UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

011550

#378A MAY 16 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Methamidophos (SRA 5172; Monitor): 82-4 Subchronic (90-Day) Inhalation Study in the Rat

DP Barcode No. D176788 (main study)
D172627 (addendum)
Submission No. S415662 (main study)
S408999 (addendum)

Rereg. Case No. 0043
EPA ID No. 101201
CAS Registry No. 10265-92-6

Case No. 819351
P.C. Code No. 101201
Tox. Chem. No. 378 A

FROM: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I
Health Effects Division (7509C)
Krystyna K. Locke 5/8/95

TO: Larry Schnaubelt / Robert Richards, PM Team No. 72
Reregistration Branch
Special Review and Reregistration Division (7508W)

THRU: Roger Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (7509C)
Roger Gardner 5/9/95
KB 5/12/95

Section I, Toxicology Branch I/HED has completed an evaluation of the following study:

SRA 5172 (Methamidophos): Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413; J. Pauluhn; Bayer AG, Wuppertal, Germany; Report Numbers: 98370 and T9022366; Study Completion Date: March 30, 1988. **MRID No. 41402401**

Addendum to Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413 (MRID No. 41402401); R.M. Cole; Valent USA Corporation; Report Numbers 98370-1 and T9022366; Study Completion Date: July 8, 1991. **MRID No. 41966301**

In this study, Wistar rats were exposed to a respirable aerosol (particle size: 1.26-1.53 um) of SRA 5172 for 3 months (head/nose only, 6 hours/day, 5 days/week). The mean analytical concentrations of SRA 5172 in the inhalation chambers were 0 (air

1

control), 0 (vehicle control), 1.1, 5.4 and 23.1 mg/m^3 or 0, 0, 0.001, 0.005 and 0.023 mg/L, respectively. Polyethylene glycol E 400:ethanol (1:1) was the vehicle in which SRA 5172 was aerosolized. There were also two satellite groups which served as recovery groups. Following a 3-month exposure to the vehicle or SRA 5172 (23.1 mg/m^3), these rats were observed for 6 weeks without exposure and were sacrificed during week 19.

Treatment-related effects were not observed in the low-dose group. Relative to the vehicle control values, the only effect observed in the mid-dose males and females was the inhibition of cholinesterase (ChE) activities in erythrocytes, plasma and brain.

The following effects were observed in the high-dose males and females when compared with the vehicle control rats: **(1)** muscle tremors and aggressive behavior; **(2)** Decreased body weight gain and food consumption; **(3)** Increase in plasma lactate dehydrogenase and glutamate oxaloacetate transaminase activities in males only; **(4)** Decrease in plasma protein, cholesterol and glucose concentrations; **(5)** Inhibition of ChE activities in erythrocytes, plasma and brain; and **(6)** Decreased spleen weight, both absolute and relative (organ/body weight ratio). When treatment was discontinued, ChE activities in the erythrocytes and plasma (not determined in the brain) returned to the pretreatment values.

Based on the inhibition of ChE activities in erythrocytes, plama and brain, **the NOEL and LOEL for both sexes are 1.1 mg/m^3 (0.001 mg/L) and 5.4 mg/m^3 (0.005 mg/L)**, respectively. This study is classified as **Core-Guideline (Acceptable)** and satisfies the requirement, § 82-4, for a subchronic inhalation toxicity study in the rat.

Krystyna K. Locke 5/8/95

Primary Review by: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I, Health Effects Division (7509C)

Roger Gardner 5/9/95

Secondary Review by: Roger Gardner, Section Head
Section I, Toxicology Branch I, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 82-4 Subchronic Inhalation Toxicity (90-Day) in the Rat

EPA IDENTIFICATION NUMBERS:

Main study: MRID No. 41402401; DP Barcode No. D176788 and Submission No. S415662. Addendum: MRID No. 41966301; DP Barcode No. D172627 and Submission No. S408999

EPA ID No. 101201
Case No. 819351
CAS Registry No. 10265-92-6

P.C. Code No. 101201
Tox. Chem. No. 378 A

TEST MATERIAL: Technical grade SRA 5172 (O,S-Dimethyl phosphoramidothioate; Methamidophos; Monitor, Tamaron); Purity: 73.4%; Batch No. 77-297-149; colorless to light yellowish crystalline solid; readily soluble in water; stable for 6 months when stored at room temperature in the dark.

REPORT NUMBERS: 98370 and T9022366 (main study)
98370-1 and T9022366 (addendum)

SPONSOR: Valent USA Corporation, Walnut Creek, California.

TESTING FACILITY: Bayer AG, Wuppertal, Germany.

TITLE OF REPORTS: SRA 5172 (Methamidophos): Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413; and Addendum to Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 413 (MRID No. 41402401)

AUTHORS: J. Pauluhn and R.M. Cole

STUDY COMPLETION DATE: March 30, 1988

EXECUTIVE SUMMARY

In this subchronic inhalation toxicity study, Wistar rats, 10/sex/dose, were exposed to an aerosol of SRA 5172 (Methamidophos) for 3 months (head/nose only, 6 hours/day, 5 days/week). The mean analytical concentrations of SRA 5172 in the exposure chambers were 0(air control), 0(vehicle control), 1.1, 5.4 and 23.1 mg/m^3 or 0, 0, 0.0011, 0.0054 and 0.0231 mg/L, respectively. Polyethylene glycol E 400:ethanol (1:1) was the vehicle in which SRA 5172 was aerosolized. There were also two satellite groups (10 rats/sex/group) which served as recovery groups. Following a 3-month exposure to the vehicle or to SRA 5172 (23.1 mg/m^3), these rats were observed for 6 weeks without exposure and were necropsied during week 19. The concentrations of SRA 5172 used in this study were based on the inhibition of plasma cholinesterase activities in the range-finding study, summarized in the current submision. The mean mass median aerodynamic diameters (MMAD) of the SRA 5172 particles in the exposure chambers for the low-dose, mid-dose and high-dose groups were 1.52 ± 0.13, 1.26 ± 0.04 and 1.53 ± 0.09 um, respectively. The potential mass-related "accessibility to the alveoli" (particles ≤ 5 um) in these groups was 98.7, 99.7 and 98.9%, respectively.

Treatment-related effects were not observed in the low-dose group. Relative to the vehicle control values, the only effect observed in the mid-dose male and female groups was the inhibition of cholinesterase (ChE) activities in erythrocytes (7-28%; P<0.05 or 0.01), plasma (44-63%; P<0.05 or 0.01) and brain (25-29%; P<0.01).

The following effects were observed in the high-dose male and female rats when compared with the vehicle control rats: **(1)** slight to moderate muscle tremors and aggressive behavior; **(2)** Decreased body weight gain (53%); **(3)** Decreased food consumption (5-28%); **(4)** Increase in plasma lactate dehydrogenase (63%) and glutamate oxaloacetate transaminase (32%) activities in males only; **(5)** Decrease in plasma protein (8%), cholesterol (16-19%) and glucose concentrations (10-11%); **(6)** inhibition of ChE activities in erythrocytes (15-44%; P<0.05 or 0.01), plasma (53-93%; P<0.01) and brain (45-47%); and **(7)** Decreased spleen weight, both absolute (15-25%; P<0.01) and relative (organ/body weight ratio, 11%; P<0.01). When treatment was discontinued, ChE activities in the erythrocytes and plasma (not determined in the brain) returned to the pretreatment values.

Based on the inhibition of ChE activities in erythrocytes, plasma and brain, **the NOEL and LOEL for both sexes are 1.1 mg/m^3 (0.001 mg/L) and 5.4 mg/m^3 (0.005 mg/L)**, respectively. This study is classified as **Core-Guideline (Acceptable)** and satisfies the requirement, § 82-4, for a subchronic inhalation toxicity study in the rat.

EXPERIMENTAL PROCEDURES

This study was conducted from July to November, 1986. Wistar rats, 10 males and 10 females per group, were exposed to an SRA 5172 aerosol for 3 months (head/nose only, 6 hours/day, 5 days/week). The mean analytical concentrations of SRA 5172 (expressed as an active ingredient, ai) in the exposure chambers were 1.1, 5.4 and 23.1 mg/m^3 of air or 0.0011, 0.0054 and 0.0231 mg/L of air, respectively. One control group was exposed only to air and another only to vehicle (polyethylene glycol E 400/ethanol). There were also two satellite groups (10 males and 10 females/group) which served as recovery groups. Following a 3-month exposure to the vehicle or to SRA 5172 (23.1 mg/m^3), these rats were observed for 6 weeks without exposure and were necropsied during week 19. The concentrations of SRA 5172 used in this study were based on the results observed in a range-finding study. In that study, male and female rats were exposed (head/nose only, 6 hours/day for 5 days) to SRA 5172 at concentrations (ai) of 0, 1.4, 5.4 and 33.1 mg/m^3, and the NOEL, based on the inhibition of plasma cholinesterase activity, was 5.4 mg/m^3 of air (0.0054 mg/L).

SRA 5172, dissolved in ethanol, was aerosolized in a mixture of polyethylene glycol E 400:ethanol (1:1) as vehicle. Direct aerosolization of SRA 5172 or aerosolization in pure solvent without the vehicle was not possible because the compound crystallized in the nozzle. Each inhalation chamber had the capacity of about 20 liters and accomodated 20 rats. SRA 5172 was fed continuously into the exposure chamber with filtered air at a flow rate 10 liters/minute. The temperature and humidity of the exposure chamber were 21-25°C and 20-60%, respectively, and the oxygen concentration was 19.5-20.9%. The air flow rate to the chamber, and the temperature, humidity and oxygen concentration inside the chamber were monitored continously. The particle size was determined using an Aerodynamic Particle Sizer with Laser Velocimeter (TSI-APS-3300) and a Berner Cascade Impactor. The air samples for the analytical determinations were taken from the exposure atmosphere in the breathing zone of the rats three times a day: at the start of exposure (after attaining a steady-state concentration), at about the middle of exposure and toward the end of exposure. **The rats were:**

(1) Obtained from Winkelmann, Borchen, Paderborn District, Germany.

(2) About 7-11 weeks old and weighed about 170 g (mean value).

(3) Housed in groups of 5, of the same sex, in Makrolon® cages, at temperature of 22 ± 2°C, relative humidity of approximately 50% and 12 hours light/12 hours dark cycles.

(4) Acclimated for at least 1 week prior to the start of treatment.

(5) Allocated to groups randomly and identified by individual color markings and cage I.D. cards. Starting at week 6, individual ear tattoos provided additionl identification.

(6) Allowed free access to food (Altromin® 1324 Feed for Rats and Mice, pelletized) and tap water (bottles).

The following parameters were examined for all rats on the study unless indicated otherwise:

(1) **Clinical Observations:** On exposure days, appearance and behavior were evaluated individually before and after exposure, but not during exposure. Evaluation in the exposure tubes was performed only if clear signs occurred, such as convulsions or severely difficult breathing. The rats were also observed for toxic signs on the days of no exposure.

(2) **Body Weights:** Were determined prior to the first exposure and once per week thereafter.

(3) **Food Consumption:** It was not planned originally to record food consumption. However, because the body weight gain of the rats in all groups was slightly decreased starting midway through the study, the food consumption was recorded by cage starting with week 5.

(4) **Hematology and Clinical Chemistry:** Most of these test were performed at the termination of the study. For the rats in the satellite groups, selected clinical parameters were determined at the end of the exposure period and during the recovery period. The blood samples were obtained by cardiac puncture of rats anesthetized with diethyl ether. The blood necessary for glucose determination was obtained during week 12 from the caudal vein of fasted nonanesthetized rats. The blood samples for the determination of cholinesterase (ChE) activities, as well as for the interim hematological examinations, were obtained from the retroorbital venous plexus of the nonanesthetized rats. For all examinations involving ChE activity, the blood samples were obtained from the rats 5 minutes after the end of exposure and the brain samples, less than 1 hour after the end of exposure. Interim examinations were performed during weeks 1, 4, 8 and 11, using 5 rats/sex/group in each case. The hematology and clinical chemistry parameters examined are listed in Attachment I of this review.

(5) **Urinalysis:** Urine was collected individually overnight from rats in metabolism cages, during week 12. The following parameters were examined: Protein, glucose, blood, bilirubin, urobilinogen, ketone bodies, urine volume and density, and pH.

(6) **Lung Function Tests:** These tests were performed on 2 males and 2 females per group at the end of the exposure period or at the end of the recovery period. The rats scheduled for these examinations were not exposed to SRA 5172 on the day of the lung function tests. Some of the many parameters examined were: Respiratory rate, intraesophageal pressure, lung resistance, inspiratory and expiratory capacities, total lung capacity and CO diffusion capacity.

(7) **Ophthalmoscopic Examination:** Eye examinations were performed on 5 rats/sex/group (without satellite groups) prior to the first exposure and at the end of the exposure period.

(8) **Necropsy:** At the end of 13-week exposure and 6-week recovery period, the rats were anesthetized with diethyl ether and sacrificed by exsanguination (cardiac puncture), and grossly examined.

(9) **Organ Weights:** The following organs were weighed after exsanguination: Adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus and thyroid. The relative organ weights (organ/body weight ratios) were also determined. The body weights used in these calculations were determined prior to necropsy.

(10) **Histological Examination:** The tissues examined and the processing and fixation techniques used are listed in Attachment II of this review. The tissues fixed in formalin were embedded in Paraplast and stained with hematoxylin and eosin. The bone marrow smears were stained with "modified" May-Gruenwald stain (MERCK).

(11) **Statistics:** Many procedures were uses in analyzing the above data and these are detailed in Attachment III of this review. In order to evaluate the significance of effects on liver weights in a more advanced manner than performed in the original report, an amended 84-page statistical report was submitted (Report No. 98370-1; MRID No. 41966301).

7

RESULTS

Concentration of SRA 5172 in the Inhalation Chambers

The target concentrations of SRA 5172 in the inhalation chambers were 0 (Control group, air), 0 (Control group, vehicle), 0.8, 6 and 30 mg/m^3. The mean analytical concentrations of SRA 5172 for these groups were 0, 0, 1.05 ± 0.45, 5.35 ± 1.23 and 23.05 ± 4.25, respectively.

Particle Size

The mean mass median aerodynamic diameters (MMAD) of the SRA 5172 particles in the inhalation chambers for Groups 3, 4 and 5 were 1.52 ± 0.13, 1.26 ± 0.04 and 1.53 ± 0.09 um, respectively. The potential mass-related " accessibility to the alveoli " (particles ≤ 5 um) in these group was 98.7, 99.7 and 98.9%, respectively.

Mortality

Two rats (male and female) died in the high-dose group, but there was no treatment-related mortality. The male rat died in connection with the lung function testing on day 84 and the female rat was sacrificed when moribund after the lung function test on day 85.

Clinical Observations

Toxic signs (slight to moderate muscle tremors and pronounced aggressive behavior) were observed only in the high-dose group. Tremors occurred in each rat during each exposure period, but were not observed prior to exposure the following day. The exact duration of tremors was not specified. Aggressive behavior was observed only during days 50-52 and coincided with the time of ear tattooing, but it was not observed in other groups. One female rat in the high-dose group, which was sacrificed when moribund, had severe breathing difficulties.

Body Weights

The test material had no effect on body weights of the low-dose and mid-dose groups, but rats in the high-dose group gained about one-half as much weight during the study as did the vehicle control group. In the satellite group, the body weights of the vehicle control and the high-dose groups differed only slightly during the exposure period and were the same at the end of the recovery period. The body weight gain data are summarized below.

	Body Weight Gains (g) During the Study #			
Test Group	Main Group		Satellite Group	
	Males	Females	Males	Females
Air control	85	8	-	-
Vehicle control	61	7	62	7
Low-dose	88	4	-	-
Mid-dose	79	9	-	-
High-dose	29	3	51	3
	Body Weight Gains (g) During the Recovery Period ##			
Vehicle control	-	-	74	21
High-dose	-	-	82	23

This table is based on Tables 4a and 4b, pages 79-80, of the submitted report (MRID 41402401). # Mean body weight during week 13 minus mean body weight during week 0. ## Mean body weight during week 19 minus mean body weight during week 13. The actual mean weekly body weights are in Attachment IV of this review.

Food Consumption

Because of " implausible body weight changes ", the weekly food consumption per cage (5 rats) was determined starting with week 6. According to the data reported on page 189 of the submission (Attachment IV in this review), male rats in the high-dose group consumed less food (5-28%) during most weeks than did the vehicle control group. However, the food consumption of the male rats in the high-dose satellite group and of the controls was similar during the exposure period. In the case of females, in both the main group and the satellite group, the vehicle control and the high-dose rats consumed similar amounts of food. Only during week 13, the high-dose females in the main group consumed 10% less food than did the vehicle controls.

Hematology

SRA 5172 had no effect on all of the parameters examined.

Clinical Chemistry (Excluding Cholinesterase)

With the exception of findings listed below and observed only in the high-dose group, SRA 5172 had no effect on the parameters examined.

	Percent Change #	
Finding	Males	Females
Plasma lactate dehydrogenase (↑)	63**	11
Glutamate oxaloacetate transaminase (↑)	32**	15
Protein (↓)	8**	8**
Cholesterol (↓)	19*	16**
Glucose (↓)	10**	11**

This table is based on Table 7, page 91, of the submitted report (MRID 41402401). # When compared with vehicle control. ↓ = Decrease and ↑ = Increase. * P<0.05 and ** P<0.01

Cholinesterase Activities

Relative to the vehicle control values, erythrocyte, plasma and brain cholinesterase (ChE) activities were inhibited in the mid-dose and high-dose male and female groups during the treatment period. However, these inhibitions were reversed during the recovery period. The ChE data are summarized below.

SRA 5172 (mg/m^3) #	Week	Erythrocytes	Plasma	Brain
ChE Activities (Percent of Vehicle Control Values): Main Group --- **Male Rats**				
0.8	1-11	82-99	71-88	-
	13	97	74	92
6	1-11	75-85* or **	41-52**	-
	13	86	62**	71**
30	1-11	69-73**	9-16**	-
	13	77	47**	53**
ChE Activities (as above): Satellite Group				
30	12	67**	15**	-
	16	100	118	-

This table is based on Table 8, page 93, of the submitted report (MRID 41402401). # Target values; the analytical values were 1.1, 5.4 and 23.1 mg/m^3, respectively. * P<0.05 and ** P<0.01. Detailed data for weekly determinations are in Attachment V of this review.

SRA 5172 (mg/m^3) #	Week	Erythrocytes	Plasma	Brain
	ChE Activities (Percent of Vehicle Control Values): Main Group --- **Female Rats**			
0.8	1-11	87-100	68-86	-
	13	93	81	89
6	1-11	72-93	37-55* or **	-
	13	82**	56**	75**
30	1-11	56-85* or **	7-9**	-
	13	71**	34**	55**
	ChE Activities (as above): Satellite Group			
30	12	65**	12**	-
	16	100	97	-

This table is based on Table 8, page 94, of the submitted report (MRID 41402401). # Target values; the analytical values were 1.1, 5.4 and 23.1 mg/m^3, respectively. * $P<0.05$ and ** $P<0.01$ Detailed data for weekly determinations are in Attachment V of this review. Cholinesterase activities were determined by the modified method of G.L. Ellmann et al. (Cholinesterases in erythrocytes, plasma and brain; Biochem. Pharmacol. 7:88; 1961).

Urinalysis

SRA 5172 had no effect on all parameters examined.

Lung Function Tests

These tests provided no evidence of lung damage.

Ophthalmoscopic Examination

Nothing remarkable was observed during this examination.

11

Necropsy

Treatment-related findings were not observed. The occasionally observed dose-unrelated "distended lungs" or "dark spleen" were regarded by the testing facility as postmortem artifacts. All of the gross pathological findings reported are summarized below.

SRA 5172 (mg/m^3)	Air Control	Vehicle Control	0.8	6	30
Finding	Number of Male Rats with Finding				
Lungs: Distended	**1**	-	-	1	-
Reddish zones	-	-	-	-	1
Suppurative, adhered to thorax	-	1	-	-	-
Spleen: Dark	-	**3**	2	3	1 & **1**
Testes: Small	1	1 & **1**	-	1	1
Finding	Number of Female Rats with Finding				
Lungs: Distended	-	1	-	1	-
Reddish zones	1	-	-	1	-
Spleen: Dark	-	-	-	1	-
Thymus: Dark zones	-	-	-	1	**1**
Liver: Portal fissures	-	-	-	-	1

The above table is based on data reported on pages 1024-1030 of the submitted report (MRID 41402401). All of the rats in the main group (10 sex/dose) and in the satellite group (10/sex in the vehicle control group and 10/sex in the high-dose group) were examined. Findings shown in bold print were observed in the satellite group.

The following findings were observed in one high-dose female which was sacrificed when moribund after the lung function test on day 85: Foamy esophagus; trachea filled with clear, viscous mucus; and yellowish foamy mucus in the small intestine. The high-dose male rat which died during the preparation for the lung function test on day 84 had only dark zones on the lungs.

Organ Weights

Compared with the air controls, the following changes in the absolute and relative organ weights were observed only in the high-dose group:

Organ	Absolute Weights		Relative Weights#	
	Males	Females	Males	Females
Liver	27% ↓ **	7% ↓ *	8% ↓ *	3% ↓
Spleen	25% ↓ **	15% ↓ **	6% ↓	11% ↓ **
Adrenals	15% ↓ *	16% ↑ *	6% ↑	21% ↑ **
Brain	3% ↓	7% ↑	23% ↑ **	12% ↑ *

The above table is based on Tables 13 and 14, pages 101-104, of the submitted report (MRID 41402401). # Organ/Body weight ratios
↓ = Decrease and ↑ = Increase * $P<0.05$ and ** $P<0.01$

Although statistically significant, some changes in organ weights, noted above, were very small. Also, as is shown below, the absolute weights of these organs were within the historical control range. Microscopic examination revealed the following findings in these organs: **Liver:** Hyperplasia in 20% males and vacuolated cell degeneration in 10% males; **Spleen:** No abnormalities; **Adrenals:** No abnormalities; and **Brain:** No abnormalities.

Organ Weights (mg)

	In this study ■		Historical Weights ■■	
Organ	Males	Females	Males	Females
Liver	6328	5825	4902-9370	4816-7708
Spleen	313	286	290-545	222-519
Adrenals	34	51	22-44	33-73
Brain	1322	1320	Not reported	

■ Group mean values

■■ These data were taken from Table 15, page 105, of the submitted report (MRID 41402401). These data were referenced as follows (translation of German citation): F. Kroetlinger and J. Pauluhn. Study of the Body Weight/Organ Weights Correlation of Wistar Rats: Control Animals from Toxicological Feed-

ing Studies and Studies Using Gavage Administration. Bayer AG Report No. 11482, dated January 21, 1983.

Histopathological Examination

Based on the very detailed incidence report (pages 551-648 in the submission, MRID 41402401), SRA 5172 did not damage organs including the respiratory tract (nasopharynx, oropharynx, larynx, trachea and lungs). The most frequent observations are summarized below.

SRA 5172 (mg/m^3) #	0(a)	0(v)	0.8	6.0	30.0
	M/F	M/F	M/F	M/F	M/F
Finding	Number of Rats with Finding in the Main Group				
Pituitary:					
Hyperemia	0/0	0/0	4/0	1/0	3/0
Eyes:					
Thick cornea	0/0	0/0	0/0	1/0	1/0
Larynx:					
Focal round-cell infiltration	1/2	0/3	1/1	1/0	2/5
Trachea:					
Focal round-cell infiltration	0/1	0/0	0/1	0/1	0/1
Lungs:					
Marginal emphysema	1/1	1/4	0/1	1/1	2/0
Focal vascular calcification	2/0	0/0	3/2	1/1	3/3
Liver:					
Hyperplasia	1/0	1/0	1/2	3/0	2/0
Periportal round-cell infiltration	0/1	0/0	1/0	1/1	1/1
Jejunum:					
Lymph. hyperplasia	3/1	0/1	1/1	1/0	0/1
Colon:					
Lymph. hyperplasia	0/0	0/1	3/1	0/2	1/0
Rectum:					
Lymph. hyperplasia	1/4	0/1	2/1	2/4	2/2
Kidneys:					
Hyperemia	9/10	8/10	10/8	10/10	10/9
Adrenals:					
Hyperemia	0/5	4/2	2/3	1/3	2/0
Nerve-Peripheral:					
Hyperemia	0/0	1/2	0/1	1/2	1/0

Continued on the next page

SRA 5172 (mg/m^3) #	0(a)	0(v)	0.8	6.0	30.0
	M/F	M/F	M/F	M/F	M/F
Finding	Number of Rats with Finding in the Satellite Group				
Larynx:					
Focal round-cell infiltration	-	1/1	-	-	3/3
Trachea:					
Focal round-cell infiltration	-	0/0	-	-	3/1
Lungs:					
Hyperemia	-	0/2	-	-	0/1
Thick septa	-	0/3	-	-	0/1
Focal vascular calcification	-	2/2	-	-	1/2
Liver:					
Hyperemia	-	3/1	-	-	0/1
Vacuolated cell degeneration	-	3/2	-	-	4/0
Jejunum:					
Lymph. hyperplasia	-	0/1	-	-	2/0
Colon:					
Lymph. hyperplasia	-	1/0	-	-	1/2
Rectum:					
Lymph. hyperplasia	-	1/0	-	-	2/1
Adrenals:					
Hyperemia	-	1/3	-	-	0/1

Target values; the analytical values were 1.1, 5.4 and 23.1 mg/m^3, respectively. In each instance, 10 rats (tissues)/sex/dose were examined.

0(a) = Air control and 0(v) = Vehicle control.

M/F = Males/Females

- Not examined. Only the vehicle control and high-dose rats were in the satellite group.

Bone Marrow (Sternum) Smears

Compared with the air control and vehicle control groups, there was a concentration-related increase in reticular cells and also an increasing trend in neutrophilic myelocytes, in male and female rats. However, there were no indications of toxicologically significant changes in the bone marrow. Microscopic examination revealed only hyperemia in one vehicle control male from

the main group and no abnormalities were observed in the satellite groups. The bone marrow findings noted above are summarized below.

SRA 5172 (mg/m^3)	0(a)	0(v)	0.8	6	30
Cell Type			Mean per Group		
Neutrophilic Myelocytes:					
Males	3.1	1.6	1.1	3.0	3.7
Females	1.4	1.2	1.7	3.5*	2.8*
Reticular cells:					
Males	0.8	1.2	1.6	3.0*	3.6*
Females	0.8	1.7	2.5	3.2	4.5*

This table is based on data reported on pages 934 and 935 of the submitted report (41402401). * $P<0.05$ (Tukey-Kramer test for significance).

COMMENTS

This study was conducted in compliance with the GLP Standards of 40 CFR Part 160 (FIFRA) and the OECD Principles of Good Laboratory Practice, C (81) 30 (Final) Annex 2 (Paris, May, 1981) The study meets the December 24, 1989 EPA Acceptance Criteria for a subchronic inhalation toxicity (90-day) in the rat (82-4).

In general, this study is well reported, but some sections are much too long. For example, the microscopic findings (group incidences) are tabulated on 97 pages, one tissue type per page. This kind of tabulation, although acceptable in the study report, is too cumbersome to use whenever these data, as submitted, may be required (inclusion in study review, peer review, etc.).

All experimental/analytical procedures used were referenced and/or described, and the Key to Abbreviations and Symbols in the Tables, and the English translations of German citations, were submitted. The following statements were also included in the report:

1. Statement of Data Confidentiality

2. Quality Assurance Statement. This study was inspected 5 times during July 3, 1986 and December 12, 1986.

16

Methamidophos TOXR 011550

Page_____ is not included in this copy.

Pages 17 through 39 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.