DIMETHOATE: REVIEW OF ITS SYSTEMIC ACTIVITY IN MAMMALS FOR CONTROL OF ECTOPARASITES.

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INTRODUCTION

Research on the possibilities of using systemic insecticides to control livestock ectoparasites was initiated in the 1940's in the United States of America at Kerville, Texas, Livestock Insects Laboratory. This followed the findings of Knipling *et al*: (1948) who found that rabbits tolerated treatments of Lindane and 2-pivalyl - 1,3 - indandione at rates that were lethal to mosquitoes - *Aedes aegypti* (Linnaeus) and human body lice, *Pediculus humanus humanus* (Linnaeus) when feeding on rabbits. Special emphasis was given to insecticides to control cattle grubs because they were the most damaging insect parasites of livestock, the larvae of which spend many months within the body of the host, and thus seemed particularly susceptible to control by a systemic insecticide (McGregor & Bushland 1956).

The development of organophosphorus insecticides which were initially used for systemic control of plant parasites, marked a new era of practical use of systemic insecticides in animal ectoparasites. Though chlorinated hydrocarbons such as lindane, dieldrin and aldrin, were found to be systemically effective against cattle grubs, their treatments were impractical because of their excessive residues (Bushland et al, 1963, Lindquist et al 1953).

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Of the organophosphorus systemic insecticides, dimethoate was among those studied for control of ectoparasite, not only for livestock, but also rodents which play hostship for fleas responsible for transmitting diseases like plague.

Advantages of using systemic insecticides as opposed to conventional methods of insecticides application include a relative ease of administration, reduction in amount of compound applied and the lack of environmental contamination by such compounds. With regard to plague control, which involves flea control by dusting or spraying an entire affected area before embarking on rodent control, use of systemic insecticides mixed with rodenticides in order to control the two pests simultaneously could reduce labour, time and costs involved significantly (Miller et al.; 1975, Dohany et al 1980).

Residues of systemic insecticides in treated animals has to some extent limited the use of some effective organophosphorus insecticides. Ideally, the insecticide should not be metabolized too rapidly, otherwise it will not persist in the animal for long enough to kill the pest. However, it should not also persist in the body for too long a time to demand a long withdrawal period. Where the use of particular insecticides was inevitable for example in lactating dairy animals several days milk had to be discarded (Bushland et al, 1963).
However, such insecticides could probably find their use in controlling

ectoparasites of animals like rodents because the problem of residues is of less importance. Dimethoate, one of the systemic organosphosphorus systemic insecticides with such low residues when used against livestock ectoparasite could be well utilized to control rodent flea ectoparasites.

This review examines the literature that has appeared on dimethoate as a broad spectrum systemic insecticide. Coherent information on this compound will hopefully be valuable in the control of rodent flea ectoparasites.

CHEMISTRY

Dimethoate (Am. Cyanamid 12880 or Rogor) belongs to diothiophosphate group of organophosphate compounds. Chemically dimethoate is known as 0,0-dimethylcarbamoylmethyl phosphoriodithoate. Its molecular structure is shown in Figure 1. It is produced by reacting salts of dimethyldithiophosphoric acid with N-methylchloroacetamide in aqueous medium in the presence of some organic solvents. It is also produced by methyl dithiophosphate at low temperature with aqueous methylamine, (Martin, 1972). The later reaction produces a less stable dimethoate due to the presence of impurities, like methylamine, traces of which tend to decompose dimethoate easily. Decomposition can also be caused by contamination of organic bases, iron or salts of iron. Thus storage of dimethoate in iron containers is not recommended.

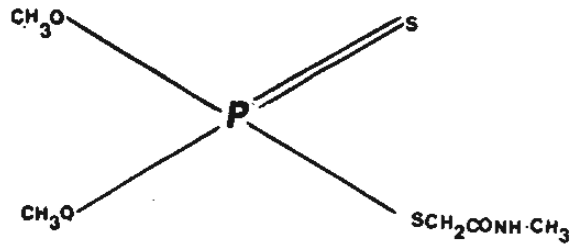

Figure 1. Chemical Structure of Dimethoate

MODE OF ACTION

The biological activity of dimethoate like that of many other organosphosphorus compounds is due to the capacity of the central phosphorus atom to phosphorylate the active site of the enzyme cholinesterase (ChE) which is an essential constituent of the nervous system (Hassall 1982, Sree Ramulu 1979).
The phosphorylated enzyme is irreversibly inhibited resulting in decreased hydrolysis of endogenous acetylcholine and intensification of its action at cholinergic receptors. In insects the immediate cause of death is uncertain but in mammals, death is due to failure of the muscles of the diaphragm (Hassall, 1982).

Dimethoate has a limited contact toxicity which arises from the fact that the sprayed substance is often a weak cholinesterase inhibitor, the actual toxicant being formed by metabolic action in the organism. It has been shown that blood from dimethoate treated cattle was approximately 40 times more toxic to stable fly (*Stomoxys calcitrans* (L) than dimethoate itself (Roberts et al 1958).

USES IN PUBLIC HEALTH AND ANIMAL HUSBANDRY

The systemic ability of dimethoate has been exploited by animal parasitologists to control ectoparasites by treating the host animal. Immediately after the introduction of dimethoate in 1956 (Martin, 1972), its systemic potential against ectoparasites was demonstrated when Hewitt *et al* (1958a) found that in tests on *Aedes aegypti* (L) it was one of the most active insecticides and showed a wide margin of safety between doses effective against

mosquitoes and doses toxic to mice. They also found that about 50–80% of rodent lice (*Polyplax* species) were killed after a single oral dose of 12.5 mg/kg body weight in mice. Following these tests, Hewitt *et al* (1958b) conducted tests against cattle grubs (*Hypoderma lineatum* (DeVill) and *H. bovis* (L) in cattle. The results obtained indicated an appreciable margin of safety between the lowest dosage which killed first instar *H. bovis* (5mg/kg) or second instar *H. lineatum* and H. *bovis*. (2.5 to 5mg/kg) and the dose which produced mild toxicity (15 to 20 mg/kg) or severe irreversible toxicity (40mg/kg) in the host animals.

Drummond (1958) using guinea pigs as hosts found that dimethoate given at 10mg/kg killed 100% of the screw worms (*Cochliomyia hominivorax*) tested; and at a dose of 25mg/kg the insecticide killed 100% of the tested lone star ticks (*Amblyomma americanum* (L). In tests with sheep and goats, dimethoate completely killed both nymphs and adults of the lone star tick at 50 mg/kg and killed screworms and stable flies at 25 mg/kg.

Control of rodent flea ectoparasites of economic importance by treating the rodent with systemic insecticides has been shown to be possible under laboratory and field conditions. In most cases the major objective has been to reduce the population of rodent fleas in recreational parks in order to reduce incidences of flea bites to holiday makers. Few attempts were geared to include candidate insecticides in baits with an aim to control rodents and their fleas simultaneously. Among the organophosphorous insecticides, dimethoate has shown some promise in this field. Hill *et al* (1963) observed that dimethoate at 50mg/kg produced high mortality of oriental fleas following a delay of 1 hour between dosing and feeding. However, no activity was obtained 4 hours following dosing. It was shown that as the time interval between host treatment and flea feeding increased, flea mortality decreased rapidly, despite an increasingly longer feeding period. This could probably be attributed to rapid decline of effective concentrations of dimethoate in plasma.

A control of up to 82% of oriental rat fleas was achieved by Harvey (1960) after feeding fleas on white rats fed dimethoate at a dose of 25mg/kg. He asserted that, at the end of day one, fleas control using dimethoate was significantly better than that obtained by other insecticides such as Dowco 109 and ronnel.

Clark and Cole (1965) in a laboratory evaluation of promising systemic insecticides in guinea pigs against oriental rat fleas (*X.cheopis*) found that dimethoate at 100 mg/kg caused complete mortality of the fleas without noticeably affecting the guinea pigs. An attempt by Clark and Cole (1968) to mix dimethoate in a bait for hooded white rats did not succeed in killing oriental rat fleas (*X.cheopis*) significantly even at a concentration of 200 mg/kg. This is because the bait containing dimethoate was not readily consumed.

Dimethoate has also been shown to be an effective systemic acaricide for the control of chiggers. Feeding habits of chiggers are unusual compared to other arthropods of medical importance in which systemic control has been effective. Chiggers feed primarily on digested tissues and not on blood (Dohany *et al.* 1977). Despite this unique feeding habit, a test done by Dohany *et al* (1977) using bait containing 0.1% dimethoate showed that 100% of the chiggers on guinea

pigs and 92.7% of the chiggers on Hispid cotton rats (*Sigmodon hispidus*) were killed. Out of several known systemic insecticides screened by Dohany (1974), only dimethoate was found to be effective against chiggers. In the field, Dohany *et al* (1980) observed a significant chiggers control demonstrated within three months following an application of rodent bait consisting of 0.2% technical grade dimethoate with a 1:1 mixture of cracked corn and ground milo. In this study there was good acceptance of bait although large food source was available in the form of oil palm fruits.

Another field trial conducted by Miller et al.(1978) showed that dimethoate controlled fleas effectively on *Dipodomys* species when applied in a bait at concentrations of 0.36% and 0.24%. Significant flea control was also noted on *Sigmodon hispidus* when dimethoate was applied for 30 days at a concentration of 0.24%. Corn milo was chosen as a suitable bait because both *Dipodomys* species and *S. hispidus* readily consumed it.

Effective uses of dimethoate as an intramuscular injection for the control of cattle grub were limited because systemically effective doses were found to have produced toxicity to the host. In other studies (Drudge *et al.*1961) it was found that dimethoate was effective against horse bots when administered for three to five days in feed. Nevertheless, effective control of all three instars of sheep bot fly using dimethoate intramuscular injection at doses tolerated by the sheep was reported by Peterson *et al.* (1959). Further studies by Peterson *et al.* (1959) showed that dimethoate was similarly effective against the sheep bot fly instars.

Injections of dimethoate have been shown to be effective against the dog follicle mite, *Demodex canis* Leydig (Colgazier *et al.* (1960).

Investigations on the use of systemic insecticides to control larvae of the human bot fly or torsalo, *Dermatobia hominis* were carried out in Central and South America. Adequate control of these larvae present in cattle at the time of treatment was achieved when dimethoate was given orally and intramuscularly (Bushland et al. 1963).

Although different preparations of dimethoate have been formulated for use as systemic insecticides in livestock, to date no such preparations have been practically used in controlling rodent fleas. Recent studies (Mbise 1990, unpublished) have shown that dimethoate is very effective in controlling fleas (*Xenopsylla cheopis*) systemically by treating the host (*Mastomys natalensis*), a common rat in the whole of African continent. However, the activity obtained was of short duration in that no significant flea mortality was observed 24 hours after dosing.

ABSORPTION AND DISTRIBUTION

Dimethoate is efficiently absorbed into the blood system. The rate of absorption is determined by the route of administration. Robert et al.(1958) reported that dimethoate and its metabolites were detectable for a longer period in cattle blood when the parent compound was administered orally than when it was given by intramuscular or intravenous routes. Lower concentrations of dimethoate and its metabolites in the feces compared to urine demonstrated further that dimethoate is efficiently absorbed following oral administration (Kaplanis et al. 1959).

Following absorption, dimethoate is distributed into most body tissues.

Table 1: Radioactivity measurements in tissues of a calf two weeks after oral administration of P^{32} dimethoate at 10mg/kg.*

Tissue	µ-equivalents/g of tissue[a] Total[b]	Chloroform extractable[c]
Liver	1.72	0.02
Kidney	0.17	0
Spleen	0.15	0
Brain	0.31	0.07
Spinal cord	0.09	0
Testes	0.18	0.02
Lung	0.27	0.02
Heart	0.09	0
Tongue	0.08	0
Gullet	0.09	0
Muscle		
Loin	0.11	0
Round	0.09	0
Shoulder	0.10	0
Blood	0.03	0
Gall	0	–
Bone		
Spongy	2.01	–
Compact	0.46	–
Fat		
Subcutaneous	–	0
Omental	–	0
Perirenal	–	0
Marrow	–	0

a Based on wet weight except bone.
b As determined from tissue homogenates, at a sensitivity of 0.034 µg-equivalents/g.
c Sensitivity for fat was 0.007 µg-equivalents/g and for the remainder of the tissues; it was 0.015 µg-equivalents/g.
* Adapted from Kaplanis et al.(1959).

Analysis of some tissues from a calf treated with dimethoate orally showed very low concentrations (0.02 to 0.07 µg/g) of organoextractable radioactive compounds present in the brain, liver, testes, and lungs (Kaplanis et al.1959). Table 1 (adapted from Kaplanis *et al.*(1959) illustrates the distribution of dimethoate in tissues of different animal species. From this table, dimethoate was not detected in fats.

METABOLISM AND EXCRETION

Studies on the metabolism of dimethoate showed that major features are similar in all organisms. These features include O- and N-dealkylation by mixed-function oxidases (MFO), hydrolysis of P-O and P-S bonds by phosphatases resulting in conversion of, P=S P=O and deamination by amidases (Cremlyn 1979).

Menzie (1969) reported that rats degraded dimethoate to various metabolites including, desmethyl dimethoate, O, O-dimethylyphosphoric and phosphorothioic and phosphorodithioic acids. Several other compounds were not identified. Highest levels of radioactive dimethoate and its metabolites in rat persisted in the liver, skin, and bone. According to Krueger *et al.* (1960), the mouse, unlike other animals, has an exceptional ability to eliminate dimethoate since 89% of a dose of 0.5 µg./g and 76% of a dose of 30 µg./g were found in the chloroform inextractables within 0.5h after treatment. Studies of dimethoate in cattle showed that it is extensively metabolized to dimethyl phosphorothioate, dimethyl phosphate and several unknown compounds, (Kaplanis *et al.*, 1959, Dauterman *et al.*, 1959), and that these metabolites, including some traces of the parent compound are largely excreted in urine (Kaplanis *et al.* 1959). Similar results were obtained from sheep (Chamberlain *et al.* (1961). Other animal studies have indicated that the predominant path of dimethoate metabolism is dependent on species, sex, and dose administered (Menzie, 1969).

It appears that elimination of dimethoate in mammals is mainly through the urine and to a lesser extent through the feces. An investigation of metabolism of P^{32} dimethoate in cattle (Kaplanis *et al.* 1959) showed that about 87 to 90% of the oral dose was eliminated in the urine within 24h. The same percentage of an intramuscular dose was excreted after 9h. In the same investigation, of the oral dose, only 3.7 to 5% and about 1.1% of the intramuscular dose were eliminated in the feces.

TOXICITY

Toxicity of dimethoate varies with purity and is considered to increase with increasing shelf-life (Meleney & Peterson, 1964). While in storage, dimethoate toxicity could increase by activation, a reaction which is catalysed by heat (Hatch 1982). This storage activation phenomenon explains the need to use freshly prepared solutions. It is also important to adhere to storage conditions which otherwise alter the toxicity of the compound.

Toxicity of dimethoate in mammals is considered to be moderate. Its LD 50 in male rats range from 185-215mg/kg and in female rats in 245mg/kg (West *et al.* 1961).

Clinical signs of dimethoate poisoning are similar to those caused by other organosphosphorus insecticides. These include profuse salivation, vomiting, defecation, tremous, convulsions, paralysis and death. Death is often

due to the failure of the muscles of the diaphragm.

Studies of the acute and subacute toxicity of dimethoate (West *et al.* 1961) revealed that the compound was not readily absorbed through the skin and was not irritating to the skin or eyes. Furthermore, upon repeated feeding to rats and dogs at a dosage of 0.6mg/kg/day for more than a year, dimethoate was not found to influence blood cholinesterase activity. However, a dosage of 10–15 mg/kg/day elicited some signs of toxicity but did not cause any mortalities. No gross or microscopic lesions due to the administration of dimethoate under these conditions were observed.

CONCLUSION

Dimethoate has a good selective toxicity for use as a systemic insecticide in both plants and animals.

The active compound is formed as a result of metabolism in the organism. It is on this basis that dimethoate is applied to control plant phytophagous or sap sucking insects and animal blood sucking insects including chiggers which feed on tissues. It is effective against a wide variety of livestock ectoparasites. It is available in the form of injectable solution and feed additives for livestock. Although dimethoate has been found to be effective against rodent flea ectoparasites, no suitable bait formulation has been available. It would therefore be important to develop an acceptable bait that will deliver sufficient dimethoate in rats to control fleas.

Toxicity, absorption and excretion studies of dimethoate in animals and plants revealed that it is a fairly mild insecticide suitable for use in different situations.

Additionally, dimethoate residues in food producing animals do not appear to be a potential health hazard.

REFERENCES

Bushland R.C., Radeleff, R.D, and Drummond, R.O. (1963). Development of systemic insecticides for pests of animals in the United States. *Ann. Rev. Ent.* 8: 215–238.

Chamberlain, W.F., Gatterdam, P.E. and Hopkins, D.E. (1961). The metabolism of p^{32} labeled dimethoate in sheep. *J. Econ. Ent.* 54: 733–740.

Clark, P.H. and Cole, M.M. (1965). Laboratory evaluation of promising systemic insecticides in guinea pigs against oriental rat fleas. *J. Econ. Ent.* 58: 83–86.

Clark, P.H. and Cole, M.M. (1968). Systemic insecticides for control of oriental rat fleas: Bait tests with hooded white rats. *J. Econ. Ent.* 61: 505–508.

Colgazier, M.L., Enzie, F.D., and Wilkens, E.H. (1960). Some chemotherapeutic trials in canine demodectic mange. *Proc. Helminthol. Soc. Wash.* D.C. 27: 139–45.

Cremlyn, R. (1978). Pesticides preparation and mode of action. John Wiley and Sons, Ltd. Chichester p. 75.

Dauterman, W.G., Casida, J.E.; Knaak, J.B.; and Tadeusz Kowalczyk (1959). Bovine metabolism of organophosphorus insecticides. Metabolism and residues associated with oral administration of dimethoate to rats and lactating cows. J. Agr. Fd. Chem. 7: 188–193.

Dohany, A.L. (1974). Potential use of systemic acaricides in control of chigger (Acarina : Tromblicudae) populations on rodents. Ph.D. Dissertation University of Florida. 115p. *In.* Dohany, A.L. Cromroy, H.L. and Cole, M.M. (1977). Laboratory Tests of Dimethoate systemic control of chigger (ACARINA: TROMBICULIDAE) populations on rodents. *J.. Med. Entomol.* 14: 79–81.

Dohany A.L., Comroy H.L. and Cole M.M. (1977) Laboratory test of dimethoate for systemic control of chigger (ACARINA TROMBICULIDAE) populations on rodents. *J. Med. Entomol.* 14: 79 – 81.

Dohany, A.L., Huxsoll, D.L., Sauders, J.P. and Phang, O.W. (1980). The efficacy of dimethoate as a systemic acaricide for the control of chiggers (Acarina:Trombiculidae). *J. Med. Entomol.* 17: 30–34.

Drudge, J.H.; Leland, S.E.; Wyant, Z.N.; Elam, G.W.; and Lyons, E.T. (1961). Critical tests with the organic phosphate insecticide, dimethoate, against Gasterophilus spp. in the horse, with observations on its anthelmintic action. *Am. J. Vet. Res,* 22: 1106–11.

Drummond, R.O. (1958). Laboratory screening tests of animal systemic insecticides *J.Econ. Ent.* 51: 425–27.

Harvey, T.L. (1960). Control of the oriental rat flea with systemic insecticides fed to rats. *J. Econ. Ent.* 53: 167–168.

Hassall, K.A. (1982). The chemistry of pesticides. Their metabolism, mode of action and uses in crop protection. The Macmillan Press Ltd., London p.77.

Hatch, R.C. (1982). Poisons causing nervous stimulation or depression In. Booth, N.H. and McDonald, L. E. (ed.). Veterinary Pharmacology and Therapeutics. Fifth edition. The Iowa state University Press, Ames, p. 985.

Hewitt, R.; Emro, J.; Entwistle, J., Pankavich, J.; Thorson, R.; Wallace, W.; and Waletaky, E.; (1958b). Carbomoyl alkyl phosphorodithioates as chemotherapeutic agents: Effects of dimethoate against grubs in cattle. *J. Econ Ent.* 51: 445–450.

Hewitt, R., Brebbia A. and Waletzky E. (1958a) Carbamoyl Alkyl Phosphorodithioates as chemotherapeutic Agents: Screening by Aedicidal properties in mammals, lambs and calves. *J. Econ. Ent.* 51 126 – 131.

Hill, A.J.; Knapp, F.W. and Knutson, H. (1963). Laboratory studies with systemic insecticides for control of the oriental rat flea on white rats. *J. Econ. Ent.* 56: 390–394.

Kaplanis, J.N.; Robbins, W.E., Darrow, D.I. Hopkins, D.E.; Manroe, R.E. and Treiber, G. (1959).The metabolism of dimethoate in cattle. *J. Econ Ent.* 52: 1190–1194.

knipling, E.F., Bushland, R.C. Babers, F.H.; Culpepper, G.H. and Raun, E.S. (1948). Evaluation of selected insecticides and drugs as chemotherapeutic agents against external bloodsucking parasites. J. Parasitol.34: 55–70.

Krueger, H.R., O'Brien, R.D. and Dauterman, W.C. (1960) Relationship between metabolism and differential toxicity in insects and mice of diazinon, dimethoate, parathion and acethion. *J. Econ. Ent.* 53: 25–31.

Lindquist, A.W.; Roth, A.R.; Hoffman, R.A. and Yates, W.W. (1953). Chemotherapeutic use of insecticides for control of bloodsucking insects *J. Econ. Ent.* 46: 610–614.

Martin, H. (Ed). (1972). Pesticides manual, 3rd ed. British Crop Protection Council. P. 195.

McGregor, W.S. and Bushland, R.C. (1956). Research on the use of systemic insecticides for the control of livestock pests. *J. Econ. Ent.* 49: 86–88.

Meleney, W.P. and Peterson, H.O. (1964). The realationship of shelf age to toxicity of dimethoate to sheep. *J. American Vet. Med. Ass.* 144: 756–758.

Menzie, C.M. (1969). Metabolism of pesticides. Bureau of Sports Fisheries and Wildlife Special Scientific Reports – Wildlife No. 127. Washington DC. July 1969, pp. 160–166.

Miller, B.E.; Bennett, W.C.; Graves, G.N.; and Wheeler, J.R.; (1975). Field studies of systemic insecticides. I. Evaluation of phoxim for control of fleas on cotton rats *J. Med. Ent.* 12: 425–430.

Miller, B.E.; Graves, G.N.; Bennett, W.C.; and Wheeler, J.R. (1978). Field studies of systemic insecticides V. Evaluation of seven organophosphate compounds for flea control on native rodents and rabbits in Southern New Mexico. *J. Med. Ent.* 14: 651661.

Peterson, H.O.; Cobbett, N.G.; and Meleney, W.P.; (1959). Treatment of *Oestrus ovis* with dimethoate: *Vet. Med.* 54: 377–383.

Robert, R.H.; Radeleff, R.D. and Kaplanis, J.n. (1958). Bioassay of the blood from cattle treated with Am.Cyanamid 12,880. *J. Econ. Ent.* 51: 861–864.

Sree Ramulu, U. S. (1985). Chemistry of insecticides and fungicides. 2nd Ed. Oxford and IBL Publishing Co. New Delhi p. 165

West, B.; Vindone, L.B. and Shaffer, C.B.; (1961). Acute and subacute toxicity of dimethoate. *Toxic. Appl. Pharmac.* 3: 210–223.