3-30-82 GS-209 TR-356

003968

TOPICAL DISCUSSIONS

METHAMIDOPHOS

(O,S - Dimethyl phosphoramidothioate)

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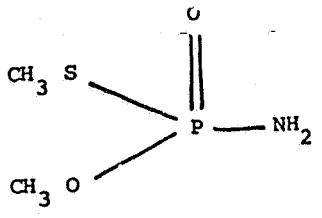

O,S - Dimethyl phosphoramidothioate

(Methamidophos)

Methamidophos is an insecticide and acaricide. It was introduced in the United States in 1969 by Chevron Chemical Company under the trade name Monitor(R) and the code number "Ortho 9006." Methamidophos was introduced in Europe by Bayer Leverkusen under the tradename Tamaron(R) and the code names "Bayer 71628" and "SRA 5172."
Methamidophos is also known as BAY 71628, CAS 10265-92-6 and ENT-27396.

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Acute Oral Toxicity (163.81-1)

The minimum data requirement for testing acute oral toxicity (LD_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the laboratory rat.

Monitor Technical (active ingredient: methamidophos) was very toxic (Category I) to male and female Sprague-Dawley rats after the animals were exposed to single oral doses ranging from 7 to 33.8 mg/kg (Cavalli and Hallesy, 1968, MRID 00014045) and from 5 to 25.4 mg/kg (Cavalli and Hallesy, 1968, MRID 00014044). Signs of toxicity included severe tremors, salivation, chromodacryorrhea, dyspnea, rhinorrhea and, rarely, clonic convulsions. These signs were evident within 5-10 minutes after intubation. Most deaths occurred between 3 and 24 hours. Animals surviving beyond 72 hours showed complete recovery within 7 days. Autopsies done on animals dying shortly after dosing showed congested lungs, and gastrointestinal tracts distended with gas. Autopsies done on survivors sacrificed 14 days after dosing showed no pathological changes in any of the organs or tissues examined (heart, lung, thymus, liver, GI tract, kidneys, adrenals, pancreas, body fat, gonads, bladder and skeletal muscle). Brain was not examined in these studies.

In the study with Monitor Technical containing 75% of methamidophos (Cavalli and Hallesy, 1968, MRID 00014045), the acute oral LD_{50} values for male and female rats were 21 mg/kg and 18.9 mg/kg, respectively. In the study with RE 9006 (Monitor) containing 95% of methamidophos (Cavalli and Hallesy, 1968, MRID 00014044), the acute oral LD_{50} values for male and female rats were 15.6 mg/kg and 13.0 mg/kg, respectively. Each one of these studies is adequate.

Monitor Technical was also very toxic (Category I) to female Swiss-Webster mice after the animals were exposed to single oral doses ranging from 7 to 33.8 mg/kg (Cavalli and Hallesy, 1968, MRID 00014048) and from 7.5 to 25.4 mg/kg (Cavalli and Hallesy, 1968, MRID 00014047). Signs of toxicity included severe tumors, Straub tail, salivation and, rarely, clonic convulsions. These signs were evident within 5-10 minutes after intubation. Animals surviving beyond 72 hours recovered completely within 7 days. Autopsies performed on animals dying shortly after dosing showed pulmonary congestion and gas-distended GI tracts. Autopsies performed on survivors sacrificed 14 days after dosing showed no pathological changes that could be attributed to the test material.

In the study with Monitor Technical containing 75% of methamidophos (Cavalli and Hallesy, 1968, MRID 00014048), and in that with RE 9006 containing 95% of methamidophos (Cavalli and Hallesy, 1968, MRID 00014047), the LD_{50} values were 18 mg/kg and 16.2 mg/kg, respectively. These studies are adequate.

The above information is sufficient to satisfy the data requirement.

Acute Dermal Toxicity (163.81-2)

The minimum data requirement for testing acute dermal toxicity (LD_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the albino rabbit.

Monitor Technical (75% a.i.) was very toxic dermally (Category I) to male New Zealand white rabbits (Cavalli and Hallesy, 1968, MRID 00014049). The test material, ranging from 100 to 222 mg/kg, was applied on the intact backs for 24 hours and the exposed skin was then washed thoroughly with water. Signs of toxicity included miosis, salivation, rhinorrhea, ataxia, and apparent CNS depression. These signs appeared within 1-3 hours after dosing. Most deaths occurred between 6 and 43 hours after dosing. Animals surviving beyond 8 days recovered fully by day 14 following exposure. Autopsies performed on the survivors sacrificed 14 days after dosing revealed no gross pathological changes in any of the tissues examined (lung, heart, thymus, liver, kidneys, spleen, GI tract, adrenals, pancreas, bladder, gonads, body fat, skeletal muscle and skin).

The acute dermal LD_{50} was 118 mg/kg. This study is adequate. Although only male rabbits were used, the Category I label should reflect the high toxicity of this compound. Additional tests with female rabbits appear, therefore, unnecessary.

The above information is sufficient to satisfy the data requirement.

Acute Inhalation Toxicity (163.81-3)

The minimum data requirement for testing acute inhalation toxicity (LC_{50}) is one test on the technical chemical and on each manufacturing use and formulated product, preferably using the laboratory rat.

An acute inhalation toxicity (LC_{50}) test is required for each formulation that causes a respirable vapor, or if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns.

Only supplementary data are available to assess the inhalation toxicity of Monitor (RE 9006). In the study conducted by Cavalli and Hallesy (1968, MRID 00014051) with 6 male Sprague-Dawley rats, there was no mortality, the concentration of the test material in the inhalation chamber was unknown, and the particles were not sized. However, it was reported that the rats were quiet and slightly cyanotic for about one hour after the exposure, and that piloerection was noted. Erythrocyte and plasma cholinesterase activities were inhibited 23% and 29%, respectively, when compared with controls. These data indicate that Monitor was moderately toxic to rats. However, it is unknown whether dermal exposure was also responsible. This test utilized a whole-body exposure technique, but Monitor is very rapidly absorbed through an intact skin (Cavalli and Hallesy, 1968, MRID 00014049). It is also unknown what concentration of Monitor caused these toxic symptoms.

The rats were exposed to RE 9006 (95% a.i.) for 4 hours and were observed for 14 days. Vapors were generated by bubbling room air through the test material which was melted by immersing it in a water bath at 40° C. Cholinesterase activity was determined at the end of the exposure.

The above information is not sufficient to satisfy the data requirement; additional testing is required. The pesticidal use of Monitor could cause a

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respirable vapor and the LC_{50} should be determined. The whole-body exposure should also be avoided in order to minimize the dermal exposure.

Primary Eye Irritation (163.81-4

The minimum data requirement for primary eye irritation is one test on each manufacturing-use product and each formulated product, preferably using the albino rabbit.

This test may be waived upon submission of data demonstrating that the test substance has a pH of 1-3 or 12-14; for regulatory purposes, a test substance with a pH of 1-3 or 12-14 will be considered corrosive to the eye.

Monitor Technical was a moderate irritant (Category II) to the unwashed eyes of six male New Zealand rabbits (Rittenhouse, 1977, MRID 00014221). Slight to moderate corneal opacity and conjunctival irritation were observed in most rabbits for 72 hours. Iritis was observed for 24 hours. By seven days, most of the conjunctival irritation had cleared, except for a slight corneal opacity and pannus which persisted in two rabbits for 10 days. All the rabbits had normal eyes at 14 days. In addition to the eye irritation, all the rabbits had tremors, salivation, diarrhea and miosis shortly after treatment. One rabbit died within 30 minutes of treatment. These symptoms of cholinesterase inhibition persisted for about 24 hours. One day after exposure, the surviving rabbits were weak, but except for eye irritation appeared normal. These data suggest that monitor was readily absorbed from the conjunctival sac of the eye into the blood stream. Cholinesterase activities in blood, tissues or brain were not determined.

This study is adequate

The above information is sufficient to satisfy the data requirement.

Primary Dermal Irritation (163.81-5)

The minimum data requirement for primary dermal irritation is one test on each manufacturing-use product and each formulated product, preferably using the albino rabbit.

This test may be waived upon submission of data demonstrating that the test substance has a pH of 1-3 or 12-14; for regulatory purposes, a test with a pH of 1-3 or 12-14 will be considered corrosive to the skin.

Monitor Technical (73% a.i.) was only a mild dermal irritant (PIS = 0.6) to male New Zealand rabbits (Levy, 1979, MRID 00014220). However, out of 9 rabbits used in this study, 5 died within 24 hours after treatment. Toxic signs observed shortly after application included ataxia, increased respiration, salivation, miosis, tremors, diarrhea and collapse. The four surviving rabbits had well-defined erythema and two of these rabbits had also slight edema at 24 hours after treatment. At 96 hours, no erythema or edema was observed. The exposure time was 24 hours and 0.1 ml of the test material was applied to one intact and one abraded area on the back of each rabbit.

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The test material was a clear viscous liquid with an odor of rotten cabbage. This study is adequate.

In another study (Rittenhouse, 1977, MRID 00014222), Monitor Technical (% a.i. not specified) was also a mild dermal irritant to male New Zealand white rabbits, but the primary dermal irritation score could not be calculated because of high mortality. In that study, 0.5 ml of the test material was applied to both intact and abraded areas on the back of each of 6 rabbits. Toxic signs, observed in all animals shortly after application, included ataxia, tremors, salivation and slight to well-defined erythema. Four rabbits died within 48 hours after treatment (3 within the first 24 hours). The two surviving rabbits had normal skin at 72 hours. This study is adequate.

Both studies show that, although Monitor Technical was only a mild skin irritant, it was readily absorbed through the skin and was lethal to 55-67% of the rabbits studied. Of the nine deaths that occurrred in both studies, eight occurred within 24 hours after exposure. Because of this high mortality, a Toxicity Category I has to be assigned to Monitor Technical.

The above information is sufficient to satisfy the data requirement.

Dermal Sensitization (163.81-6)

The minimum data requirement for dermal sensitization is an intradermal test for each manufacturing-use product and each formulated product, preferably using the guinea pig.

No data are available on the dermal sensitization of Monitor. Testing, therefore, is required.

Acute Delayed Neurotoxicity (163.81-7)

The minimum data requirement for acute delayed neurotoxicity is one test for the technical chemical, using the adult hen.

An acute delayed neurotoxicity test is required if the active ingredient or any of its metabolites, degradation products, or impurities cause esterase depression or are structurally related to a substance that induces delayed neurotoxicity.

Monitor Technical (74% a.i.), in the absence of atropine sulfate, did not cause delayed neurotoxicity or spinal cord lesions at the 33.75 mg/kg level, with or without redosing. However, only 3 hens were redosed at this level. White leghorn hens, 9-18 months old, were used in this study (Kruckenberg et al., 1979, MRID 00041317).

Monitor, in the presence of atropine sulfate (50 mg/kg of body weight), did not cause neurotoxicity or spinal cord lesions in hens at the 50.63 mg/kg level (highest tested), with or without redosing. Atropine sulfate (50 mg/kg) given intramuscularly was not totally successful in preventing deaths from the acute toxic effects of Monitor. Two out of 10 test hens and four out of 12 test hens died at the 30 mg/kg and 50.63 mg/kg level of Monitor, respectively.

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Triorthocresol phosphate (TOCP; positive control), 500 mg/kg of body weight, administered orally in the presence of atropine sulfate (50 mg/kg) caused severe leg paralysis and moderate to marked neuronal degeneration in 7 out of 10 hens tested. Three hens did not develop visible signs of neurotoxicity, but showed slight to moderate degeneration of neurons during the histological examination. The absence of neurotoxic symptoms in hens with spinal cord lesions suggests that changes at the cellular level precede visible signs of neurotoxicity.

The acute oral LD_{50} for Technical Monitor (74% a.i.) was 29.75 mg/kg. No toxic symptoms and no deaths occurred at the 10 and 15 mg/kg levels. Deaths and signs of poisoning were observed at the remaining levels (22.5, 33.75, 50.63 and 75.94 mg/kg). The higher the dose, the sooner toxic symptoms appeared and the faster the death occurred. The acute signs of poisoning were muscular weakness, unsteadiness (leg weakness), diarrhea, excessive salivation, anorexia, lateral and sternal recumbency, dyspnea, and cyanotic combs and wattles shortly before death. Death was caused by respiratory paralysis.

This study is adequate.

The above information is sufficient to satisfy the data requirement.

Special Acute Studies: Intraperitoneal Toxicity of Methamidophos--Effects of Atropine or Pralidoxime (2-PAM) and Potentiation of Acute Oral Toxicity.

There are currently no specific data requirements under 40 CFR 163 for these studies.

Intraperitoneal Toxicity of Methamidophos - Effects of Atropine or Pralidoxime (2-PAM)

The acute intraperitoneal LD_{50} of methamidophos (Monitor, RE 9006; 98% pure) was 15 mg/kg of body weight (Robinson et al., 1978, MRID 05010274). Atropine sulfate (10 mg/kg) and pralidoxime (2-PAM iodide; 60 mg/kg) increased this value to 60 mg/kg and 52 mg/kg, respectively.

All rats treated with methamidophos exhibited typical peripheral and central signs of cholinergic stimulation including salivation, lacrimation, fasciculations, urination, piloerection, respiratory depression and confulsions. All rats that died after administration of methamidophos alone did so within 15 minutes after injection. After four hours, the survivors showed marked improvement. Those animals that died following treatment with methamidophos and atropine showed generally less frequent tremors and convulsions. The signs of cholinergic stimulation in the methamidophos and pralidoxime-treated rats were as apparent as those of rats given only methamidophos.

Cholinesterase activity was measured in brain of all animals at the time of unscheduled death, and in brain, blood (plasma) and stomach tissue at 24 hours after dosing, when all survivors were sacrificed. Brain cholinesterase

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activity at the time of death was markedly depressed after all doses of methamidophos, with activities ranging from 5.3% to 12.4% of controls. These data are summarized below. 003968

Brain Cholinesterase Activity of Male Rats at Unscheduled Death Following Treatment with Methamidophos.

Methamidophos (mg/kg)	Protectant	Number of Animals	Cholinesterase Activity*	Percent of Control Activity
12.5	None	19	0.81	11.5
15.0	None	5	0.87	12.4
17.5	None	8	0.52	7.4
30.0	A	1	0.69	9.8
40.0	P	1	0.37	5.3
45.0	A	3	0.62	8.8
45.0	P	3	0.57	8.1
60.0	A	5	0.64	9.1
60.0	P	7	0.45	6.4

* Expressed as μMoles of acetylcholine hydrolyzed/min/g wet weight of tissue. Control brain cholinesterase activity was 7.3. A = Atropine; P = Pralidoxime (2-PAM).

The degree of depression of brain cholinesterase activities following large doses of methamidophos plus pralidoxime or atropine was similar to that seen after smaller doses of methamidophos alone. Cholinesterase activities of brain tissue from atropine-treated rats given 60 mg/kg of methamidophos were about 30% higher than brain cholinesterase activities of rats that received pralidoxime and 60 mg/kg of methamidophos (ChE activities of 0.64 vs. 0.45).

Twenty-four hours after injection of 12.5 - 60 mg/kg of methamidophos, the cholinesterase activities in plasma, stomach and brain were still inhibited about 40-75%, 75-85% and 32-55%, respectively. A linear relationship existed between the degrees of depression of cholinesterase activity and the dose of methamidophos administered. Both atropine and pralidoxime were essentially without effect on the cholinesterase inhibition and recovery.

In another phase of this study, concerned with the recovery of cholinesterase activity, one group of male Holtzman rats received (i.p.) 12.5 mg/kg of methamidophos (LD_{20}) and the other group received 12.5 mg/kg of methamidophos plus 60 mg/kg pralidoxime (i.m.). Forty-eight hours after

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dosing, cholinesterase activities in plasma, brain and stomach tissue had returned to above 60% of the control values. Only slight differences in tissue cholinesterase activities were observed between the unprotected and the pralidoxime-protected rats.

This study is acceptable.

Potentiation of Acute Oral Toxicity (Rat)

The purpose of this study was to determine if Monitor Technical potentiated the acute oral toxicity of Orthene Technical. It was found that this potentiation was insignificant in male and female Charles River rats (Kretchman, 1972, MRID 00014934).

This study was conducted in two phases. First, the acute oral LD_{50} values for each Monitor Technical and Orthene Technical were determined in rats. The LD_{50} value of an equitoxic mixture of Orthene and Monitor was then determined experimentally and compared with a theoretical LD_{50} value of the same mixture. The theoretical LD_{50} value for the equitoxic mixture was calculated with the assumption that, in the absence of potentiation, the toxicities of Monitor Technical and Orthene Technical would be strictly additive. The LD_{50} values obtained in this study are listed below.

Orthene Technical	2025	mg/kg
Monitor Technical	21.15	mg/kg
Equitoxic Mixture (experimental)	813.2	mg/kg
Equitoxic Mixture (theoretical)	1023	mg/kg

All doses are expressed in terms of Orthene Technical and/or Monitor Technical and not in terms of their active ingredients. The acephate content (a.i.) of Orthene Technical and the methamidophos content (a.i.) of Monitor Technical were not reported.

The ratio of 1023 mg/kg to 813.2 mg/kg = 1.25 indicates that the potentiation of Orthene toxicity by Monitor was insignificant. However, these data are based on only 2 rats/sex/level, or on too few rats. Body weight gains were unaffected in all survivors.

These data are acceptable as Supplementary.

Subchronic Oral Toxicity (163.82-1)

The minimum data requirement for subchronic oral toxicity is one test for the technical chemical in two mammalian species, preferably using the rat and dog.

A subchronic oral toxicity test is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires the issuance of a food

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additive regulation, or is likely to result in repeated human exposure through the oral route.

A 90-day rat feeding study (Loser, 1970, MRID 00014155) and a 90-day dog feeding study (Loser, 1970, MRID 00014153) are available, but both are classified as Supplementary.

Male and female Wistar rats were fed the technical grade of BAY 71 628 (Monitor) for 90 days at the following levels (ppm): 0, 2, 6, 20 and 60. The methamidophos (a.i.) content of this material was not stated. This treatment had no effect on the hematology, clinical chemistry, urinalysis, mortality and gross necropsy (histopathology was not performed). At the 60 ppm level, appearance, behavior, food intake, body weight gain and organ weights were affected in the male rats. The following organs weighed significantly less ($p < 0.01$ or 0.05) than in the control male group: thyroids, thymus, heart, lung, liver, spleen, kidney, adrenals and gonads. These differences were due to the reduced body weights.

Data for cholinesterase activities are summarized below.

Inhibition (%) of Plasma Cholinesterase Activity

BAY 71628 ppm	Sampling time (weeks after feeding)							
	1		4		8		13	
	M	F	M	F	M	F	M	F
2	0	0	7	4	0	0	11	0
6	17	16	1	23	5	22	25	15
20	39	46	41	56	27	56	42	49
60	51	65	51	71	38	70	55	71

Inhibition (%) of Erythrocyte Cholinesterase Activity

BAY 71628 ppm	Sampling time (weeks after feeding)							
	1		4		8		13	
	M	F	M	F	M	F	M	F
2	2	7	17	16	2	9	14	0
6	16	12	34	19	27	30	24	14
20	43	49	55	63	58	56	63	43
60	65	69	76	73	70	71	75	71

M = Males, F = Females

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he inhibition of cholinesterase activity in plasma and erythrocytes increased ith dose. At the 2 ppm level, the inhibition ranged, in most instances, from to 9%. At the 6, 20 and 60 ppm levels, cholinesterase activity was nhibited, in most instances, 15%-34%, 39%-63% and 51%-76%, respectively. At he 60 ppm level, the rats were quiet and appeared weak. Symptoms of holinesterase inhibition, such as tremors, were not observed.

)EL = 2 ppm (0.1 mg/kg of body weight), based on the inhibition of holinesterase activity in plasma and erythrocytes, in males and females.

)EL = 20 ppm (1.0 mg/kg), based on systemic effects.

:Ls = 6 ppm (0.3 mg/kg) for cholinesterase inhibition and 60 ppm (3 mg/kg) or systemic effects.

iese data should be considered as Supplementary because none of the tissues is examined histopathologically.

n another study (Loser, 1970, MRID 00014153), beagle dogs, 2/level/sex, were 3d the technical grade of BAY 71628 (Monitor) for 90 days at the following evels (ppm): 1.5, 5 and 15. The methamidophos (a.i.) content of this iterial was not stated.

iis treatment had no effect on the appearance, behavior, food intake, body eights, hematology, clinical biochemistry, urinalysis and organ weights. iere was no cloudiness of the cornea or lens, and no abnormalities in organs ere detected at gross necropsy. Histopathology was not performed.

ita for cholinesterase activities are summarized below.

Inhibition (%) of plasma cholinesterase activity

BAY 71628 ppm	Sampling Time							
	1 Week		1 Month		2 Months		3 Months	
	M	F	M	F	M	F	M	F
1.5	9	0	0	9	16	4	10	8
5.0	26	17	6	38	21	36	13	35
15.0	--	17	17	54	23	61	30	32

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Inhibition (%) of erythrocyte cholinesterase activity

BAY 71628 ppm	Sampling Time							
	1 Week		1 Month		2 Months		3 Months	
	M	F	M	F	M	F	M	F
1.5	0	9	0	10	5	15	0	20
5.0	16	7	20	31	41	42	9	41
15.0	--	37	49	54	60	81	56	74

M = males, F = females

The inhibition of cholinesterase activity in plasma and erthrocytes increased with dose. At the 1.5 ppm level, the inhibition ranged generally from 0% to 10%, in both sexes. At the 5 ppm level, plasma and erythrocyte cholinesterase activities were inhibited in most instances, 31%-42% in the females and 17%-26% in the males. At the 15 ppm level, most of the cholinesterase inhibitions in males and females were 37%-81%.

NOEL = 1.5 ppm (0.0375 mg/kg), based on the inhibition of cholinesterase activity in plasma and erythrocytes, in males and females.

NOEL = 15 ppm (0.375 mg/kg), based on systemic effects.

LEL = 5 ppm (0.125 mg/kg), based on the inhibition of cholinesterase activity in plasma and erythrocytes, in males and females.

This study should be regarded as supplementary for the following reasons: (1) too few animals/sex/dose were used; (2) histopathology was not performed; and (3) unclarities exist in the reporting of data.

Although Monitor is a pesticide in its own right, about 5%-10% of Orthene (acephate) can be converted to Monitor by plants (Crossley and Lee, 1972, MRID 00015222). The animals fed Orthene-sprayed crops could, therefore, be exposed to both pesticides. The toxic effects of such an exposure have been the subject of at least two subchronic feeding studies.

In one study (Ladd, et al., 1972, MRID 00015183), dairy cattle were fed 0.6, 2, or 6 ppm of Ortho 9006 (Monitor) and 3, 10, or 30 ppm of Orthene, respectively, for 30 consecutive days. This treatment had no effect on their behavior, food consumption, milk production, mortality, and gross pathology. This study is acceptable.

In another study (Ladd, 1972, MRID 00015227), crossbred pigs received in their diets 0.6, 2, or 6 ppm of Ortho 9006 and 3, 10, or 30 ppm of Orthene, respectively, for 21, 27, or 30 consecutive days. This treatment caused no adverse behavioral reactions, mortality, or adverse gross pathology. However,

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all test groups exhibited lower food consumption when compared to controls. There was also a downward trend in body weight gains with increased exposure levels. This study is acceptable.

The above information is not sufficient to satisfy the data requirement; additional testing is required. Both the rat and the dog subchronic feeding studies contain only supplementary data.

Subchronic Oral Toxicity (163.82-1): Cholinesterase Inhibition Test.

According to the Proposed Guidelines 40 CFR 163.82-1, if the test substance contains a carbamate, an organophosphate, or any chemical that produces acetylcholinesterase inhibition, the enzyme activity for plasma, red blood cell, and brain shall be monitored. In the pre-Guideline era, separate studies of cholinesterase activity have frequently been conducted and submitted to the regulatory agencies. One such study involving human subjects was conducted by Garofalo (1973, MRID 00015160).

Plasma and erythrocyte cholinesterase activity was studied in adult human subjects (7 men and 7 women) during and after a subchronic oral dosing with RE 9006 (Monitor) and RE 12420 (Orthene). Monitor and Orthene were fed as mixtures in ratios of 1:4 or 1:9 until plasma and/or erythrocyte cholinesterase inhibition occurred. The 1:9 Monitor:Orthene group was fed 0.1, 0.2, 0.3, and 0.4 mg/kg of body weight of the mixture. The 1:4 Monitor:Orthene group received only 0.1 and 0.2 mg/kg levels.

All subjects were in good health at the completion of the study. Erythrocyte cholinesterase activity was not inhibited during the 37-73 days of feeding the test materials. Data for plasma cholinesterase inhibition are summarized below.

Test Material Combination Monitor:Orthene	NOEL (mg/kg/day)		LEL (mg/kg/day)
1:4	0.1	M + F	0.2
1:9	0.2	M	0.3
	0.3	F	0.4

Plasma cholinesterase activities were inhibited significantly in the 1:4 and 1:9 (Monitor:Orthene) groups. The inhibition in the 1:4 group was first noted at the 0.2 mg/kg level after 16 days of dosing and occurred in all subjects studied (2 males and 2 females). The first significant inhibition in the 1:9 group was observed at the 0.3 mg/kg level after 21 days of dosing and only in the male subjects. The first significant inhibition in the female subjects was noted at the 0.4 mg/kg level after 10 days of dosing. All depressed cholinesterase activities returned to the pretest levels during the 7-day observation period. The inhibition of cholinesterase activity was considered significant when it "was greater than two standard deviations below mean pretest activity for two consecutive bleedings."

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The pretest cholinesterase activities in the erythrocytes were about the same in males and females. However, nearly all plasma cholinesterase activities in the female subjects were about one-half of those reported for the males.

The results from this study are acceptable as supplementary data. Unsupervised weekend dosing and lack of urine analysis for the test materials constitute weak points in this study.

Subchronic 21-Day Dermal Toxicity (163.82-2)

The minimum data requirement for subchronic 21-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

A subchronic 21-day dermal toxicity test is required if pesticidal use is likely to result in repeated human skin contact.

The above information is not sufficient to satisfy the data requirement; additional testing is required.

A 21-day dermal toxicity study with Monitor Technical is missing and this is considered a toxicity data gap. The commercial use of Monitor as an insecticide and acaricide is increasing rapidly and could readily result in repeated human skin contact.

Subchronic 90-Day Dermal Toxicity (163.82-3)

The minimum data requirement for subchronic 90-day dermal toxicity is one test for the technical chemical, preferably using the albino rabbit.

The subchronic 90-day dermal toxicity is required if pesticidal use will involve purposeful application to the skin or will result in human exposure comparable to that, for example, from swimming pool additives or pesticide-impregnated fabrics.

This study is not required. The pesticidal use of Monitor excludes swimming pools and does not involve purposeful application to the skin.

Subchronic Inhalation Toxicity (163.82-4)

The minimun data requirement for subchronic inhalation toxicity is one test for the technical chemical, preferably using the laboratory rat.

A subchronic inhalation toxicity test is required if pesticidal use may result in repeated inhalation exposure at a concentration that is likely to be toxic, as determined from results of acute inhalation testing.

This study is not required. Although the results of acute inhalation testing are only supplementary and the LC_{50} was not determined (Cavalli and Hallesy, 1968, MRID 00014051), it is unlikely that the pesticidal use of Monitor Technical will involve repeated inhalation exposures to toxic levels.

Subchronic Neurotoxicity (163.82-5)

The minimum data requirement for subchronic neurotoxicity testing is one test for the technical chemical, using either the adult hen or a mammalian species.

A subchronic neurotoxicity test is required if the pesticide has shown positive results in the acute delayed neurotoxicity test or induced irreversible neurological toxicity in a mammalian species.

This test is not required. Negative results were obtained in the acute delayed neurotoxicity test (Kruckenberg, et al., 1979, MRID 00041317).

Chronic Feeding (163.83-1)

The minimum data requirement for chronic feeding is one test for the technical chemical, preferably using the laboratory rat.

A chronic feeding study is required if pesticidal use requires a tolerance or exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the life-span.

The above information is not sufficient to satisfy the data requirement; additional testing is required.

A rat chronic feeding study is missing and this constitutes a toxicity data gap. According to Mobay Chemical Corporation (memo to W.H. Miller, Registration Division; 2/24/82), this study is currently being conducted. The estimated completion date is August, 1984.

Oncogenicity (163.83-2)

The minimum data requirement for oncogenicity is testing in two mammalian species, preferably the rat and mouse, using the technical chemical.

An oncogenicity test is required if the active ingredient, or any of its metabolites, degradation products or impurities is/are structurally related to a recognized carcinogen or causes a mutagenic effect, requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the life-span.

Only an interim (one-year) report on an ongoing mouse oncogenic study is currently available (Mobay Chemical Corporation, 1981, MRID GS0043-001). This study was initiated on January 14, 1980, and the anticipated completion date is January, 1983.

CD1 Outbred Strain white mice, obtained from the Charles River Breeding Laboratories, were assigned randomly to either a reserve group (80 animals; 10 males, and 10 females/level) or a regular study group (400 animals; 50 males, and 50 females/level). Both groups were fed concurrently a diet containing 0, 1, 5, or 25 ppm of technical grade methamidophos (Monitor). The purpose of the reserve group was to provide the interim clinical and gross necropsy data.

It was reported that there were no compound-related trends in body weights, food consumption, hematology, gross necropsy, or observations at this interval of the study. There were a total of 6 deaths (7.5%) in the reserve group and 26 deaths (6.5%) in the regular study group during the initial 53 and 54 test weeks, respectively. Enlarged abdomen was listed as a course of death. There were no behavioral abnormalities or toxic symptoms. The gross necropsy observations are summarized below.

Gross Necropsy of Mice from the Reserve Group

Females	Control	1 ppm	5 ppm	25 ppm
Ovaries-cystic	3	4	5	4
Uterus-thickened	2	3	3	3
Stomach-thickened	1	1		1
Thymus-enlarged			1	
Kidney-cystic			1	
Males				
Lymph nodes-enlarged	1			
Thymus-enlarged	1			
Spleen-enlarged	1			
Liver-enlarged	1			
Kidney-cystic	1		1	
Lung-mass	1		1	
Liver-mass		1	1	
Stomach-thickened			2	
Urethral blockage	1			

Gross necropsy did not reveal any masses in females, although one mass (not stated where) was detected by palpation at the 1 ppm level. A dose-relationship cannot certainly be attributed to the one lung mass and the two liver masses detected at autopsy in the Monitor-fed male mice. Histopathological examinations have not yet been performed.

This report contains supplementary data. Most of these data were submitted either in the form of short summaries or as one-sentence statements.

The rat chronic feeding/oncogenic study is currently in progress. The anticipated completion date is August, 1984 (memo from Mobay Chemical Co. to W.H. Miller, Registration Division, 2/24/82).

This information is not sufficient to satisfy the data requirement; additional testing is required.

Teratogenicity (163.83-3)

The minimum data requirement for teratogenicity is testing in two mammalian species using the technical chemical.

Teratogenicity testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in a significant exposure to females.

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Only a rabbit teratology study is currently available (Machemer and Lorke, 1979, MRID 00041315). A rat teratogenic study will be completed in October, 1982 (memo from Mobay Chemical Co. to W.H. Miller, Registration Division, 2/24/82).

Monitor (known also as SRA 5172) was not embryotoxic or teratogenic to Himalayan rabbits at the 2.5 mg/kg level (highest tested). It did not affect the appearance and behavior of the dams, or cause death. However, Monitor was maternally toxic at all levels tested (0.1, 0.5, and 2.5 mg/kg). Although not strictly dose-related, there was a 53-63% decrease in the weight gain of the dams during the treatment period. At the conclusion of the experiment (gestation day 29), the average weight of the experimental animals was about 47%-48% of the weight attained by the controls. The reduced weight gain was not caused by a small litter size or a lower fetus weight. No information was provided on the food consumption of the animals. Female rabbits were treated with Monitor during gestation days 6-18. This study is adequate.

This information is not sufficient to satisfy the data requirement; additional testing is required. Only one (rabbit) teratogenic study is currently available.

Reproduction (163.83-4)

The minimum data requirement for reproduction is testing in one mammalian species, preferably the laboratory rat, using the technical chemical and lasting for two generations.

Reproduction testing is required if pesticidal use requires a tolerance or an exemption from a tolerance, requires an issuance of a food additive regulation or is likely to result in repeated human exposure over a significant portion of the life-span.

This information is not sufficient to satisfy the data requirement; additional testing is required.

A reproduction study is currently unavailable and this constitutes a toxicity data gap. According to Mobay Chemical Corporation (memo to W.H. Miller, Registration Division, 2/24/82), a rat reproduction study will be completed in June, 1984.

Mutagenicity (163.84-1 through -4)

The minimum data requirements for mutagenicity testing will be finalized pending formulation of Agency Guidelines.

No data on the mutagenic properties of Monitor are currently available and this constitutes a toxicity data gap. According to Mobay Chemical Corporation (memo to W.H. Miller, Registration Division, 2/24/82), one mutagenic test (Ames) was completed in February, 1982 and another test (Dominant lethal) will be completed in August, 1982.

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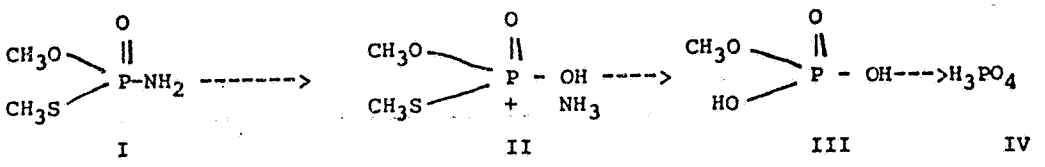
Metabolism (163.85-1)

The minimum data requirement for metabolism is a single dose using the analytically pure grade of the active ingredient in the radioactively labelled form.

Studies with radioactive and nonradioactive Monitor have shown that Monitor is rapidly degraded and/or excreted by the animals. It does not accumulate in tissues.

Crossley and Tutass (1969, MRID 00015224) studied the metabolism of Monitor by male and female Sprague-Dawley rats, using Monitor labeled with either ^{14}C in the S-methyl group or with ^{32}P. Most of the administered radioactivity was eliminated in the first 24 hours following oral dosing. In the ^{14}C studies, about 60% of the radioactivity was detected in CO_2 (breath) and 11% appeared in urine. In the ^{32}P experiments, about 70% of the ingested radioactivity appeared in urine. Feces contained only 1.5%-2.8% of the administered radiolabel. About 70% of the radioactivity in urine and feces was associated with unchanged Monitor. There was no difference in the rate of metabolism, excretion, and nature of the metabolites between male and female rats.

The following compounds were identified in urine: Monitor (I), O,S-dimethyl phosphorathioate (II), methyl dihydrogen phosphate (III), and phosphoric acid (IV). As the quantities of I, II, and III decreased with time after dosing, the quantities of IV increased. Based on these and other data (activity in CO_2, feces and in natural products), the following degradation pathway for Monitor was proposed:



The degradation of Monitor was hydrolytic in nature. None of these metabolites (II, III, and IV) were considered toxic.

The radioactivity remaining in the animals after the initial rapid excretion consisted of minute traces of Monitor, its metabolites and natural constituents of the body (proteins, lipids, nucleic acids, etc.) which had incorporated the radiolabel. This radioactivity was evenly distributed throughout the body and it represented the second or slow phase of excretion. The amount of unchanged Monitor found in the tissues 14 days after dosing was less than 0.004 ppm.

Similar results were obtained in another study with male Sprague-Dawley rats (Cheng, 1974, MRID 00014518). This study showed that treatment of rats with single oral doses of S-methyl-^{14}C-Ortho 9006 did not result in the hepatic binding or conjugation of the test material. Analysis of liver tissue at 3 hours after exposure and urine, collected for 24 hours after exposure, showed that most of ^{14}C was a free unchanged Ortho 9006 (Monitor). Both studies are acceptable.

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Dairy cattle, like rats, excreted the ingested Monitor rapidly in urine and did not accumulate it in tissues. In the study by Tucker (1973, MRID 00015225), lactating cows received 0.6, 2, or 6 ppm of Monitor (Ortho 9006) and 3, 10, or 30 ppm of Orthene, respectively, in a gelatin capsule for 30 consecutive days. The cows were observed for 6 days after the dosing stopped. Monitor was rapidly eliminated from the body. On the recovery day 1, urine contained only about one-tenth of the administered daily dose and no Monitor was detected on the recovery day 4. Milk contained about 0.03% to 0.10% of the daily dose of Monitor. These levels remained constant during the test, but there was no Monitor in milk on the recovery day 2. None of the tissues studied (liver, heart, kidney, muscle, and subcutaneous and peritoneal fat) contained Monitor on the recovery day 1. This study is acceptable.

In the study by Baychem Corporation (1972, MRID 00014230 and MRID 00014229), Holstein dairy cattle were fed 0.2, 1, or 5 ppm of methamidophos for 28 days. Methamidophos (Monitor) did not accumulate in the brain, heart, liver, kidney, muscle, and fat of these cows. The methamidophos content of all tissues studied was <0.01 ppm.

Milk obtained from cows at the 0.2 and 1 ppm levels (0.006 and 0.03 mg/kg, respectively) contained <0.001 ppm of Monitor after 27-28 days of dosing. Milk obtained from cows fed 5 ppm of Monitor (0.15 mg/kg) contained 0.004-0.008 ppm and 0.011-0.021 ppm of Monitor residues after 27 and 28 days of dosing, respectively. This study is acceptable.

One goat, dosed orally with 4 mg (2 ppm) of ^{14}C-S-methyl Ortho 9006 for 7 consecutive days, also degraded rapidly and excreted Monitor (Crossley and Lee, 1972, MRID 00015222). About 33% of the daily ^{14}C was detected in the general metabolic pool (that is, incorporated into proteins, lipids, nucleic acids, etc.); 17% and 4% appeared in urine and feces, respectively; and about 30% (unaccounted for radioactivity) was apparently lost in CO_2. Monitor level in milk was about 0.002 ppm during dosing and none was found during the recovery period.

Because these data were obtained from only one animal, they are acceptable as Supplementary.

Monitor residues in the hen tissues were low or very low, but substantial amounts of Monitor appeared in the eggs (Ackerman et al., 1975, MRID 00014279). Laying hens were fed 0, 2, 6, or 20 ppm of Monitor for 28 consecutive days. At the 20 ppm level, liver, fat, kidneys, heart (and gizzard) and muscle contained 0.003, 0.003, 0.005, 0.022, 0.026, and 0.033 ppm of Monitor, respectively at the termination of the study. At the 2, 6, and 20 ppm levels, eggs contained 0.008, 0.032, and 0.198 ppm of Monitor on test day 28. At the 20 ppm dose, a constant level of Monitor in eggs was already reached on test day 3. There was no recovery period in this study. This study is acceptable.

The above information is sufficient to satisfy the data requirement.

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