff, 1957
CATTLE (calf)	Oral	10 mg/kg		EChE	↓	Radeleff, 1957
CATTLE	Oral	0.91 mg/kg daily for 7 days	Technical*	EChE	↓~33%	Tracy <i>et al.</i> , 1960
	Oral	2.28 mg/kg daily for 12 days	Technical*	EChE	↓~87%	
HORSE	Oral	35.8 mg/kg	Formulated**	PChE W.B. ChE	↓>90% ↓~75%	Bello <i>et al.</i> , 1974
HORSE (foal)	Oral	10&20 mg/kg	Formulated***	PChE W.B. ChE	↓~70% ↓~60%	Bello <i>et al.</i> , 1974
HORSE	Oral	25&50 mg/kg	Technical	W.B. ChE	↓ 85%	Jackson <i>et al.</i> , 1960
HORSE	Inhalation	0.5 mg/ft ³ daily	Technical*	EChE	↓transitory	Tracy <i>et al.</i> , 1960
PIG	Oral	1-16 mg/kg daily for 30 days	Formulated**	EChE PChE	↓ 48% ↓~47%	Stanton <i>et al.</i> , 1979
PIG (preg-nant)	Oral	5&25 mg/kg daily for last 30 days of gestation	Formulated**	EChE PChE	↓ 90% ↓ 82%	Stanton <i>et al.</i> , 1979
DOG	Oral	29.7-148.5 mg/kg	Formulated**	EChE	↓~60%	Hazelwood <i>et al.</i> , 1979
DOG	Oral	11&22 mg/kg	Technical	EChE PChE	↓>90% ↓>85%	Snow and Watson, 1973
DOG	Oral	41.58 mg/kg	Formulated**	EChE PChE	↓ 37% ↓ 67%	Ward and Glicksberg, 1971
MOUSE	Oral	500 mg/kg diet for 24 hours	V-2	PChE	↓~50%	Wagner and Johnson, 1970
RAT	Oral	500 mg/kg diet for 90 days	Technical	EChE PChE	↓~60% ↓~50%	Durham <i>et al.</i> , 1957

*Redistilled
 **Polyvinyl chloride resin pelleted formulation
 ***Polyvinyl chloride paste formulation

↓ = decrease
 ~ = approximately
 > = more than
 EChE = erythrocyte cholinesterase
 PChE = plasma cholinesterase
 W.B. ChE = whole blood cholinesterase

organophosphorus compounds including crotoxyphos (Knapp et al., 1967; Collins et al., 1971; Vestweber and Kruckenberg, 1972; Carter and Maddux, 1974; Cohen and Ehrich, 1976).

b. Crotoxyphos Induced Anticholinesterase Effects:

The effects of crotoxyphos on the blood cholinesterase activity in several animal species are presented in table 9.

Two hundred and fifty parts per million of crotoxyphos in the diet of rats had no inhibitory effect on the brain cholinesterase activity (Midwest Res. Inst., 1975). Seven hundred and fifty parts per million, however, depress the enzyme in the brain of rats (Midwest Res. Inst., 1975). Chronic administration of crotoxyphos (0.01 mg/kg) to rats for 10 months, did not inhibit the cholinesterase activity (Midwest Res. Inst., 1975).

6. Other Physiological Effects:

a. Dichlorvos: Elevated hematocrit and total plasma protein values may occur in adult dogs treated with dichlorvos (Snow and Watson, 1973). In puppies and cats, however, there are no changes in the hematocrit, serum cholesterol, and total plasma protein values following dichlorvos administration (Grey, 1974).

Daily administration of dichlorvos (1-16 mg/kg) to young pigs (30 days) has no effect on weight gain or feed consumption (Stanton et al., 1979). Similar results are observed in suckling piglets after treatment of their dams (Collins et al., 1971). Following the administration of a

TABLE 9

EFFECTS OF CROTOXYPHOS ON BLOOD CHOLINESTERASE ACTIVITY IN DIFFERENT ANIMAL SPECIES

SPECIES	ROUTE OF ADMINISTRATION	DOSE	ESTERASE	EFFECT	REFERENCE
SHEEP	Dermal	0.5% emulsion	W.B. ChE	↓ 42%	Weidenbach and Younger, 1962
GOAT	Dermal	0.5% emulsion	W.B. ChE	↓ 61%	Weidenbach and Younger, 1962
	Dermal	1.0% emulsion	W.B. ChE	↓ 100%	
CATTLE (Calf)	Dermal	0.5% emulsion	W.B. ChE	↓ 69%	Weidenbach and Younger, 1962
	Dermal	2.0% emulsion	W.B. ChE	↓ 100%	
CATTLE (Calf)	Dermal	0.15-0.6% emulsion	W.B. ChE	No Change	Matthysse and Lisk, 1968
CATTLE	Dermal	0.5% emulsion, weekly for 16 wks	W.B. ChE	↓ 85%	Weidenbach and Younger, 1962
	Dermal	2.0%		↓ 76%	
HORSE	Dermal	2.0% in oil, 4 oz/ day for 7 days	PChE	↓ 89%	Knapp <u>et al.</u> , 1967
	Dermal	2.0% emulsion 1 pt/3 days for 5 times	PChE	↓ 76%	
PIG	Dermal	1.0% emulsion (1 liter)	W.B. ChE	↓ 50%	Palmer and Schlinke, 1971
DOG	Oral	2.02 mg/kg/day for 30 days	EChE	↓ 50%	Vorob'eva and Lapchenko, 1976

W.B. ChE = whole blood cholinesterase

PChE = plasma cholinesterase

EChE = erythrocyte cholinesterase

single or repeated recommended dosages of dichlorvos to cattle (Ribelin and Macklin, 1971), sows (Collins et al., 1971; Witherup et al., 1971; Grey, 1974; Stanton et al., 1979), rat (Tracy et al., 1960; Pambska et al., 1978), rabbit (Pambska et al., 1978), or bitches (Grey, 1974) during various stages of pregnancy, no adverse drug effects are seen during gestation, at parturition, or during the postnatal development of the progenies. Clinical and experimental data have demonstrated that dichlorvos induces parturition and reduces the farrowing period when administered during the last trimester of pregnancy (Batte et al., 1969; Shell, 1975; Young et al., 1979). Currently it is recommended as an ecobolic drug to reduce stillbirths in farrowing sows (Shell, 1975). Dichlorvos is generally reported to be nonteratogenic in rabbits (Vogin and Carson, 1971; Schwetz et al., 1979), mice (Schwetz et al., 1979), chicken (WHO/FAO, 1970), or rats (WHO/FAO, 1970). Teratogenic effects, however, have been observed in chicken embryos (WHO/FAO, 1970). Recent reports indicate that other organophosphorus compounds have overt or subtle embryotoxic and fetotoxic effects in animals (Derache, 1977; Knox et al., 1978).

b. Crotoxyphos: The daily administration of this compound to dogs (2.02 mg/kg for 30 days), results in a decreased serum albumin level and increased globulin level (Vorob'eva and Lapchenko, 1973). Following topical application of crotoxyphos (1.0%) to pigs, no significant

difference in weight gain is seen between the drug-treated and nontreated animals (Palmer and Schlinke, 1971).

Similarly, feeding different levels of the drug (5, 15 and 45 ppm) to dogs for 12 weeks do not affect the growth rate or organ weight (Midwest Res. Inst., 1975). Crotoxyphos is nonteratogenic in the chicken embryo (Midwest Res. Inst., 1975). The drug does not adversely affect gestation in the cow (Ribelin and Macklin, 1971).

C. COMBINED EFFECTS OF PHENOTHIAZINE
ANTHELMINTIC AND ORGANOPHOSPHORUS
INSECTICIDES.

Under field conditions more than one drug may be used concurrently to treat livestock diseases because of the convenience and economy of this practice. Drug potentiation or adverse reactions may arise as a result of drug interaction (Gaines, 1962; Gopal, 1976; Khan, 1973). The phenothiazine anthelmintic is often used concurrently with other anthelmintics or ectoparasiticides (Kingsbury, 1961; Sloan et al., 1961; Hungerford, 1975).

Numerous reports indicate that phenothiazine tranquilizers potentiate organophosphorus poisoning in several animal species, such as man (Arterberry et al., 1962), rat (Gaines, 1962; Michalek and Stavinocha, 1978), and sheep (Gopal et al., 1976).

The potentiated inhibition of brain cholinesterase following phenothiazine tranquilizer (chlorpromazine) administration is less when dichlorvos rather than physostigmine is used concurrently (Michalek and Stavinocha, 1978).

Gopal et al. (1976) have shown, however, that the phenothiazine tranquilizer triflupromazine not only increases the signs of coumaphos toxicosis in sheep, but also potentiates the coumaphos-induced inhibition of erythrocyte and plasma cholinesterase activities.

The use of phenothiazine tranquilizers as an adjunctive agent in the treatment of organophosphorus poisoning is therefore very controversial (Arterberry, 1962; Wills, 1970; Michalek and Stavinoha, 1978). Phenothiazine tranquilizers, however, are used in the treatment of organophosphorus poisoning in man (Wills, 1970), although fatal drug interactions may occur (Arterberry, 1962). The observation that the anticholinesterase agent physostigmine is efficacious in antagonizing the CNS effects of phenothiazine tranquilizer poisoning in man (Wang and Marlowe, 1977; Weisdorf et al., 1978), emphasizes the fact that the mechanism by which the drug potentiates the adverse CNS effects of the organophosphorus compounds is not fully known.

The concurrent use of the phenothiazine anthelmintic and certain organophosphorus pesticides, produced synergistic anthelmintic action in sheep (Kingsbury, 1961; Sloan et al., 1961). In contrast, phenothiazine anthelmintic does not potentiate the toxicity of several organophosphorus pesticides (including crotoxyphos and dichlorvos) when therapeutic doses of both types of compounds are used in healthy calves (Schlinke and Palmer, 1973). Similarly, significant potentiation is not observed when phenothiazine anthelmintic and coroxon or coumaphos are used in sheep (Malone, 1962). Phenothiazine in combination with coumaphos, however, depresses blood cholinesterase activity more than does coumaphos alone (Malone, 1962).

The above effect is not observed with coroxon-phenothiazine combination (Malone, 1962). The organophosphorus compounds differ quantitatively with reference to their pharmacological and toxicological properties and these differences may determine the nature of drug potentiation seen when used concurrently with phenothiazine. It is interesting to note also, that phenothiazine anthelmintic when used alone does not depress the blood cholinesterase activity of sheep at dose levels between 0.4-2 gm/kg body weight (Malone, 1962).

The role stressors play in iatrogenic diseases can not be overlooked when drug interactions are being evaluated. Factors such as species, age, sex, health and nutritional state of the animal may modify or enhance organophosphorus poisoning (Gaines, 1962; Durham, 1967; Radeleff, 1970; Natoff, 1971; Khan, 1973; Gopal et al., 1976). With regards to livestock animals, Gopal et al. (1976) showed that sheep maintained on low dietary protein were more susceptible to the organophosphorus (coumaphos) toxicity than those on normal protein diet. These investigators also observed that lambs fed a low dietary protein ration were more susceptible than lambs fed a normal ration to the potentiation effect of coumaphos and triflupromazine. In contrast, the effects of other stressors on the drug interaction of organophosphates and phenothiazine in sheep are not fully known.

D. MODIFICATIONS OF MICHEL'S ELECTROMETRIC METHOD
TO MEASURE BLOOD CHOLINESTERASE ACTIVITY
IN ANIMALS.

Numerous procedures have been developed to determine blood cholinesterase activities of man and animals (Witter, 1963; Aldrich, 1969; Augustinsson, 1971; MacQueen and Plaut, 1973; Silk et al., 1979). Modifications of the method originally described by Michel (1949) are most commonly used. The method used here in this thesis is a modification of Michel's electrometric method.

Michel's electrometric method for measurement of the erythrocyte or plasma cholinesterase activity is principally based on the hydrolysis of the choline ester substrate (acetylcholine) by the cholinesterase enzyme of the biologic sample used (Michel, 1949):

This enzymatic reaction results in acetic acid production. The acetic acid dissociates liberating hydrogen ions which decrease the pH of the reaction mixture.

Electrometric determination of the change in the pH

produced over a definite period of time (e.g. 1 hr) at a specific temperature (e.g. 25°C) represents the enzyme activity (e.g., $\Delta\text{pH/hr}$). The pH is measured with a glass electrode using a pH meter.

Heparin is used as the only anticoagulant in order to avoid enzyme inactivation due to removal of magnesium and calcium ions present in the blood (Witter, 1963; Augustinsson, 1971).

The temperature of the reaction medium plays a critical role in the rate of the reaction and is thus important in determining the cholinesterase activity. A 1°C change in temperature of the reaction medium results in a 5.5% and 3.0% change in plasma and erythrocyte cholinesterase activity respectively (Ellin and Vicario, 1975).

One may consider the fact that during a reaction the ΔpH is measured after a fixed time interval rather than the amount of acid production at different times, a minor drawback of Michel's electrometric method. In addition, the instability of the pH of the phosphate buffer creates an inconvenience (Witter, 1963; Augustinsson, 1971). Personal observations indicate a significant decrease in the pH shelf-life of the buffer reagent after 7-10 days. Michel's technique, however is as sensitive and reproducible as other standard methods (such as pH-stat, Hestrin color reaction, and Acholest methods) in measuring small variation in the blood cholinesterase activity (Witter,

1963; Pearson and Walker, 1968; Aldrich, 1969; Augustinsson, 1971; MacQueen and Plaut, 1973). The simplicity of Michel's method, therefore, makes it a very valuable assay technique for research in the determination of cholinesterase activity (Aldrich, 1969; MacQueen and Plaut, 1973), and for the routine diagnosis of organophosphorus poisoning (Aldrich, 1969; Holmstedt, 1971).

Since domestic animals (especially ruminants) are characterized by having relatively low blood cholinesterase activity, various modifications of the original Michel's method are used to enhance the products of the enzymic reaction and thus the ΔpH (table 10). To obtain satisfactory results with the electrometric method as originally described by Michel (1949), the volume of the blood sample used is increased (Frawley and Fuyat, 1957; Callahan and Kruckenberg, 1967; Kruckenberg and Vestweber, 1973), the incubation time is lengthened (Callahan and Kruckenberg, 1967), or the reaction temperature is increased (Silvestri, 1977). The recent modifications described by Silvestri (1977) to measure erythrocyte and plasma cholinesterase activity in domestic animals involve using shorter times of incubation (15-60 minutes depending on the animal species) coupled with an increase in the reaction temperature to 37° C. No significant difference between washed and non-washed erythrocyte cholinesterase activity occurs using these modifications (Silvestri, 1977).

The procedural modification of Ellin et al. (1973)

TABLE 10
MODIFICATIONS OF THE ELECTROMETRIC METHOD OF MICHEL USED TO MEASURE
BLOOD CHOLINESTERASE ACTIVITIES IN DIFFERENT ANIMAL SPECIES

SPECIES	ESTERASE	MAIN MODIFICATIONS*	ADVANTAGES	REFERENCE
Dog	EChE	Higher concentration of washed erythrocytes	Useful in animals with low cholinesterase activity	Frawley and Fuyat, 1957
Horse, Goat	W.B.ChE	Substituting whole blood for the washed erythrocytes	Faster than Michel's method	Palmer <u>et al.</u> , 1963
Pig	EChE	Doubling the volume of erythrocytes and acetylcholine	Useful in animals with low cholinesterase activity	Moncol and Batte, 1964
Goat, Horse, Pig, Dog, Cat, Rabbit, Guinea pig	EChE	Increasing erythrocytes volume eightfold, and various incubation times are used	Useful in animals with low cholinesterase activity	Callahan and Kruckenberg, 1967
Guinea pig, Goat, Cattle, Rabbit, Cat, Horse, Rat, Sheep, Dog, Mouse	W.B.ChE, EChE and PChE	Doubling the volume of erythrocytes, and tripling the volume of plasma	Useful in animals with low cholinesterase activity	Kruckenberg and Vestweber, 1973
Sheep, Goat, Cattle, Pig, Horse, Dog	EChE and PChE	Incubation temperature is increased to 37 C. and time of incubation is reduced	Sensitive, high Δ pH reading short incubation time, both macro and semimicro method could be used, and nonwashed erythrocyte may be used	Silvestri, 1977

*Consult the original references for procedural details of the modifications of Michel's electrometric method.

EChE = Erythrocyte cholinesterase; PChE = Plasma cholinesterase; W.B.ChE = Whole blood cholinesterase

involves shortening the incubation time from 60 to 17 minutes, and increasing the sample volume five-fold. This modification may prove to be of diagnostic usefulness in veterinary medicine.

III. MATERIALS AND METHODS

1. Animals:

Forty, approximately 3-month-old lambs of mixed breeds (mean body weight 26.38 ± 0.45 lb) were used in this study. The animals were from an area endemic for nematodes. The lambs were individually weighed and randomly numbered 1-40. They were divided into two major groups, A (1-20), and B (21-40). The animals in both groups were vaccinated with ovine ecthyma vaccine, and Clostridium perfringens antitoxin type C and D. Following 20 days of acclimatization, each major group was randomly subdivided into four groups (A_1 , A_2 , A_3 , A_4 and B_1 , B_2 , B_3 , B_4) of five lambs each, and housed in individual pens. Each group received concentrate given twice a day while hay and water were available ad libitum.

All the groups of lambs, upon parasitological examination of their fecal samples were found to be clinically infected with Haemonchus and Trichostrongylus species. Each lamb in groups B_1 - B_4 was drenched on the first day of acclimatization with 0.5 ounce levamisole hydrochloride per 50 lb. body weight. On the 16th day of acclimatization, the lambs in groups B_1 - B_4 were also treated orally with thiabendazole, 1 gm per lamb. All the lambs in groups B_1 - B_4 were certified free of the above mentioned nematodes.

2. Experimental Procedures:

Experiment I: Prior to initiation of the drug treatments, each lamb was sheared, exposing the entire spinal portion of the animal.

During the experiment, the lambs in each group were treated during a 29 day period with phenothiazine anthelmintic^a and Ciovap^{®b} (2.3% Dichlorvos and 10.0% Crotoxyphos) as outlined in Table 11. This was followed by a 30 day posttreatment period.

Each lamb in groups A₁, A₂, B₁, and B₂ was sprayed with approximately 1550 ml of 0.25% Ciovap[®] emulsion. Spraying with Ciovap[®] was repeated every two weeks for a total of three treatments. Concurrently with the initial Ciovap[®] application a phenothiazine anthelmintic bolus (12.5 gm) was administered orally with a balling gun to each lamb in groups A₁, A₃, B₁, and B₃. Four days later, each phenothiazine treated lamb was given one half of a bolus (6.25 gm). This treatment was repeated every three days for a total of nine treatments.

The lambs were kept under constant observation during the 29 day treatment period, and examined each day for the remaining 30 days (posttreatment period).

Experiment II: After experiment I was concluded a 21 day study was carried out to determine the effect of a

^aSioux City Serum Co., Sioux City, Iowa.

^bShell Chemical Co., Agricultural Division, Animal Health, San Ramon, California.

TABLE 11

TREATMENT SCHEDULE AND CALENDER OF EXPERIMENTAL EVENTS
OF LAMBS SPRAYED WITH CIOVAP® AND/OR GIVEN
PHENOTHIAZINE ANTHELMINTIC

GROUP		TREATMENT
Clinical Parasitism	No Clinical Parasitism	
A ₁	B ₁	C&P
A ₂	B ₂	C
A ₃	B ₃	P
A ₄	B ₄	Control

CALENDER OF EXPERIMENTAL EVENTS

<u>-1</u>	<u>0</u>	<u>1</u> (C,P)	<u>2</u>	<u>3</u>	<u>4</u>	5(P)	<u>6</u>	<u>7</u>
8(P)	<u>9</u>	<u>10</u>	<u>11</u> (P)	12	<u>13</u>	<u>14</u> (P)	<u>15</u> (C)	<u>16</u>
<u>17</u> (P)	18	19	<u>20</u> (P)	<u>21</u>	<u>22</u>	<u>23</u> (P)	<u>24</u>	25
26(P)	<u>27</u>	<u>28</u>	<u>29</u> (C,P)	<u>30</u>	<u>31</u>	32	33	<u>34</u>
35	36	<u>37</u>	38	39	40	<u>41</u>	42	43
<u>44</u>	45	46	47	<u>48</u>	49	50	<u>51</u>	52
53	54	<u>55</u>	56	57	<u>58</u>	59	60(P)	61(P)
62(C,P)	<u>63</u>	64	<u>65</u>	66	67	68	69	70
71	72	73	74	75	76	77	78	79
<u>80</u>								

-1 to 0	Pretreatment Period - - - - -	(2 days)
1 to 29	Treatment Period (Experiment I) - - - - -	(29 days)
30 to 59	Posttreatment Period (Experiment I) - - - - -	(30 days)
60 to 62	Treatment Period (Experiment II) - - - - -	(3 days)
63 to 80	Posttreatment Period (Experiment II) - - - - -	(18 days)

Blood samples collection days are underlined.

P - Phenothiazine anthelmintic treatment

C - Ciovap® Spray

second 3 day drug exposure period on the animals used in experiment I. Each lamb in groups A₁, A₃, B₁, and B₃ received one gram of phenothiazine powder^C (54% phenothiazine as the active ingredient) mixed in the feed for three consecutive days. On the third day of phenothiazine administration, each lamb in groups A₁, A₂, B₁, and B₂ was sprayed with one gallon of 0.25% Ciovap[®] emulsion. All the groups were kept under observation for 18 days before termination of the experiment.

3. Parasitological Examination:

Fecal samples were collected from all the groups prior to the initiation of experiment I, at the end of the 29-day treatment regimen (experiment I), and at the end of the experiment II. A fecal concentration-centrifugation technique was used to identify the helminthic's eggs so as to determine the nature of clinical parasitism.

4. Clinical Examination:

The time of onset of clinical signs, the nature of signs observed, and the time of death were recorded throughout both experiments. Dead animals were necropsied.

5. Collection and Assays of Blood Samples:

Baseline values of erythrocyte (EChE) and plasma

^CPhenothiazine Premix[®], West Agro-Chemical Inc.

cholinesterase (PChE) activity, and total plasma protein (TPP) were determined on two consecutive days just prior to initiation of the treatments. During experiment I, determinations of cholinesterase (ChE) activities were conducted on blood samples collected from all groups six hours following the first treatment with phenothiazine and Ciovap[®], and thereafter at 24 hour intervals for 31 days with the exception of days: 5, 8, 12, 18, 19, 25 and 26. After the 31st day, blood samples were collected twice a week for 5 weeks and then 15 days later on the termination day of the experiment II.

Heparinized vacutainer tubes^d were used to collect approximately 5 ml of blood by jugular venipuncture. The samples were immediately kept in crushed ice until they were centrifuged. The blood samples were centrifuged for 15 minutes at 3,000 rpm at 4°C, and the plasma and erythrocytes were separated. The plasma was transferred to clean dry rubber-stoppered test tubes. The erythrocyte samples were washed once with approximately the same volume of cold 0.9% sodium chloride solution by mixing and then centrifugation for another 15 minutes at 3000 rpm at 4°C. The supernatant fluid was discarded to obtain the erythrocytes. The washed erythrocyte and plasma samples were stored at -40°C until the EChE and PChE activities were determined by a modification of Michel's electrometric method (Silvestri,

^dB-D Vacutainer[®], Becton-Dickenson, Rutherford, New Jersey.

1977).

One aliquot of 0.2 ml of plasma or erythrocytes sample was added to 3 ml of distilled water in a 10 ml beaker and mixed. Erythrocyte solutions were hemolyzed by incubation for 10 minutes at room temperature. Three ml of the buffer (pH 8.10) were added, mixed and incubated in a 37°C water bath for 10 minutes. At the end of 10 minutes the pH value of the sample was measured with a glass electrode using a Corning pH meter^e, to the nearest 0.01 pH unit (pH₁). One aliquot of 0.12 ml of a 7.5% acetylcholine iodide aqueous solution was added to the mixture, mixed and incubated in the water bath at 37°C for 30 minutes. The pH (pH₂) of the reaction mixture was measured at the end of 30 minutes. The change in the pH representing the enzymatic activity ($\Delta\text{pH}/30$ minutes at 37°C) was calculated:

$$\Delta\text{pH} = \text{pH}_1 - \text{pH}_2 - \text{pH}(\text{control})$$

The assay was conducted in duplicates. A control to which no acetylcholine iodide solution was added was also included.

Total plasma protein values (gm/100 ml) were determined with a clinical refractometer^f.

6. Statistical Analysis of Data:

An analysis of variance and least square analysis were used for all the groups.

^eCorning Digital 109, general purpose pH meter.

^fNational Instrument, Baltimore, Maryland.

IV. RESULTS

Experiment I

Clinical Signs of Toxicity: When compared to the control groups A₄ and B₄ there was no observable adverse effects of phenothiazine anthelmintic treatment alone on the behavior of the lambs in groups A₃ and B₃ over the period of the trial (table 12). In contrast, following each Ciovap[®] spray application (table 12) signs of toxicity were observed within 40 minutes in 20% to 60% of lambs that received only Ciovap[®] (groups A₂ and B₂), and within 30 minutes in 20% to 80% of lambs that received concurrent phenothiazine treatment (groups A₁ and B₁). The affected lambs were from both parasitized A₁ and A₂, and nonparasitized B₁ and B₂ groups.

In the affected groups (A₁, A₂, B₁, and B₂) the severity of the signs of toxicity varied from one lamb to another, but qualitatively the signs were characteristic of cholinesterase inhibition. There were no observable differences in the qualitative signs of Ciovap[®] toxicity between affected groups A₁, A₂, B₁, and B₂. Affected lambs were restless and manifested respiratory distress (dyspnea) with mucous nasal discharge. Muscular fasciculation and tremors were seen along the abdominal muscles and hind limbs. Frequent urination and/or defecation accompanied with straining were seen during Ciovap[®]

TABLE 12

MEAN TIME OF ONSET OF CLINICAL SIGNS OF TOXICITY
AND THE NUMBER OF LAMBS AFFECTED AFTER CIOVAP[®]
AND/OR PHENOTHIAZINE ANTHELMINTIC TREATMENT.

Group	Treatment	Number of Ciovap [®] Application	Mean Time of Onset of Signs (minutes)	Number of Lambs Affected
Clinical Parasitism				
A ₁	Ciovap [®] & Phenothiazine	1	30±9.0*	3
		2	15±10.0	2
		3	25±3.0	3
A ₂	Ciovap [®]	1	10±5.0	2
		2	40	1
		3	10±3.0	3
A ₃	Phenothiazine	0	0	0
No Clinical Parasitism				
B ₁	Ciovap [®] & Phenothiazine	1	12±3.0	4
		2	11	1
		3	15±5.0	3
B ₂	Ciovap [®]	1	30±10.0	2
		2	30	1
		3	26	1
B ₃	Phenothiazine	0	0	0

*±SEM

toxicity. As the signs of toxicity progressed, some of the affected lambs suffered from muscular weakness which was manifested as difficulty in supporting body weight on the hind limbs (figure 1), and ataxic gait. Consequently, some of the affected lambs became depressed (figure 2), hypokinetic, weak, and recumbent. Twenty-four hours following Ciovap[®] spray, some lambs still manifested mild signs of straining during defecation or urination, diarrhea or anorexia. Generally these toxic signs gradually disappeared within 2-3 days except in one lamb (group B₁) which became progressively depressed, emaciated and recumbent after the third Ciovap[®] spray. The lamb developed respiratory complications (dyspnea and extensive nasal discharges) and died on the fifth day following the third Ciovap[®] application.

Mortality and Necropsy Findings: Two lambs died, one from group A₃ on day 4, and another lamb from group B₃ on day 8 of the trial from causes unrelated to the study. Pleuropneumonia and extensive thoracic adhesions were seen following necropsy examinations of the lambs. One lamb died from group B₁ 5 days following the third Ciovap[®] spray. Necropsy examination of the group B₁ lamb indicated congestion of the tracheal and laryngeal mucosal lining with petechial hemorrhages (figure 3). The lungs and liver were congested. There were lesions of pleuropneumonia with extensive thoracic adhesions. Extensive petechial hemorrhages were seen on the myocardium and myocardial membranes

Figure 1: Lordosis in a lamb from group A₂ manifesting difficulty in supporting body weight on the hind limbs (one hour after the first Ciovap[®] spray in experiment I).

Figure 2a-2b: Signs of depression in some group A₁
(figure 2a) and B₁ (figure 2b) lambs after
Ciovap[®] spray.

2-a

2-b

Figure 3: Congestion and petechial hemorrhages in the mucosal lining of the larynx and trachea of a lamb (group B₁) which died 5 days after the third Ciovap[®] spray (experiment I).

(figure 4). Hemorrhagic areas in the mucosal lining of the small and large intestine, and congested areas on the rumen serosal membrane were also seen.

Erythrocyte Cholinesterase (EChE) Activity: The long-term treatment effects on the EChE activity of the parasitized and nonparasitized lambs are shown in figures 5 and 6 respectively. The EChE activities measured weekly of groups A₁ and A₂ lambs were significantly decreased from those of the phenothiazine treated group (A₃) and the untreated control group (A₄) following each of three applications of Ciovap[®] (figure 5). Similarly, the EChE activities of lambs in groups B₁ and B₂ were significantly decreased from those of groups B₃ and B₄ (figure 6). The extent of EChE inhibition between parasitized (A₁ and A₂) and nonparasitized (B₁ and B₂) groups was not significantly different.

Concurrent phenothiazine anthelmintic administration to groups A₁ and B₁ did not significantly change the extent of EChE inhibition from the Ciovap[®] treated groups A₂ and B₂. Phenothiazine treatment alone (groups A₃ and B₃) did not significantly change EChE activities from their respective control values (A₄ and B₄).

The short term effect of each of three Ciovap[®] applications on EChE activities of (A₁, A₂, B₁, and B₂) lambs is shown in figure 7. The inhibition of EChE activities was most significantly different from the phenothiazine

Figure 4: Severe petechial hemorrhages on the myocardium and myocardial membranes of the lamb (group B₁) which died 5 days after the third Ciovap[®] spray (experiment I).

Figure 5: Changes in EChE activities (experiment I) of clinically parasitized lambs treated with Ciovap[®] spray and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except A₃, n=4). The values of week 0 represent average pretreatment levels of 2 successive days prior to treatment. (a) is significantly ($P < 0.05$) different from control (A₄) value. (b) is significantly ($P < 0.05$) different from phenothiazine treated (A₃) value.

Figure 6: Changes in EChE activities (experiment I) of clinically nonparasitized lambs treated with Ciovap[®] spray and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except B₃ and B₁ 5 days after the 3rd Ciovap[®] spray, n=4). The values of week 0 represent average pretreatment levels of 2 successive days prior to treatment. (a) is significantly ($P < 0.05$) different from control (B₄) value. (b) is significantly ($P < 0.05$) different from phenothiazine treated (B₃) value.

Figure 7: The short term treatment effects during experiment I of the three (●1st, ○2nd, ▲3rd) biweekly applications of Ciovap[®] spray on mean EChE activities in clinically parasitized and nonparasitized groups of lambs. Each point represents the mean $\pm$ SEM of 5 lambs (except A₃ and B₃, n=4). The mean EChE activities of the control groups (□A₄, ○B₄) and the phenothiazine treated (■A₃, ●B₃) during the entire time interval are shown at the extreme left of the graph. (a) is significantly ($P < 0.05$) different from control value. (b) is significantly ($P < 0.05$) different from the phenothiazine treated value.

treated or control groups 24 hours following the Ciovap[®] applications. The severity of EChE inhibition increased with each Ciovap[®] spray. In each of the Ciovap[®] treated groups rapid recovery of the inhibited EChE activity occurred within 48 hours following a Ciovap[®] spray. In each case the 6-hour posttreatment level was reestablished. The pretreatment levels of EChE activities, which ranged from 0.65 to 0.72 Δ pH/30 min., of the Ciovap[®] treated lambs were never attained during the posttreatment period (figure 8). They remained consistently lower than pretreatment levels.

Plasma Cholinesterase (PChE) Activity: The treatment effects on PChE activities of the parasitized and nonparasitized lambs are shown in figures 9 and 10. It was noticed that during the trial, the control as well as the treatment values progressively decreased to levels below the pretreatment values.

Relative to PChE activities of the control A₄ and the phenothiazine treated A₃ groups, each of the three Ciovap[®] sprays resulted (within one week of application) in a significant inhibition of PChE activities of group A₁ lambs, while PChE activities of group A₂ lambs were only significantly inhibited after the first and third Ciovap[®] application (figure 9). The PChE activities of concurrently phenothiazine treated lambs (A₁) were significantly lower than those of the Ciovap[®] treated A₂ lambs after the second

Figure 8: The EChE activities during posttreatment period of experiment I after the third Ciovap[®] application of clinically parasitized and nonparasitized lambs. Each point represents the mean $\pm$ SEM of 5 lambs (except B₁, n=4 after day 5). The mean $\pm$ SEM of pretreatment levels of each group are shown at the extreme left of the graph.

Figure 9: Changes in PChE activities (experiment I) of clinically parasitized lambs treated with Ciovap[®] spray and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except A₃, n=4). The values of week 0 represent average pretreatment levels of 2 successive days prior to treatment. (a) is significantly ($P<0.05$) different from control (A₄) value. (b) is significantly ($P<0.05$) different from phenothiazine treated (A₃) value. (c) is significantly ($P<0.05$) different from Ciovap[®] treated (A₂) value.

Figure 10: Changes in PChE activities (experiment I) of clinically nonparasitized lambs treated with Ciovap[®] spray and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except B₃ and B₁ 5 days after the 3rd Ciovap[®] spray; n=4). The values of week 0 represent the average pretreatment levels of 2 successive days prior to treatment. (a) is significantly ($P < 0.05$) different from control (B₄) value. (b) is significantly ($P < 0.05$) different from phenothiazine treated (B₃) value.

Ciovap[®] spray (figure 9). In the nonparasitized lambs, PChE activities of B₁ lambs were significantly inhibited relative to the phenothiazine treated B₃ and control B₄ groups after the first and third Ciovap[®] applications (figure 10). Throughout the trial there was no significant difference between the PChE values of B₂, B₃, and B₄ groups (figure 10). The PChE activities of the B₁ lambs that received concurrent phenothiazine treatment were consistently lower than those of the Ciovap[®] treated B₂ lambs (figure 10).

The extent of PChE inhibition between parasitized and nonparasitized groups was not significantly different (figures 9 and 10).

Total Plasma Protein (TPP) Concentration: The treatment effects on TPP levels of parasitized and nonparasitized lambs are shown in figure 11. Generally, during the trial, parasitized control lambs (A₄) manifested higher TPP values than nonparasitized control (B₄) lambs. Groups A₂ and B₂ lambs that received only the Ciovap[®] treatment manifested a transient but significant decrease in TPP values from the control A₄ and B₄ values respectively. The TPP values of A₂ lambs were only significantly lower than those of the control A₄ values on days 15, 20, 27 and 28 of the treatment period. Similarly, TPP values of B₂ lambs were significantly lower than those of control B₄ values only on days 3, 4, and 30 of the treatment period.

Figure 11: Changes in TPP values (experiment I) of lambs treated with Ciovap[®] (C) and/or phenothiazine anthelmintic (P). Each point represents the mean of 5 lambs (except A₃ and B₃, n=4). The values of day 0 represents average pretreatment levels of 2 successive days prior to treatments. (a) is significantly (P<0.05) different from control value.

The TPP values of B_2 lambs were consistently lower than those of A_2 lambs during the trial.

During the trial, group A_1 and B_1 lambs that received both Ciovap[®] spray and phenothiazine manifested different TPP levels in comparison to control A_4 and B_4 values respectively. Relative to control A_4 TPP values, the A_1 lambs manifested significantly lower TPP concentration on the days shown in figure 11. In contrast, B_1 lambs manifested significantly higher TPP values than the control B_4 lambs.

The TPP values of A_1 lambs tended to be lower than those of A_2 lambs during the trial. The decrease was significant toward the end of the treatment period. In contrast, TPP values of B_2 lambs were significantly lower than the values of B_1 lambs throughout most of the trial period.

Phenothiazine treatment of group A_3 lambs resulted in significantly lower TPP values than those of control A_4 lambs. In contrast, TPP concentrations of B_3 lambs were significantly higher than those of the control B_4 lambs. No significant difference was seen between TPP values of A_3 and B_3 lambs (figure 11).

Weight Gain: When the lambs were weighed 65 days after the initial weighing at the beginning of the trial, all the groups gained weight (table 13). The phenothiazine treated groups A_3 and B_3 , however, gained significantly more body weight than the other groups. There were no

TABLE 13
 MEAN $\pm$ SEM WEIGHT GAIN OF THE LAMBS
 IN 65 DAYS DURING EXPERIMENT I

Group*	Treatment	Mean Weight Gain (lb)
Clinical Parasitism		
A ₁	Ciovap & Phenothiazine	3.7 $\pm$ 1.5
A ₂	Ciovap	5.4 $\pm$ 1.9
A ₃	Phenothiazine	14.4 $\pm$ 5.0 ^{a**}
A ₄	None	7.1 $\pm$ 2.7
No Clinical Parasitism		
B ₁	Ciovap & Phenothiazine	5.6 $\pm$ 1.4
B ₂	Ciovap	5.5 $\pm$ 1.1
B ₃	Phenothiazine	15.0 $\pm$ 3.9 ^a
B ₄	None	4.6 $\pm$ 0.8

* n = 5, except A₃, B₁ and B₃; n = 4

** Mean values not showing the same superscript letter are significantly different (P<0.05).

significant differences in the weight gain among the other groups (table 13).

Experiment II

Clinical Signs of Toxicity: Relative to untreated control A₄ and B₄ lambs, phenothiazine anthelmintic treatment alone (groups A₃ and B₃) had no observable adverse effects on the animal behavior over the period of the trial (table 14).

Similarly, in experiment II, the challenge dose of Ciovap[®] spray application (1 gallon of 0.25% emulsion) produced signs of toxicity in the sprayed lambs (A₁, A₂, B₁, and B₂) (table 14). The signs of toxicity were observed within 16 minutes in 40% to 60% of lambs that received Ciovap[®] alone (A₂ and B₂) and within 18 minutes in 50% to 69% of lambs that received concurrent phenothiazine treatment (A₁ and B₁). The severity of the observed signs of toxicity varied from one lamb to another but they were qualitatively characteristic of ChE inhibition. There was no observable difference in the signs of Ciovap toxicity between the affected groups. Affected lambs were restless, manifested dyspnea with mucous nasal discharge. Frequent urination and/or defecation accompanied with straining were also seen. Some of the lambs became depressed at a later stage of Ciovap[®] toxicity. One to two days following Ciovap[®] spray, some lambs still manifested mild signs of diarrhea, anorexia or depression. These toxic signs

TABLE 14

MEAN TIME OF ONSET OF CLINICAL SIGNS OF TOXICITY
AND THE NUMBER OF LAMBS AFFECTED AFTER
CIOVAP AND/OR PHENOTHIAZINE
ANTHELMINTIC TREATMENT

Group	Treatment	Mean Time of Onset of Signs (Minutes)	No. of Lambs Affected
A ₁	Ciovap & Phenothiazine	18±7.0*	3
A ₂	Ciovap	16±5.0	2
A ₃	Phenothiazine	0	0
B ₁	Ciovap & Phenothiazine	17±2.0	2
B ₂	Ciovap	13±4.0	3
B ₃	Phenothiazine	0	0

*±SEM

gradually disappeared within 2 to 3 days. No mortality occurred during the trial.

Erythrocyte Cholinesterase Activity: The treatment effects of phenothiazine and Ciovap[®] on the EChE activities of the lambs previously used in experiment I are shown in figure 12. A challenge dose of Ciovap[®] spray application significantly decreased the EChE activities of group A₂ lambs relative to values for the phenothiazine treated A₃ and control A₄ groups; while the EChE activities of group A₁ lambs which received concurrent phenothiazine treatment was inhibited to a lesser extent. Compared to the control A₄ values, the EChE activities of A₁ lambs were significantly inhibited on day 3 following Ciovap[®] spray. Similarly, the EChE activities of group B₁ and B₂ lambs were significantly decreased from those of the phenothiazine treated B₃ or control B₄ groups (figure 12). Concurrent phenothiazine treatment (A₁ and B₁) did not significantly change the extent of EChE inhibition from the Ciovap[®] treated A₂ and B₂ lambs.

Phenothiazine administration alone to groups A₃ and B₃ for 3 consecutive days did not significantly change EChE activities from the control values A₄ and B₄ (figure 12).

Plasma Cholinesterase Activities: The treatment effects of phenothiazine and Ciovap[®] on the PChE activities

Figure 12: Changes in EChE activities (experiment II) of lambs treated with Ciovap[®] and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except A₃, B₃, and B₁; n=4). Preexperimental EChE values are shown at the extreme left of the graph. (a) is significantly ($P < 0.05$) different from control value. (b) is significantly ($P < 0.05$) different from phenothiazine treated value.

of the lambs are shown in figure 13. Group A₂ manifested significantly lower PChE activities from the phenothiazine treated A₃ and the control A₄ groups on day 3 following Ciovap[®] spray. No significant changes occurred in PChE activities of group A₁ lambs. One day after Ciovap[®] application, PChE activities of group B₁ lambs were significantly decreased from the values of the phenothiazine treated B₃ or control B₄ groups. Values of B₂ lambs were not significantly different from B₃ and B₄ groups (figure 13). Three days following Ciovap[®] spray, PChE activities of both B₁ and B₂ lambs became significantly decreased from control values (B₄).

Prior administration of phenothiazine to groups A₁ and B₁ lambs for 3 consecutive days did not significantly affect the extent of PChE inhibition relative to the values of the Ciovap[®] treated A₂ and B₂ lambs (figure 13).

Phenothiazine administration alone for 3 consecutive days (A₃ and B₃) did not significantly change PChE activities from the values of control (A₄ and B₄) lambs as seen 24 hours after the last phenothiazine dose (figure 13). On the third day after the last phenothiazine dose, PChE activities of only groups (B₃) lambs were significantly lower than the control (B₄) values (figure 13).

Total Plasma Protein (TPP) Concentration: The treatment effect on TPP levels of both the major groups (A & B) lambs are shown in figure 14. Similar to experiment I,

Figure 13: Changes in PChE activities (experiment II) of lambs treated with Ciovap[®] and/or phenothiazine anthelmintic. Each point represents the mean $\pm$ SEM of 5 lambs (except A₃, B₃, B₁; n=4). Preexperimental PChE values are shown at the extreme left of the graph. (a) is significantly ($P < 0.05$) different from control value. (b) is significantly ($P < 0.05$) different from phenothiazine treated value.

DAYS AFTER GIOVAP SPRAY APPLICATION

Figure 14: Changes in TPP levels (experiment II) of the lambs treated with Ciovap[®] and/or phenothiazine anthelmintic. Each point represents the mean of 5 lambs (except A₃, B₁, B₃; n=4). Preexperimental TPP values are shown at the extreme left of the graph. (a) is significantly different from the respective control value (P<0.05).

control A₄ lambs manifested higher TPP levels than those of B₄ control lambs. The single Ciovap[®] spray alone to groups A₂ and B₂ did not significantly change TPP concentration from control A₄ and B₄ lambs respectively (figure 14). During the experiment TPP values of B₂ lambs were consistently lower than those of A₂ lambs (figure 14).

In this experiment, group A₁ and B₁ lambs that received both Ciovap[®] spray and phenothiazine manifested different TPP levels relative to those of control A₄ and B₄ lambs respectively (figure 14). In comparison to control A₄ TPP values, A₁ lambs showed lower TPP concentrations which became significantly low on day 3 after Ciovap[®] spray (figure 14). In contrast, throughout the experiment, B₁ lambs manifested higher TPP values than those of control B₄ lambs. The TPP values of A₁ lambs were consistently but not significantly lower than those of A₂ lambs, whereas TPP values of B₁ lambs were significantly higher than those of B₂ lambs (figure 14).

Group A₃ lambs that received phenothiazine alone manifested significantly lower TPP values than those of control A₄ lambs (figure 14). In contrast, TPP of B₃ lambs that received phenothiazine alone were significantly higher than control B₄ values on day 1 after the last phenothiazine dosage (figure 14). These values of TPP became lower on day 3 with no significant difference from control B₄ lambs.

V. DISCUSSION AND CONCLUSION

Experiment I

Clinical Signs of Toxicity: Ciovap[®] spray applications of 1550 ml/lamb/2 weeks for 3 applications (table 11) produced signs of toxicity characteristic of ChE inhibition. Some of the Ciovap[®] sprayed lambs, however, did not manifest any observable signs of toxicity (table 12). Individual differences within an animal species in response to organophosphorus toxicity are not unexpected (Khan, 1973). There were no differences in the signs of Ciovap[®] toxicity between parasitized (A_1 and A_2) and nonparasitized (B_1 and B_2) lambs. This could be due to the fact that the clinically parasitized lambs were in good physical condition throughout the trial, and no adverse effects were seen due to parasitism. The weight gain of the parasitized lambs were also comparable to those of nonparasitized ones (table 13).

Combinations of phenothiazine anthelmintic and organophosphorus compounds were reported to act synergistically as endoparasitocides in sheep (Kingsbury, 1961). Phenothiazine tranquilizers, however, are well known potentiators of organophosphorus compounds in several animal species such as man (Arterberry et al., 1962), rat (Gaines, 1962; Michalek and Stavinoha, 1978), and sheep (Gopal et al., 1976). In this study, however, the concurrent administration of phenothiazine anthelmintic with Ciovap[®] sprays

did not potentiate the Ciovap[®] toxicity in the lambs (table 12). Schlinke and Palmer (1973) also observed no potentiation of toxicity when phenothiazine anthelmintic was used concurrently with a variety of organophosphorus insecticide sprays in calves. Similarly, Malone (1962) found no potentiation in sheep when phenothiazine anthelmintic and organophosphorus pesticide combinations were administered orally.

Phenothiazine anthelmintic treatments alone did not produce any observable adverse effects in A₃ and B₃ lambs over the period of the trial. This was not surprising since sheep are highly resistant to phenothiazine anthelmintic toxicity (Clarke and Clarke, 1967; Buck *et al.*, 1976a). Severe stress factors such as debilitating diseases and dehydration, however, may enhance the toxicity of phenothiazine anthelmintic in sheep (Koch, 1963; Salisbury, 1969; Salisbury *et al.*, 1969). It is possible, therefore, that in this study the two lambs which died from the phenothiazine treated groups A₃ and B₃ at the beginning of the experiment were under severe stress as judged by their extensive pleuropneumonic conditions seen upon necropsy examination.

Erythrocyte Cholinesterase (EChE) Activity: Significant inhibition of EChE activity was an important feature of Ciovap[®] spray applications (figures 5, 6). There was no significant difference in the extent of EChE inhibition

between the parasitized and nonparasitized groups. This lack of differential effect may be due to the fact that the parasitized lambs were in good physical condition and did not show any of the adverse clinical effects associated with severe parasitism. Severe parasitism can stimulate malnutrition. Rats (Natoff, 1971) and sheep (Gopal et al., 1976) fed protein deficient diet were observed to be hyperreactive to organophosphorus toxicity.

Concurrent phenothiazine administration did not potentiate the EChE inhibition caused by Ciovap[®] applications. Furthermore, phenothiazine treatments alone did not inhibit EChE activity. These results are in agreement with previous reports concerning the nonpotentiating effect of phenothiazine anthelmintic in sheep and calves concurrently treated with organophosphorus insecticides (Malone, 1962; Schlinke and Palmer, 1973).

Maximum inhibition of EChE activity occurred 24 hours following each of the three Ciovap[®] sprays. Significant recovery of the inhibited EChE activity occurred rapidly within 48 hours following the Ciovap[®] sprays. This period seemed to correspond to the time (2-3 days) required for the Ciovap[®] sprayed lambs to recover from clinical signs of Ciovap[®] toxicosis. Recovery of the inhibited EChE by organophosphorus compounds was reported to occur in two phases (Silvestri, 1975; Gopal et al., 1976). A rapid recovery phase was shown to occur in a short period of time after exposure to the organophosphorus compound

because of the spontaneous hydrolysis of the enzyme-organophosphorus complex. The prolonged recovery phase was attributed to the synthesis of new erythrocytes. This process may last up to 120 days or more depending on the extent of enzymatic inhibition. In this experiment complete recovery of pretreatment EChE levels of the Ciovap[®] treated lambs was not attained during the posttreatment period which lasted only 30 days.

Plasma Cholinesterase (PChE) Activity: During the trial, the PChE activities of all the control as well as all the treatment groups progressively decreased to levels below the pretreatment values (figures 9 and 10). Morizono and Kaba (1977) reported that storage of serum samples from cattle at -20°C for a 9 week period of time decreased serum ChE activity up to 5% (table 15). In this study the samples were stored at -40°C for 13 weeks or until they were assayed for the ChE activity. It is possible, however, that early experimental factors (e.g. initial stressors) and not storage alone were causative in lowering the PChE activities of all the groups. It is therefore difficult to attribute the reduction of PChE activities of all the groups solely to the longer storage period used in this study.

Ciovap[®] sprays significantly inhibited PChE activities of the parasitized A₂ lambs, whereas those of the nonparasitized B₂ lambs were not significantly different from control values. This difference in susceptibility to the ChE

TABLE 15

REDUCTION IN SChE* ACTIVITY AFTER STORING AT LOW TEMPERATURES

Species	Esterase	Storage Temp.	Duration of Storage	% Reduction	Reference
Horse, Dog	SChE	-20°C	9 weeks	no change	Morizono and Kaba, 1977
Cattle, Swine, Cat	SChE	-20°C	9 weeks	2-5%	
Horse	SChE	-17°C	8 weeks	13%	Schindler and Kruckenberg, 1972
	SChE	-17°C	12 weeks	56%	

* SChE - serum cholinesterase

inhibitory action of Ciovap[®] between A₂ and B₂ lambs could be due to the fact that A₂ lambs were clinically parasitized, although in good physical condition; and the disease condition enhanced the susceptibility of the animal to organophosphorus toxicity (Khan, 1973). Group A₁ and B₁ lambs which received both phenothiazine and Ciovap[®], however, manifested significantly decreased PChE activities from respective control values. Concurrent phenothiazine treatments did not potentiate PChE inhibition of A₁ and B₁ lambs, except after the second Ciovap spray when the PChE of A₁ lambs were significantly lower than those of A₂ lambs. However, no significant differences were seen in the signs of Ciovap[®] toxicity between the A₁ and A₂ lambs.

Relative to PChE activities of the control groups A₄ and B₄, the variations in the PChE activities of the phenothiazine treated A₃ and B₃ lambs could not be attributed to phenothiazine treatment.

Weight Gain: The phenothiazine treated groups A₃ and B₃ significantly gained more weight than did the other treatment and control groups (table 13). With the exception of groups A₃ and B₃ the remaining groups were similar in their weight gains. The significance of these observations are presently unknown. Increased weight gain and increased appetite, however, have been associated with the use of phenothiazine tranquilizers in man (Pfister, 1978; Mathues et al., 1959; Gordon, 1967; Byck, 1975). Varshney

and Singh (1976) found that the use of phenothiazine anthelmintic in growing lambs was associated with increased body weight gain. Similarly, Allen and Oldfield (1959) reported significant weight gain and improved carcass quality in parasitized lambs treated with phenothiazine anthelmintic. In contrast, Cauthen (1957) observed in one experiment that moderately parasitized calves treated with various phenothiazine formulations for more than 121 days gained approximately 14% less weight than the parasitized untreated calves. However, when Cauthen (1952) fed small amounts of phenothiazine daily to parasitized cows for 3 consecutive years, he observed no significant differences in weight gain between treated and untreated groups. Other than a beneficial antiparasitic effect of phenothiazine anthelmintic, it is difficult to postulate a mechanism for the increased weight gain of the phenothiazine treated animals.

Total Plasma Protein (TPP): During the trial parasitized A₄ lambs manifested higher TPP levels than the nonparasitized B₄ lambs. This difference could be due to the mildness of the parasitic infection of A₄ lambs. The parasitized lambs in this study, however, were in good physical condition, and did not show any adverse clinical effects due to parasitism. Debilitated and chronically parasitized lambs, however, have been shown to manifest lower TPP levels (Sheriff and Habel, 1976).

The pattern of fluctuation of TPP levels associated

with the Ciovap , phenothiazine or Ciovap and phenothiazine treated groups could not be meaningfully interpreted although temporal significant changes were observed (figure 11). High doses of phenothiazine anthelmintic were reported to decrease serum albumin levels in cattle, especially in animals on low protein ration (Ross, 1959). Snow and Watson (1973) reported that dichlorvos increased TPP levels of the adult dog. In contrast no changes were seen in the TPP levels of puppies and cats treated with dichlorvos (Grey, 1974). Vorob'eva and Lapchenko (1973) observed that daily administration of crotoxyphos to dogs for 30 days decreased serum albumin level and increased globulin level. Therefore, determination of the individual components of the plasma proteins should clarify this aspect.

Experiment II

Thirty-two days following the third Ciovap[®] application in experiment I, a challenge dose of Ciovap[®] (1 gallon of 0.25% emulsion) did not significantly increase the toxicosis more than that observed during experiment I.

The EChE activities of Ciovap[®] sprayed lambs were significantly decreased. The extent of inhibition, however, was less than that observed after the third Ciovap[®] spray in experiment I. The time period allowed between the last Ciovap[®] application in experiment I and this experiment exceeded the 4 week period during which the Ciovap[®] exposed lambs allowed to recover from any drug induced adverse

effects. The truism of this observation is emphasized by the fact that the EChE activities also recovered from the severe inhibition seen after the last Ciovap[®] spray in experiment I. The clinical significance of this observation is that a relatively longer unmedicated period (more than 2 weeks) is needed between subsequent Ciovap[®] applications.

Phenothiazine anthelmintic administration as a mixture in feed for 3 consecutive days did not potentiate Ciovap[®] toxicity, EChE or PChE inhibition. Phenothiazine treatment alone did produce any observable adverse effects in the treated lambs.

Conclusions

There was no apparent potentiation of Ciovap[®] toxicity in the lambs by concurrent phenothiazine anthelmintic administrations.

Clinical parasitism with Haemonchus and Trichostrongylus species was not a factor in Ciovap[®] toxicity, since the parasitized lambs were in good physical condition, and they did not show any observable adverse clinical effects associated with parasitism.

A nonmedicated period of at least 2 weeks should be allowed between subsequent Ciovap[®] sprays because of the increased inhibition of EChE activity after each Ciovap[®] application. Erythrocyte cholinesterase activity was the

best indicator of an animal's exposure to Ciovap®.

Under field conditions phenothiazine anthelmintic treatment of gastrointestinal parasitic infection could be practiced concurrently with topical application of organophosphorus insecticides to control external parasites. This is because of the economy and convenience of the practice.

VI. SUMMARY

The temporal interaction of the organophosphorus insecticide (Ciovap®) and phenothiazine anthelmintic was studied in 8 groups of 5 lambs, clinically free from or parasitized with Haemonchus and Trichostrongylus spp. In the first experiment each lamb in one of 3 parasitized groups and one of 3 nonparasitized groups was treated with phenothiazine orally (12.5 gm initially and 4 days later with 6.25 gm every 3 days for 9 treatments), or Ciovap® dermally (1550 ml of 0.25% emulsion sprayed every 2 weeks for 3 applications) or with both. Two groups served as controls. Onset of clinical signs, lethality, plasma cholinesterase (PChE) and erythrocyte cholinesterase (EChE) activities, and total plasma protein (TPP) levels were monitored. Following each Ciovap® spray signs of toxicity were seen within 40 minutes in both parasitized and nonparasitized lambs regardless of concurrent phenothiazine treatment. Phenothiazine alone was not toxic and did not inhibit PChE or EChE activities. EChE activities of Ciovap® sprayed lambs were significantly depressed regardless of parasitism or concurrent phenothiazine treatment. Transient but significant reduction of TPP levels occurred in the groups that just received Ciovap®. Thirty days following the last Ciovap® spray in experiment I, the same groups of lambs were used in experiment II and were either sprayed with 1 gallon of 0.25% Ciovap® emulsion

or treated orally with phenothiazine anthelmintic (54% active ingredient) 1 gm/lamb/day for 3 days mixed in the feed, or with both. Signs of toxicity were seen within 18 minutes in all the groups sprayed with Ciovap[®]. Phenothiazine alone was not toxic. Significant inhibition of EChE and PChE activities occurred in the Ciovap[®] treated groups.

Data suggested no apparent potentiation of Ciovap[®] toxicity by concurrent phenothiazine anthelmintic treatment. EChE inhibition was a better index of exposure to Ciovap[®] than PChE.

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APPENDIX

TABLE 16: PRE- AND POSTTREATMENTS ERYTHROCYTE CHOLINESTERASE ACTIVITY* (Δ pH/30 MIN)
OF THE PARASITIZED (A) AND NONPARASITIZED (B) LAMBS.

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
-1 *	0.72±0.03	0.69±0.03	0.73±0.01	0.67±0.03	0.72±0.02	0.68±0.04	0.67±0.04	0.66±0.02
α	0.64-0.80	0.61-0.79	0.69-0.76	0.57-0.76	0.68-0.77	0.57-0.80	0.53-0.76	0.59-0.70
0 *	0.71±0.03	0.68±0.03	0.72±0.01	0.65±0.01	0.72±0.01	0.70±0.03	0.69±0.04	0.65±0.02
α	0.63-0.77	0.62-0.78	0.68-0.76	0.58-0.72	0.68-0.75	0.61-0.79	0.56-0.74	0.60-0.70
1 *	0.62±0.03	0.58±0.02	0.71±0.03	0.67±0.04	0.56±0.01	0.63±0.03	0.66±0.04	0.66±0.02
α	0.55-0.69	0.50-0.65	0.62-0.76	0.56-0.79	0.50-0.59	0.55-0.70	0.52-0.73	0.61-0.70
2 *	0.55±0.03	0.53±0.02	0.68±0.04	0.66±0.03	0.54±0.02	0.57±0.03	0.66±0.04	0.65±0.02
α	0.48-0.67	0.49-0.60	0.61-0.86	0.60-0.75	0.50-0.58	0.50-0.65	0.54-0.75	0.58-0.71
3 *	0.58±0.03	0.57±0.01	0.65±0.05	0.66±0.02	0.59±0.02	0.58±0.03	0.64±0.04	0.63±0.02
α	0.51-0.66	0.54-0.60	0.56-0.87	0.58-0.73	0.54-0.68	0.50-0.66	0.52-0.74	0.55-0.67
4 *	0.62±0.03	0.61±0.03	0.66±0.02	0.67±0.05	0.59±0.04	0.59±0.04	0.65±0.05	0.64±0.02
α	0.53-0.70	0.56-0.70	0.61-0.70	0.49-0.78	0.54-0.73	0.50-0.69	0.50-0.77	0.53-0.69
6 *	0.61±0.04	0.60±0.03	0.75±0.03	0.64±0.04	0.57±0.04	0.59±0.03	0.63±0.04	0.67±0.03
α	0.50-0.71	0.53-0.67	0.66-0.81	0.56-0.77	0.45-0.67	0.53-0.72	0.52-0.73	0.61-0.76
7 *	0.62±0.05	0.61±0.02	0.71±0.04	0.62±0.03	0.59±0.03	0.64±0.05	0.60±0.03	0.62±0.02
α	0.48-0.75	0.53-0.67	0.60-0.82	0.51-0.66	0.52-0.72	0.51-0.82	0.51-0.67	0.54-0.66
9 *	0.64±0.07	0.58±0.04	0.71±0.04	0.66±0.04	0.59±0.04	0.63±0.05	0.59±0.03	0.61±0.03
α	0.43-0.80	0.44-0.66	0.62-0.81	0.54-0.76	0.50-0.74	0.52-0.78	0.52-0.66	0.52-0.67

* Mean ±SEM of each group.

α The range of each group.

Cvp & Phetz = Ciovap and Phenothiazine

Continued pg 1 of 4

TABLE 16 pg 2 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
10 *	0.66±0.03	0.60±0.01	0.69±0.03	0.67±0.02	0.62±0.04	0.67±0.07	0.67±0.07	0.60±0.04
α	0.58-0.73	0.57-0.63	0.63-0.77	0.61-0.73	0.52-0.76	0.53-0.87	0.50-0.81	0.48-0.67
11 *	0.60±0.03	0.56±0.02	0.67±0.04	0.67±0.03	0.60±0.05	0.65±0.08	0.60±0.08	0.61±0.02
α	0.52-0.69	0.52-0.62	0.58-0.76	0.60-0.75	0.44-0.72	0.41-0.88	0.48-0.72	0.57-0.64
13 *	0.60±0.03	0.57±0.02	0.69±0.04	0.65±0.04	0.54±0.04	0.62±0.06	0.63±0.05	0.62±0.02
α	0.50-0.69	0.50-0.62	0.58-0.72	0.53-0.72	0.48-0.67	0.47-0.86	0.50-0.70	0.54-0.65
14 *	0.61±0.04	0.56±0.03	0.71±0.04	0.61±0.03	0.54±0.04	0.55±0.06	0.59±0.05	0.54±0.03
α	0.52-0.73	0.50-0.63	0.60-0.80	0.54-0.70	0.42-0.62	0.43-0.76	0.44-0.69	0.46-0.61
15 *	0.58±0.04	0.54±0.02	0.64±0.03	0.60±0.03	0.53±0.03	0.58±0.05	0.58±0.06	0.56±0.02
α	0.48-0.68	0.50-0.58	0.58-0.71	0.51-0.66	0.48-0.62	0.46-0.77	0.42-0.70	0.52-0.63
16 *	0.40±0.04	0.33±0.02	0.68±0.03	0.62±0.03	0.32±0.04	0.35±0.06	0.63±0.04	0.58±0.04
α	0.27-0.48	0.30-0.37	0.61-0.74	0.52-0.70	0.20-0.40	0.20-0.52	0.55-0.71	0.48-0.72
17 *	0.59±0.04	0.55±0.03	0.68±0.03	0.62±0.03	0.51±0.03	0.56±0.03	0.60±0.05	0.59±0.02
α	0.47-0.73	0.50-0.65	0.59-0.75	0.53-0.66	0.43-0.61	0.50-0.68	0.47-0.68	0.54-0.63
20 *	0.56±0.05	0.57±0.03	0.70±0.05	0.59±0.02	0.52±0.03	0.59±0.05	0.66±0.03	0.57±0.01
α	0.45-0.65	0.49-0.66	0.61-0.83	0.54-0.63	0.43-0.61	0.48-0.75	0.57-0.69	0.53-0.62
21 *	0.56±0.03	0.53±0.02	0.68±0.03	0.63±0.04	0.52±0.03	0.57±0.05	0.62±0.04	0.56±0.02
α	0.49-0.68	0.47-0.60	0.63-0.76	0.51-0.74	0.44-0.60	0.46-0.76	0.51-0.67	0.50-0.59
22 *	0.58±0.03	0.55±0.03	0.69±0.03	0.60±0.03	0.51±0.03	0.59±0.06	0.60±0.03	0.58±0.03
α	0.49-0.68	0.47-0.61	0.61-0.78	0.52-0.66	0.41-0.60	0.46-0.80	0.50-0.65	0.48-0.65
23 *	0.55±0.04	0.53±0.02	0.63±0.04	0.62±0.04	0.53±0.02	0.58±0.05	0.61±0.07	0.58±0.02
α	0.43-0.68	0.47-0.61	0.56-0.71	0.52-0.74	0.46-0.60	0.45-0.75	0.41-0.69	0.50-0.62

* Mean ±SEM of each group; α Range of each group; Cvp & Phetz = Ciovap & Phenothiazine

TABLE 16 pg 3 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
24 *	0.59±0.04	0.53±0.01	0.65±0.04	0.62±0.02	0.51±0.03	0.58±0.06	0.64±0.06	0.56±0.03
α	0.53-0.71	0.50-0.56	0.55-0.73	0.56-0.66	0.42-0.56	0.46-0.71	0.50-0.70	0.49-0.64
27 *	0.59±0.03	0.56±0.02	0.72±0.03	0.69±0.02	0.57±0.03	0.59±0.05	0.63±0.05	0.54±0.03
α	0.50-0.67	0.51-0.61	0.65-0.79	0.65-0.74	0.48-0.66	0.47-0.78	0.51-0.73	0.44-0.62
28 *	0.61±0.03	0.59±0.02	0.70±0.02	0.67±0.02	0.62±0.02	0.63±0.05	0.63±0.05	0.58±0.03
α	0.53-0.70	0.53-0.62	0.66-0.73	0.65-0.73	0.59-0.68	0.50-0.80	0.50-0.72	0.50-0.63
29 *	0.56±0.04	0.46±0.02	0.69±0.02	0.63±0.03	0.45±0.04	0.56±0.06	0.60±0.04	0.56±0.04
α	0.48-0.66	0.40-0.52	0.64-0.73	0.52-0.70	0.37-0.60	0.40-0.72	0.49-0.69	0.44-0.65
30 *	0.36±0.04	0.29±0.02	0.71±0.03	0.64±0.02	0.26±0.04	0.37±0.05	0.65±0.04	0.59±0.03
α	0.24-0.43	0.21-0.33	0.67-0.77	0.58-0.72	0.18-0.35	0.25-0.51	0.51-0.72	0.51-0.69
31 *	0.52±0.02	0.47±0.03	0.67±0.05	0.64±0.03	0.46±0.03	0.50±0.05	0.57±0.04	0.54±0.02
α	0.47-0.57	0.38-0.52	0.63-0.84	0.58-0.74	0.36-0.56	0.37-0.66	0.45-0.64	0.49-0.63
34 *	0.52±0.04	0.47±0.02	0.68±0.04	0.64±0.02	0.48±0.02	0.53±0.05	0.58±0.04	0.53±0.02
α	0.42-0.61	0.41-0.52	0.60-0.75	0.58-0.72	0.40-0.54	0.42-0.67	0.47-0.65	0.47-0.56
37 *	0.57±0.03	0.51±0.03	0.66±0.03	0.61±0.03	0.50±0.04	0.55±0.05	0.64±0.05	0.55±0.03
α	0.51-0.63	0.41-0.57	0.62-0.73	0.49-0.67	0.41-0.58	0.43-0.67	0.49-0.71	0.48-0.64
41 *	0.61±0.02	0.55±0.02	0.69±0.02	0.66±0.03	0.49±0.05	0.57±0.05	0.65±0.06	0.57±0.03
α	0.52-0.66	0.50-0.66	0.65-0.75	0.55-0.74	0.40-0.59	0.45-0.70	0.48-0.74	0.49-0.63
44 *	0.63±0.03	0.54±0.03	0.70±0.01	0.66±0.03	0.52±0.04	0.57±0.05	0.66±0.05	0.55±0.02
α	0.52-0.67	0.48-0.60	0.67-0.73	0.55-0.75	0.43-0.61	0.46-0.70	0.52-0.73	0.49-0.62
48 *	0.63±0.03	0.58±0.02	0.68±0.02	0.65±0.03	0.55±0.02	0.60±0.04	0.68±0.05	0.60±0.02
α	0.50-0.68	0.53-0.64	0.64-0.73	0.54-0.69	0.51-0.58	0.47-0.71	0.52-0.75	0.53-0.66

* Mean ±SEM of each group; α Range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 16 pg 4 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
51 *	0.61±0.04	0.59±0.02	0.68±0.03	0.64±0.02	0.51±0.04	0.56±0.05	0.68±0.07	0.59±0.02
α	0.49-0.66	0.55-0.63	0.63-0.76	0.57-0.68	0.40-0.58	0.45-0.72	0.53-0.81	0.55-0.65
55 *	0.59±0.03	0.50±0.02	0.61±0.04	0.59±0.03	0.49±0.03	0.54±0.04	0.64±0.02	0.55±0.02
α	0.49-0.64	0.45-0.55	0.54-0.71	0.49-0.65	0.43-0.57	0.42-0.64	0.57-0.67	0.50-0.60
58 *	0.60±0.03	0.51±0.02	0.60±0.02	0.60±0.03	0.51±0.01	0.57±0.03	0.59±0.05	0.53±0.01
α	0.49-0.66	0.47-0.58	0.55-0.66	0.50-0.65	0.49-0.54	0.49-0.67	0.46-0.67	0.49-0.55
63 *	0.52±0.03	0.45±0.02	0.61±0.03	0.60±0.03	0.40±0.02	0.45±0.04	0.58±0.04	0.55±0.03
α	0.42-0.58	0.40-0.48	0.56-0.68	0.47-0.65	0.36-0.44	0.33-0.56	0.47-0.62	0.46-0.64
65 *	0.47±0.03	0.44±0.02	0.55±0.03	0.60±0.02	0.35±0.02	0.33±0.04	0.54±0.03	0.57±0.03
α	0.40-0.57	0.37-0.48	0.50-0.61	0.54-0.66	0.30-0.40	0.24-0.44	0.48-0.63	0.52-0.68
80 *	0.66±0.05	0.57±0.02	0.69±0.03	0.68±0.04	0.53±0.03	0.57±0.04	0.68±0.08	0.61±0.03
α	0.48-0.74	0.48-0.60	0.64-0.77	0.54-0.75	0.45-0.57	0.45-0.69	0.45-0.76	0.52-0.66

* Mean ±SEM of each group; α Range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 17: PRE- AND POSTTREATMENTS PLASMA CHOLINESTERASE ACTIVITY (Δ pH/30 MIN)
OF THE PARASITIZED (A) AND NONPARASITIZED (B) LAMBS.

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
-1 *	0.19±0.01	0.18±0.01	0.17±0.02	0.18±0.02	0.18±0.01	0.19±0.01	0.17±0.01	0.20±0.02
α	0.16-0.21	0.14-0.21	0.11-0.22	0.12-0.21	0.16-0.20	0.16-0.21	0.14-0.20	0.16-0.25
0 *	0.13±0.02	0.10±0.02	0.12±0.02	0.14±0.02	0.12±0.01	0.14±0.02	0.13±0.01	0.14±0.02
α	0.08-0.18	0.09-0.18	0.08-0.18	0.09-0.18	0.09-0.15	0.10-0.18	0.09-0.17	0.10-0.18
1 *	0.14±0.004	0.14±0.01	0.17±0.02	0.19±0.01	0.13±0.01	0.16±0.01	0.15±0.01	0.18±0.02
α	0.13-0.15	0.10-0.17	0.12-0.20	0.16-0.21	0.10-0.14	0.12-0.20	0.12±0.19	0.13-0.22
2 *	0.11±0.01	0.09±0.005	0.15±0.01	0.17±0.01	0.12±0.01	0.15±0.01	0.15±0.01	0.15±0.01
α	0.09-0.14	0.08-0.11	0.10-0.17	0.13-0.20	0.09-0.14	0.12-0.17	0.12-0.20	0.14-0.19
3 *	0.12±0.01	0.11±0.01	0.14±0.01	0.16±0.02	0.12±0.01	0.13±0.01	0.13±0.01	0.16±0.01
α	0.09-0.15	0.09-0.14	0.11-0.15	0.09-0.21	0.10-0.14	0.11-0.15	0.09-0.16	0.12-0.21
4 *	0.12±0.01	0.12±0.01	0.14±0.01	0.17±0.01	0.11±0.01	0.14±0.01	0.15±0.01	0.16±0.01
α	0.10-0.14	0.10-0.13	0.10-0.16	0.14-0.20	0.08-0.14	0.11-0.18	0.08-0.16	0.13-0.18
6 *	0.12±0.005	0.13±0.004	0.16±0.01	0.15±0.02	0.16±0.01	0.12±0.01	0.13±0.01	0.15±0.01
α	0.10-0.13	0.12-0.14	0.13-0.18	0.09-0.18	0.13-0.17	0.10-0.14	0.08-0.14	0.11-0.18
7 *	0.09±0.02	0.16±0.01	0.16±0.01	0.13±0.01	0.13±0.01	0.16±0.01	0.14±0.02	0.14±0.01
α	0.04-0.14	0.13-0.21	0.13-0.18	0.11-0.15	0.10-0.14	0.15-0.19	0.10-0.19	0.10-0.17
9 *	0.12±0.01	0.10±0.01	0.12±0.02	0.11±0.01	0.10±0.01	0.13±0.01	0.12±0.004	0.08±0.01
α	0.10-0.13	0.08-0.14	0.06-0.16	0.09-0.13	0.08-0.13	0.11-0.15	0.12-0.13	0.07-0.09
10 *	0.11±0.01	0.12±0.01	0.16±0.01	0.14±0.01	0.12±0.01	0.14±0.004	0.11±0.02	0.13±0.01
α	0.09-0.13	0.09-0.15	0.13-0.18	0.12-0.17	0.10-0.13	0.13-0.15	0.08-0.14	0.11-0.14

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Ciovap and Phenothiazine
Continued, pg 1 of 4

TABLE 17 pg 2 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
11 *	0.10±0.01	0.12±0.02	0.13±0.01	0.12±0.01	0.11±0.01	0.10±0.01	0.10±0.005	0.13±0.005
α	0.07-0.14	0.08-0.18	0.10-0.16	0.10-0.13	0.08-0.13	0.06-0.13	0.08-0.10	0.12-0.14
13 *	0.12±0.01	0.09±0.01	0.09±0.01	0.08±0.01	0.09±0.01	0.09±0.01	0.09±0.01	0.08±0.01
α	0.09-0.15	0.08-0.11	0.08-0.11	0.06-0.12	0.06-0.11	0.06-0.13	0.08-0.11	0.06-0.11
14 *	0.09±0.01	0.07±0.004	0.09±0.01	0.08±0.01	0.07±0.004	0.09±0.01	0.07±0.01	0.07±0.003
α	0.08-0.11	0.06-0.09	0.07-0.10	0.05-0.09	0.06-0.08	0.05-0.11	0.05-0.09	0.06-0.08
15 *	0.05±0.01	0.08±0.01	0.06±0.01	0.08±0.01	0.06±0.03	0.05±0.004	0.07±0.003	0.08±0.01
α	0.02-0.07	0.07-0.10	0.03-0.08	0.07-0.11	0.05-0.06	0.04-0.07	0.06-0.07	0.05-0.10
16 *	0.03±0.004	0.06±0.02	0.09±0.02	0.08±0.01	0.05±0.005	0.08±0.004	0.04±0.01	0.06±0.01
α	0.02-0.04	0.03-0.10	0.05-0.14	0.05-0.11	0.04-0.06	0.07-0.09	0.01-0.06	0.04-0.07
17 *	0.07±0.01	0.07±0.005	0.10±0.01	0.06±0.01	0.04±0.01	0.06±0.004	0.07±0.005	0.06±0.01
α	0.05-0.08	0.05-0.08	0.08-0.11	0.04-0.07	0.02-0.08	0.04-0.07	0.06-0.08	0.03-0.09
20 *	0.06±0.01	0.07±0.005	0.09±0.01	0.08±0.005	0.05±0.01	0.05±0.003	0.06±0.003	0.06±0.01
α	0.04-0.07	0.06-0.09	0.06-0.10	0.06-0.09	0.02-0.07	0.04-0.06	0.05-0.07	0.04-0.09
21 *	0.07±0.004	0.07±0.004	0.09±0.01	0.08±0.01	0.05±0.01	0.06±0.01	0.05±0.01	0.05±0.01
α	0.06-0.08	0.07-0.09	0.07-0.12	0.05-0.11	0.03-0.06	0.04-0.08	0.03-0.06	0.04-0.07
22 *	0.04±0.01	0.06±0.01	0.09±0.01	0.09±0.01	0.05±0.004	0.05±0.01	0.05±0.01	0.07±0.01
α	0.02-0.07	0.04-0.08	0.07-0.10	0.08-0.11	0.04-0.06	0.03-0.08	0.04-0.06	0.03-0.10
23 *	0.04±0.01	0.06±0.01	0.08±0.01	0.05±0.01	0.05±0.01	0.06±0.005	0.07±0.003	0.07±0.01
α	0.02-0.07	0.04-0.07	0.07-0.10	0.04-0.07	0.03±0.07	0.05-0.08	0.06-0.07	0.05-0.09

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 17 pg 3 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Clovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Clovap	B ₃ Phetz	B ₄ Control
24	* 0.08±0.01 α 0.05-0.09	0.07±0.01 0.04-0.09	0.07±0.01 0.04-0.09	0.07±0.002 0.06-0.07	0.05±0.004 0.04-0.06	0.09±0.01 0.07-0.11	0.08±0.01 0.06-0.10	0.08±0.01 0.05-0.11
27	* 0.08±0.004 α 0.07-0.09	0.08±0.01 0.06-0.10	0.08±0.01 0.06-0.09	0.06±0.01 0.05-0.08	0.06±0.01 0.04-0.08	0.07±0.01 0.05-0.10	0.07±0.01 0.04-0.09	0.08±0.01 0.05-0.11
28	* 0.08±0.01 α 0.07-0.10	0.09±0.01 0.07-0.10	0.08±0.01 0.06-0.09	0.07±0.004 0.06-0.08	0.06±0.004 0.05-0.07	0.07±0.01 0.05-0.10	0.09±0.005 0.08-0.10	0.08±0.01 0.06-0.10
29	* 0.05±0.01 α 0.04-0.07	0.04±0.01 0.02-0.06	0.08±0.01 0.05-0.10	0.08±0.01 0.06-0.09	0.05±0.01 0.03-0.06	0.06±0.01 0.04-0.07	0.08±0.01 0.06-0.09	0.08±0.004 0.07-0.09
30	* 0.03±0.01 α 0.02-0.05	0.04±0.01 0.03-0.06	0.07±0.01 0.05-0.08	0.07±0.01 0.04-0.09	0.03±0.01 0.00-0.05	0.05±0.01 0.02-0.07	0.08±0.01 0.05-0.10	0.07±0.01 0.04-0.10
31	* 0.04±0.01 α 0.02-0.07	0.06±0.01 0.03-0.08	0.07±0.01 0.06-0.09	0.05±0.01 0.02-0.08	0.05±0.01 0.00-0.08	0.05±0.01 0.02-0.08	0.05±0.01 0.04-0.07	0.06±0.003 0.06-0.07
34	* 0.06±0.01 α 0.04-0.07	0.07±0.002 0.06-0.07	0.07±0.01 0.06-0.08	0.07±0.002 0.06-0.07	0.05±0.01 0.02-0.05	0.06±0.01 0.04-0.08	0.08±0.01 0.06-0.10	0.09±0.01 0.07-0.12
37	* 0.07±0.01 α 0.05-0.08	0.07±0.01 0.06-0.09	0.07±0.004 0.06-0.08	0.07±0.004 0.06-0.08	0.06±0.01 0.05-0.09	0.08±0.01 0.06-0.10	0.07±0.004 0.06-0.08	0.07±0.01 0.06-0.09
41	* 0.07±0.004 α 0.06-0.08	0.07±0.01 0.06-0.10	0.08±0.01 0.05-0.09	0.08±0.01 0.06-0.10	0.07±0.01 0.05-0.09	0.07±0.01 0.05-0.10	0.07±0.01 0.05-0.08	0.10±0.01 0.09-0.12
44	* 0.06±0.01 α 0.05-0.08	0.06±0.005 0.05-0.07	0.07±0.004 0.06-0.08	0.07±0.004 0.06-0.08	0.08±0.01 0.06-0.09	0.08±0.01 0.06-0.10	0.07±0.005 0.06-0.08	0.08±0.01 0.06-0.11

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Clovap and Phenothiazine

TABLE 17 pg 4 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
48 *	0.08±0.01	0.08±0.01	0.09±0.005	0.09±0.01	0.09±0.003	0.08±0.01	0.08±0.005	0.08±0.01
α	0.07-0.10	0.07-0.10	0.08-0.10	0.07-0.10	0.09-0.10	0.05-0.10	0.07-0.09	0.06-0.10
51 *	0.08±0.01	0.07±0.01	0.08±0.003	0.09±0.01	0.06±0.01	0.07±0.01	0.05±0.01	0.07±0.01
α	0.05-0.13	0.06-0.08	0.07-0.08	0.07-0.11	0.04-0.08	0.05-0.09	0.03-0.08	0.05-0.08
55 *	0.07±0.01	0.07±0.01	0.08±0.01	0.07±0.004	0.06±0.01	0.07±0.004	0.07±0.01	0.07±0.01
α	0.05-0.10	0.05-0.09	0.06-0.10	0.06-0.08	0.05-0.08	0.06-0.08	0.04-0.08	0.05-0.09
58 *	0.08±0.01	0.06 ±0.01	0.06 ±0.003	0.06±0.04	0.06±0.005	0.05±0.01	0.07±0.01	0.07±0.01
α	0.06-0.10	0.05-0.08	0.05-0.07	0.05-0.08	0.05-0.07	0.03-0.08	0.04-0.08	0.06-0.10
63 *	0.06±0.01	0.06±0.01	0.06±0.01	0.06±0.002	0.05±0.01	0.06±0.01	0.09±0.01	0.08±0.003
α	0.02-0.09	0.05-0.07	0.04-0.07	0.05-0.06	0.02-0.06	0.04-0.08	0.07-0.11	0.07-0.09
65 *	0.06±0.01	0.04±0.003	0.08±0.01	0.07±0.01	0.02±0.01	0.04±0.01	0.04±0.01	0.06±0.01
α	0.04-0.08	0.04-0.05	0.06-0.09	0.06-0.09	0.00-0.04	0.02-0.06	0.02-0.05	0.04-0.09
80 *	0.08±0.004	0.08±0.01	0.09±0.002	0.08±0.01	0.07±0.01	0.07±0.01	0.06±0.01	0.07±0.01
α	0.07-0.09	0.06-0.10	0.07-0.08	0.06-0.09	0.06-0.08	0.06-0.09	0.04-0.07	0.05-0.09

* Mean ±SEM of each group; ^αThe range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 18 PRE- AND POSTTREATMENTS TOTAL PLASMA PROTEIN CONCENTRATIONS
(gm/dl) OF THE PARASITIZED(A) AND NONPARASITIZED(B) LAMBS

# of Days	A ₁ Cvp & Phetz	A ₂ Clovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Clovap	B ₃ Phetz	B ₄ Control
-1 *	8.3±0.3	8.0±0.3	8.2±0.3	8.2±0.3	8.0±0.2	7.7±0.2	7.8±0.4	8.3±0.1
α	7.5-8.7	7.1-8.5	7.9-8.7	7.1-8.9	7.5-8.5	7.3-8.1	7.1-8.9	7.9-8.7
0 *	8.5±0.3	8.5±0.1	8.0±0.1	8.6±0.3	8.6 ±0.3	8.5±0.1	8.3±0.3	8.6±0.2
α	8.2-9.7	8.4-8.8	7.9-8.3	8.2-8.9	7.7-9.3	8.4-8.8	7.8-9.1	8.2-8.9
1 *	8.6±0.3	7.8±0.2	7.7±0.1	8.0±0.2	8.0±0.2	7.6±0.3	8.1±0.3	8.0±0.2
α	7.9-9.4	7.1-8.3	7.5-7.9	7.4-8.3	7.5-8.5	6.7-8.1	7.7-9.1	7.7-8.4
2 *	8.0±0.1	8.3±0.1	7.8±0.2	8.5±0.1	8.3±0.3	7.5±0.2	8.1±0.3	7.7±0.1
α	7.8-8.2	7.9-8.5	7.5-8.2	8.2-9.0	7.9-9.1	6.6-8.0	7.5-8.5	7.4-8.1
3 *	8.2±0.2	8.4±0.1	7.7±0.2	8.6±0.3	8.3±0.4	7.4±0.3	8.0±0.2	7.9±0.1
α	7.7-8.7	8.1-8.5	7.3-8.0	8.0-9.3	7.9-9.0	6.9-7.9	7.4-8.6	6.5-8.3
4 *	8.3±0.2	8.4±0.1	8.0±0.2	8.6±0.2	8.1±0.2	7.5±0.2	7.7±0.2	8.0±0.1
α	7.9-8.7	8.1-8.9	7.5-8.3	8.1-9.3	7.8-9.1	7.0-8.0	7.4-8.2	7.8-8.3
6 *	8.4±0.1	8.6±0.2	7.8±0.1	8.6±0.2	7.9±0.5	7.6±0.2	7.8±0.4	7.6±0.2
α	8.2-8.7	8.0-9.3	7.5-8.1	8.2-9.3	6.9-9.9	6.9-8.1	6.6-8.5	6.9-8.1
7 *	8.4±0.1	8.6±0.1	7.9±0.3	8.1±0.2	8.9±0.3	7.9±0.2	8.1±0.2	7.4±0.3
α	8.3-8.7	8.3-8.9	7.3-8.5	7.5-8.5	8.3-9.9	7.3-8.5	7.4-8.5	6.3-7.9
9 *	8.1±0.2	9.3±0.2	8.2±0.2	8.4±0.2	7.9±0.2	7.7±0.1	8.1±0.2	7.8±0.1
α	7.5-8.7	7.9-8.7	7.7-8.5	8.1-8.9	7.4-8.5	7.4-8.1	7.7-8.7	7.5-8.2
10 *	8.1±0.2	8.2±0.2	8.1±0.1	8.1±0.1	8.3±0.2	7.3±0.3	8.5±0.2	7.8±0.2
α	7.7-8.7	7.7-8.5	7.8-8.3	7.7-8.3	7.9-9.3	6.3-7.9	8.0-9.1	7.5-8.7

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Clovap and Phenothiazine
Continued pg 1 of 4

TABLE 18 pg 2 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
11 *	8.2±0.2	8.2±0.1	7.9±0.1	8.0±0.1	8.4±0.2	7.6±0.1	8.2±0.1	7.8±0.2
α	7.8-8.7	7.9-8.3	7.7-8.1	7.7-8.3	7.9-9.2	7.3-8.0	7.8-8.5	7.4-8.5
13 *	8.7±0.4	8.6±0.1	8.4±0.05	8.8±0.2	8.5±0.3	7.7±0.2	8.4±0.2	8.1±0.1
α	7.9-9.1	8.4-9.0	8.3-8.5	8.3-9.3	7.9-9.7	7.3-8.3	8.1-8.9	8.0-8.3
14 *	7.8±0.2	7.8±0.05	7.4±0.1	7.9±0.1	8.2±0.3	7.6±0.2	7.7±0.2	7.1±0.1
α	7.1-8.1	7.7-7.9	7.2-7.7	7.5-8.1	7.3-9.3	7.2-8.3	7.4-8.3	6.7-7.4
15 *	7.3±0.2	7.7±0.1	7.4±0.1	8.2±0.1	8.1±0.2	7.3±0.1	7.8±0.2	7.3±0.1
α	6.8-7.8	7.5-8.1	7.1-7.8	7.7-8.5	7.4-8.7	7.1-7.8	7.5-8.4	7.0-7.5
16 *	7.7±0.2	8.4±0.2	7.7±0.1	8.3±0.2	7.9±0.3	7.2±0.1	7.6±0.1	7.5±0.1
α	7.1-8.2	8.0-9.1	7.5-8.0	7.7-8.7	7.2-8.9	6.9-7.6	7.3-7.9	7.3-7.7
17 *	7.6±0.2	7.8±0.1	7.7±0.2	8.0±0.2	7.8±0.1	7.4±0.1	7.5±0.1	7.5±0.1
α	7.0-8.3	7.5-8.3	7.4-8.1	7.6-8.6	7.1-8.1	7.0-7.7	7.5-7.7	7.3-7.7
20 *	7.3±0.2	7.6±0.1	7.7±0.1	8.1±0.1	7.8±0.2	7.2±0.2	7.7±0.1	7.3±0.1
α	6.6-7.9	7.5-8.1	7.3-7.9	7.8-8.5	7.2-8.5	6.7-7.5	7.4-7.9	7.1-7.5
21 *	7.6±0.3	7.6±0.1	7.8±0.2	7.8±0.1	7.7±0.2	7.1±0.1	7.5±0.1	7.4±0.1
α	6.8-8.3	7.5-8.3	7.4-8.2	7.5-8.3	7.3-8.3	6.9-7.2	7.3-7.7	7.2-7.6
22 *	7.8±0.2	8.0±0.1	7.7±0.1	8.1±0.1	8.0±0.2	7.3±0.1	7.9±0.1	7.5±0.1
α	7.1-8.3	7.7-8.3	7.5-8.0	7.7-8.5	7.6-8.5	7.1-7.5	7.7-8.0	7.3-7.7
23 *	7.7±0.3	8.0±0.1	7.8±0.2	8.2±0.2	8.3±0.2	7.3±0.2	8.1±0.1	7.5±0.1
α	6.9-8.5	7.9-8.3	7.5-8.0	7.9-8.9	7.7-8.8	6.9-7.8	7.9-8.4	7.3-7.7

* Mean ±SEM of each group; ^α The range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 18 pg 3 of 4

of	A ₁	A ₂	A ₃	A ₄	B ₁	B ₂	B ₃	B ₄
Days Cvp & Phetz	Clovap	Phetz	Control	Cvp & Phetz	Clovap	Phetz	Control	
24 *	7.7±0.2	8.0±0.2	7.6±0.2	7.9±0.2	8.3±0.3	7.3±0.1	7.9±0.2	7.9±0.1
α	7.1-8.2	7.6-8.5	7.3-8.1	7.6-8.6	7.4-9.0	7.1-7.5	7.5-8.3	7.7-8.2
27 *	7.5±0.2	7.8±0.1	7.7±0.2	8.4±0.2	8.1±0.2	7.3±0.1	7.7±0.2	7.5±0.1
α	7.1-7.9	7.5-8.1	7.4-8.1	8.0-9.1	7.7-8.8	7.0-7.5	7.5-7.9	7.3-7.7
28 *	7.5±0.2	7.9±0.1	7.8±0.2	8.3±0.2	8.1±0.2	7.3±0.1	7.7±0.1	7.4±0.1
α	7.1-7.9	7.4-8.2	7.5-8.2	7.9-9.2	7.8-8.8	7.1-7.6	7.4-8.0	7.2-7.6
29 *	7.5±0.2	7.9±0.1	7.8±0.1	8.3 0.3	8.2±0.2	7.3±0.1	7.8±0.2	7.3±0.1
α	6.9-8.0	7.5-8.3	7.6-8.1	7.7-9.3	7.8-8.9	7.1-7.6	7.3-8.2	7.1-7.7
30 *	7.3±0.2	8.0±0.1	7.9±0.1	8.0±0.2	7.9±0.2	7.1±0.1	7.8±0.1	7.7±0.2
α	6.8-7.7	7.7-8.5	7.7-8.1	7.5-8.9	7.5-8.5	6.9-7.4	7.5-8.0	7.1-8.3
31 *	7.7±0.2	8.3±0.2	7.8±0.1	8.3±0.3	8.1±0.1	7.2±0.1	7.8±0.1	7.6±0.1
α	7.1-8.3	7.8-8.8	7.7-8.1	7.5-9.3	7.7-8.5	7.1-7.5	7.4-8.0	7.2-7.8
34 *	7.6±0.2	8.1±0.2	8.0±0.2	8.5±0.2	8.4±0.4	7.3±0.1	7.7±0.2	7.6±0.1
α	7.1-7.9	7.5-8.8	7.5-8.3	8.1-9.1	7.7-9.7	6.9-7.7	7.3-8.2	7.4-8.0
37 *	8.1±0.1	8.1±0.1	8.0±0.2	8.0±0.3	8.1±0.2	7.2±0.2	7.9±0.1	7.3±0.1
α	7.9-8.3	7.8-8.3	7.4-8.5	7.6-9.2	7.6-8.4	6.8-7.6	7.5-8.1	7.1-7.7
41 *	7.7±0.3	8.2±0.2	7.5±0.3	8.1±0.2	8.1±0.1	7.3±0.1	7.8±0.2	7.7±0.1
α	6.8-8.5	7.6-8.6	6.8-8.0	7.6-8.5	7.8-8.3	7.1-7.7	7.5-8.3	7.5-7.8
44 *	7.5±0.2	7.9±0.1	7.4±0.1	7.7±0.2	7.7±0.1	7.2±0.2	7.3±0.1	7.2±0.1
α	7.0-8.1	7.7-8.2	7.1-7.6	7.3-8.3	7.5-8.1	6.8-7.8	7.1-7.7	6.9-7.3

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Clovap and Phenothiazine

TABLE 18 pg 4 of 4

# of Days	A ₁ Cvp & Phetz	A ₂ Ciovap	A ₃ Phetz	A ₄ Control	B ₁ Cvp & Phetz	B ₂ Ciovap	B ₃ Phetz	B ₄ Control
48 *	7.9±0.3	8.0±0.1	7.5±0.1	8.0±0.1	8.2±0.03	7.7±0.2	8.1±0.2	7.4±0.04
α	7.1-8.5	7.8-8.3	7.3-7.8	7.6-8.3	8.1-8.3	7.3-8.2	7.7-8.7	7.3-7.5
51 *	7.8±0.1	8.1±0.1	7.8±0.2	7.9±0.1	7.9±0.1	7.4±0.1	7.8±0.1	7.2±0.1
α	7.5-8.1	7.9-8.3	7.3-8.2	7.7-8.3	7.8-8.1	7.1-7.7	7.4-8.1	6.9-7.4
55 *	7.7±0.2	8.1±0.1	7.6±0.2	8.1±0.2	8.0±0.1	7.3±0.1	8.0±0.1	7.5±0.1
α	7.1-8.1	7.9-8.4	7.5-8.3	7.9-8.7	7.9-8.1	7.1-7.5	7.7-8.3	7.3-7.8
58 *	8.1±0.2	8.2±0.1	7.6±0.2	8.1±0.1	8.2±0.1	7.8±0.1	8.3±0.1	7.5±0.2
α	7.4-8.7	7.9-8.3	7.3-8.2	7.9-8.3	7.9-8.6	7.6-7.9	7.9-8.5	7.2-8.1
63 *	8.2±0.3	8.5±0.1	8.0±0.04	8.9±0.3	8.7±0.3	7.9±0.2	9.0±0.3	7.7±0.1
α	7.6-9.3	8.3-8.8	7.9-8.1	8.2-9.7	8.1-9.7	7.5-8.7	8.4-9.4	7.5-7.8
65 *	7.9±0.2	8.3±0.1	7.8±0.1	8.4±0.3	8.3±0.2	7.7±0.2	7.7±0.1	7.6±0.1
α	7.1-8.2	7.9-8.8	7.6-8.2	7.8-9.1	8.0-8.8	7.3-8.4	7.5-7.9	7.4-7.9
80 *	8.0±0.2	8.1±0.1	8.2±0.2	8.1±0.1	8.2±0.2	7.5±0.2	8.0±0.2	7.6±0.1
α	7.5-8.7	7.9-8.5	7.8-8.8	7.8-8.5	7.8-8.6	7.1-8.0	7.6-8.5	7.3-7.8

* Mean ±SEM of each group; α The range of each group; Cvp & Phetz = Ciovap and Phenothiazine

TABLE 19
 MEAN $\pm$ SEM WEIGHT GAIN OF THE LAMBS
 IN 65 DAYS (EXPERIMENT I)

Group	Mean Weight Gain (lb)
Clinical Parasitism	
A ₁	3.7 $\pm$ 1.5 (-2 - 6.5) *
A ₂	5.4 $\pm$ 1.9 (-1 - 9.5)
A ₃	14.4 $\pm$ 5.0 (3.5 - 25)
A ₄	7.1 $\pm$ 2.7 (2 - 16.5)
No Clinical Parasitism	
B ₁	5.6 $\pm$ 1.4 (2 - 8)
B ₂	5.5 $\pm$ 1.1 (3 - 9)
B ₃	15.0 $\pm$ 3.9 (3.5 - 21)
B ₄	4.6 $\pm$ 0.8 (2.5 - 6.5)

* The range is shown in parenthesis.

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Digitization Information

Local identifier Mohammad1981

Source information

Identifier	FILM T1981 -198
Format	Microfilm; filmed with others
Content type	Text, photographs
Notes	

Capture information

Date captured	2017 July
Scanner model	ScanPro 3000
Scanning software	PowerScan 3000™ Ver.5.309
Optical resolution	600 dpi, LZW compression
Color settings	grayscale
File types	tiff
Notes	

Derivatives - Access copy

Compression	
Editing software	Adobe Acrobat XI
Resolution	600 dpi, LZW compression
Color	grayscale
File types	pdf
Notes	Page backgrounds lightened, text darkened. Pages straightened.