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

008846

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No.: 101201. Methamidophos: Subchronic Feeding (Cholinesterase) Study in the Rat and Position Paper on Establishing a Reference Dose

Case Number. 819351
Submission No.: S397164
HED Project No.: 1-1450
Tox. Chem. No.: 378A

FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 11/15/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

TO: Larry Schnaubelt/Robert Richards, PM 72
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Roger Gardner, Section Head Roger Gardner 11-15-91 KB 11/24/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Toxicology Branch (TB)/HED has completed an evaluation of the following submissions:

1. Technical Grade Methamidophos (MONITOR): An Eight-Week Subchronic Cholinesterase Study in Fischer 344 Rats. W.R. Christenson; Mobay Corporation; Study No.: 89-972-CV; Report No.: 100667; March 19, 1991.
MRID No.: 41867201
Guideline No.: 82-1 (Special Study)

2. Position Paper, entitled "Discussion of the Toxicological Basis for Revising the Reference Dose (RfD) for Chronic Exposure to MONITOR (Methamidophos)". D.L. Van Goethem, Mobay Corporation; J.H. Kinzell, Chevron; and R.A. Zimmerman, Valent; April 16, 1991. Study, MRID and Guideline Nos.: None

Each submission was classified by TB/HED as Acceptable.

The objective of the 8-week study was to establish a NOEL for the methamidophos-induced cholinesterase inhibition in plasma, erythrocytes and brain of the rat.

Technical grade methamidophos was administered in the feed to Fischer 344 rats (25/dose/sex) for 56 days at nominal concentrations of 0 (not detected), 0.5, 1, 2 and 4 ppm (analytical concentrations were 0, 0.49, 0.97, 2.12 and 4.30 ppm, respectively), expressed as an active ingredient.

According to the registrants, this study clearly defined a cholinesterase NOEL of 0.5 ppm (0.03 mg/kg/day; analytical value) for plasma (PChE), erythrocytes (RChE) and brain (BChE), in both sexes. Statistically significant inhibitions ($p \leq 0.05$) of cholinesterase activities observed at this level (PChE and RChE, in females and BChE, in males and females) were considered to be of no toxicological significance.

According to the TB/HED's interpretation of the reported cholinesterase activities in the 8-week rat feeding study, the NOELs for the inhibition of cholinesterase activities were as follows:

Plasma acetyl cholinesterase (PChE): 0.5 ppm; males
< 0.5 ppm; females

Plasma butyryl cholinesterase (BPChE): 0.5 ppm; males and females

Erythrocyte acetyl cholinesterase (RChE): 0.5 ppm; males
≤ 0.5 ppm; females

Brain acetyl cholinesterase (BChE): < 0.5 ppm; males and females

The Position Paper is concerned with the establishing of the Reference Dose (RfD; ADI) for methamidophos, based on the inhibition of cholinesterase activities in plasma, erythrocytes and brain. Currently, the published tolerances for methamidophos represent 5254% of the Provisional RfD (PADI) of 0.00005 mg/kg/day, established in 1987.

Using a NOEL of 0.03 mg/kg/day (0.5 ppm) from the 8-week rat feeding study and an Uncertainty Factor (UF) of 15, the registrants proposed a RfD of 0.002 mg/kg/day. Since the establishing of a RfD is the responsibility of the Agency's RfD Committee, the Position Paper, the new 8-week rat feeding (cholinesterase) study, and the relevant toxicological studies from the TB files are currently being submitted to this Committee.

GUIDELINE: 82-1 (Special Study)

Primary Review by: Krystyna K. Locke 11/15/91
Krystyna K. Locke, Review Section I, Toxicology Branch I/HED

Secondary Review by: Roger Gardner Roger Gardner 11-15-91
Section Head, Review Section I, Toxicology Branch I/HED

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Feeding: Cholinesterase Study (Rat)

EPA IDENTIFICATION NOS: Tox. Chem. No.: 378A
MRID No.: 41867201

TEST MATERIAL: Methamidophos, technical grade; Purity (a.i.): 77.6%; Batch No.: 0067009; Clear liquid. Chemical name: O,S-Dimethyl phosphoramidothioate.

SYNONYMS: Monitor, Tamaron

STUDY NUMBER: 89-972-CV

REPORT NUMBER: 100667

SPONSOR: Mobay Corporation, Agricultural Chemicals Division, Kansas City, Missouri.

TESTING FACILITY: Mobay Corporation, Corporate Toxicology Department, Stilwell, Kansas.

TITLE OF REPORT: Technical Grade Methamidophos (MONITOR): An Eight-Week Subchronic Cholinesterase Study in Fischer 344 Rats

AUTHOR: W.R. Christenson

REPORT ISSUED: March 19, 1991

CONCLUSIONS:

Classification of Study: Acceptable

The objective of this study was to establish a NOEL for the methamidophos-induced cholinesterase inhibition in plasma, erythrocytes and brain of the rat.

Technical grade methamidophos was administered in the feed to Fischer 344 rats (25/dose/sex) for 56 days at nominal concentrations of 0 (not detected), 0.5, 1, 2 and 4 ppm (analytical concentrations were 0, 0.49, 0.97, 2.12 and 4.30 ppm, respectively), expressed as an active ingredient. Plasma and erythrocyte cholinesterase activities were determined on study days 14, 28, 42, and 51, and brain cholinesterase activity was

determined on study days 14, 35 and 56. Acetylthiocholine was used as the substrate in all of these determinations. In the case of plasma cholinesterase activity, both acetylthiocholine and butyrylthiocholine were used as the substrates. Other parameters examined were toxic signs, body weight gain and food consumption.

The NOELs, based on the inhibition of cholinesterase activities, were as follows:

Plasma acetyl cholinesterase (PChE): 0.5 ppm; males*
< 0.5 ppm; females

Plasma butyryl cholinesterase (BPChE): 0.5 ppm; males and females

Erythrocyte acetyl cholinesterase (RChE): 0.5 ppm; males
≤ 0.5 ppm; females

Brain acetyl cholinesterase (BChE): < 0.5 ppm; males and females

Where applicable, a LOEL for cholinesterase inhibition was 1 ppm for both sexes.**

Methamidophos had no effect on body weight gain and food consumption of both sexes. There were no mortalities and no toxic signs, usually associated with cholinesterase inhibition, were observed.

EXPERIMENTAL PROCEDURES

The purpose of this study was to establish a "No-Observed-Effect-Level" (NOEL), based on cholinesterase inhibition, in the rat. This study was initiated on March 26, 1990, and was terminated on May 25, 1990.

Fischer 344 rats, 25 males and 25 females/group, received the test material in diet at the following nominal dose levels: 0, 0.5, 1, 2 and 4 ppm (expressed as O,S-Dimethyl phosphoramidothioate or active ingredient, a.i.). These dose levels were based on the cholinesterase results obtained in a rat chronic feeding/oncogenicity study in which technical grade methamidophos

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*Based on the daily consumption of methamidophos (page 6 of this review), 0.5 ppm of methamidophos = 0.03 mg/kg b.w. (male rats) and 0.06 mg/kg b.w. (female rats).

**1.0 ppm of methamidophos = 0.07 mg/kg b.w. (male rats). For female rats, 1.0 ppm (and also 0.5 ppm) of methamidophos = 0.06 mg/kg b.w.

was administered in diet at nominal concentrations (a.i.) of 0, 2, 6, 18 and 54 ppm*. The diets were prepared weekly, stored at -23° C until used, and checked for homogeneity (0.5 and 4.0 ppm doses only), stability (0.5 and 4.0 ppm doses only) and concentration of the test compound. Technical grade methamidophos was analyzed (by gas chromatography) prior to initiation of dosing to determine the percent of a.i. (purity). Corn oil, at 1% by weight of the diet, was used as a vehicle for the test material. The rats were:

1. Obtained from SASCO, Inc., Madison, Wisconsin.

2. About 12 weeks old when placed on study.

3. Acclimated for at least 7 days.

4. Assigned to groups randomly on the weight basis; those weighing more or less than 20% of the mean body weight were rejected.

5. Housed individually in suspended stainless steel cages at temperatures of 18-26° C, relative humidity of 40-70%, and 12 hours light/dark cycle.

6. Identified by numbers tattooed on their tails.

7. Offered unrestricted amounts of food (Purina Mills Rodent Chow 5001-4, pelleted) and tap water.

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

1. Observation for toxic signs and mortality, twice daily (once on weekends and holidays).

2. Body weight and food consumption, weekly.

3. Cholinesterase activities in plasma (PChE), erythrocytes (RChE) and brain (BChE) using acetylthiocholine as the substrate, and in plasma using butyrylthiocholine as the substrate (PBChE).

PChE, RChE and BChE activities were determined according to the methods of Ellman et al. (1961), modified by Talbott (1975) and described by Hackathorn (1983). These procedures are referenced and briefly summarized in Attachment I. A commercial kit was used for the determination of PBChE activity. PChE, PBChE and RChE activities were determined prior to dosing and on

*R.H. Hayes, Mobay Corporation, Corporate Toxicology, Mobay Agricultural Chemicals Division Report Number 88687, MRID Number 00148452, November 13, 1984.

study days 14, 28 and 42 using the first 15 available males and 15 females of each test group, and on day 51 using all of the surviving rats. Blood was collected by orbital sinus bleeding. BChE activity was determined on study days 14 and 35 using 5 males and 5 females of each group, and at the termination of the study (day 56) using all of the surviving rats. At gross necropsy, brains were removed, divided in half and frozen, and then assayed for ChE activity at a later time.

Statistical analyses were performed as follows:

"Continuous data examined statistically were evaluated initially for equality of variance or homogeneity using Bartlett's test. Group means were further analyzed by Analysis of Variance (ANOVA) followed by a Dunnett's test if significant F value was obtained in the ANOVA.

All statistical evaluations were performed using software from either INSTEM Computer Systems, Stone, Staffordshire, England and/or SAS Institute, Inc., Cary, North Carolina. With the exception of Bartlett's test ($p \leq .001$), probability values of $p \leq 0.05$ were accepted as significant."

RESULTS

Homogeneity and Stability of Methamidophos in Diets

Methamidophos added to the rat diets at concentrations of 0.5 and 4 ppm (only levels checked) was homogeneously distributed. Based on nine samples taken from the three layers of the mixing bowl, the mean concentration of methamidophos in the top, middle and bottom layer of the 0.5 ppm level was 0.46, 0.46 and 0.49 ppm, respectively. The corresponding values for the 4 ppm level were 3.47, 3.67 and 3.68 ppm, respectively.

Diets containing 0.5 or 4 ppm of methamidophos (only levels checked) and stored at -23° C for 28 days showed no decline in concentration. An 8% and 5% decline in methamidophos concentration was observed in diets containing 0.5 and 4 ppm of methamidophos, respectively, and stored at room temperature (about 22° C) for 7 days.

Analytical Concentration of Methamidophos in Diets*

The methamidophos concentrations in the rat diets were determined by gas chromatography during the study weeks 1, 4 and 8. The following results were obtained:

Nominal Concentration (ppm)	0	0.5	1.0	2.0	4.0
Mean Analytical Concentration (ppm)	0	0.49	0.97	2.12	4.30

SD	--	0.065	0.030	0.081	0.26
CV (%)**	--	13	3	4	6
Percent of Nominal	--	98	97	106	108

*Based on Table 5, page 137 of the submission (Project No. 100667; MRID No. 418672-01)

**Coefficient of Variation

Clinical Observations

These observations were not tabulated, but were reported only for individual animals. There were no unscheduled deaths and no behavioral changes were noted in any group. The only findings observed (listed below) did not appear to be treatment-related.

1. Dark-red discharge (right eye) in single males from the control, 0.5 ppm and 1 ppm groups; and in one female from the 2 ppm group.

2. Opacity (right eye) in single males from the 1, 2 and 4 ppm groups; and in one female from the 1 ppm group.

3. Exophthalmus (right eye) in one male from the 0.5 ppm group and one female from the control group.

4. Ulceration of the right eye in one male from the 1 ppm group.

Body Weight

Methamidophos had no effect on the body weight gains in both males and females. Relative to the control values, a slightly decreased weight gain in the 4 ppm male group and dose unrelated decreased weight gains in the 1, 2 and 4 ppm female groups (each statistically insignificant) did not appear to be treatment-related. The mean body weight gains are summarized below.

Methamidophos (ppm)	Males		Females	
	Weight Gain (g)*	Percent Decrease	Weight Gain (g)*	Percent Decrease
0	51.9	--	25.3	--
0.5	54.2	0	25.9	0
1	55.5	0	21.6	14.6

7

2	53.6	0	23.4	7.5
4	48.5	6.6	22.5	11.1

*Based on Table 2, pages 24 and 25 of the submission (Report No. 100667; MRID No. 41867201). Weight gain = mean body weight on study day 56 minus mean body weight on study day 0.

Food Consumption

Methamidophos had no effect on food consumption of males and females, reported as g/animal/day (mean and individual values). Relative to the control values, decreases in mean food consumption, observed in the 4 ppm rat group and in all of the treated female groups, were very small, dose-unrelated, statistically insignificant and did not appear to be biologically significant. These data are summarized below.

Methamidophos (ppm)	Food Consumption (g/rat/day): Males*		
	Mean	Percent decrease	Range
0	17.01	--	16.49-17.80
0.5	17.17	0	16.76-17.65
1	17.04	0	16.62-17.37
2	17.06	0	16.57-17.53
4	16.80	1.2	16.32-17.02
	Food Consumption (g/rat/day): Females*		
0	12.22	--	11.48-12.91
0.5	12.06	1.3	11.57-12.58
1	11.98	2.0	11.61-12.28
2	11.99	1.9	11.47-12.39
4	11.75	3.9	11.29-12.19

*Based on Table 1, page 23 and Table 4, pages 36 and 37 of the submission (Report No. 100667; MRID No. 41867201)

Consumption of Methamidophos

On the mg/kg/day basis, female rats in the 2 and 4 ppm groups consumed slightly more methamidophos than did male rats in the same groups. Also, females in the 0.5 and 1 ppm groups

consumed the same amounts of methamidophos. The data are summarized below.

Dietary level of methamidophos (ppm)		Daily consumption of methamidophos*	
Nominal	Actual	mg/rat	mg/kg b.w.
		Males	
0	0	0	0
0.5	0.49	0.01	0.03
1	0.97	0.02	0.07
2	2.12	0.04	0.13
4	4.30	0.07	0.24
		Females	
0	0	0	0
0.5	0.49	0.01	0.06
1	0.97	0.01	0.06
2	2.12	0.03	0.17
4	4.30	0.05	0.28

*Based on Table 1, page 23 of the submission (Report No. 100667; MRID No. 41867201).

Cholinesterase Activities

Cholinesterase activities were determined in plasma (PChE and BPChE), erythrocytes (RChE) and brain (BChE). In plasma, both acetylthiocholine and butyrylthiocholine were used as the substrates. The findings obtained are summarized in the three tables below.

Percent Inhibition, Relative to the Control Values, of Plasma and Erythrocyte Cholinesterase Activities in Male Rats*

Study Day	14	28	42	51
Methamidophos (ppm)	Plasma Cholinesterase (PChE)			
0.5	0	5	0	0
1	7	10*	0	0
2	12*	13*	8*	8*
4	19*	20*	18*	14*

	Plasma Cholinesterase (BPChE)			
0.5	0	13	6	0
1	7	13*	6	0
2	20*	27*	19*	6
4	27*	27*	31*	25*
	Erythrocyte Cholinesterase (RChE)			
0.5	0	4	2	1
1	0	5*	4*	4*
2	5	12*	9*	8*
4	17*	25*	22*	16*

*Based on Tables 11, 12 and 13, pages 119-121, of the submission (Project No. 100667; MRID No. 41867201). Fifteen rats/group/sampling time were used. Acetylthiocholine was used as the substrate in the determinations of PChE and RChE activities, and butyrylthiocholine in the determination of BPChE activity. For cholinesterase activities, reported as IU/ml, see Attachment II.

*Significantly different from control at $p \leq 0.05$.

Percent Inhibition, Relative to the Control Values, of Plasma and Erythrocyte Cholinesterase Activities in Female Rats*

Study Day	14	28	42	51
Methamidophos (ppm)	Plasma Cholinesterase (PChE)			
0.5	17*	14*	3	5
1	20*	14*	14*	15*
2	35*	27*	22*	19*
4	41*	36*	33*	31*
	Plasma Cholinesterase (BPChE)			
0.5	11	4	5	3
1	19*	12*	17*	16*
2	30*	24*	25*	20*
4	34*	25*	30*	27*
	Erythrocyte Cholinesterase (RChE)			
0.5	5	3	3*	2
1	0	3	4*	3*
2	4	11*	9*	9*
4	17*	27*	23*	19*

*Based on Tables 11, 12 and 13, pages 119-121, of the submission (Project No. 100667; MRID No. 41867201). Fifteen rats/group/sampling time were used, with the exception of day 14 when 6 control and 12 low-dose (0.5ppm) rats were used for the determination of PChE and RChE activities.

Acetylthiocholine was used as the substrate in the determinations of PChE and RChE activities, and butyrylthiocholine in the determination of BPChE activity. For cholinesterase activities, reported as IU/ml, see Attachment II.

*Significantly different from control at $p \leq 0.05$.

Percent Inhibition, Relative to the Control Values, of Brain Cholinesterase (BChE) Activity in Male and Female Rats*

Study Days	14	35	56
Methamidophos (ppm)	Males		
0.5	5	3	3*
1	7*	7*	7*
2	13*	11*	14*
4	22*	26*	26*
	Females		
0.5	0	5*	4
1	12*	9*	6*
2	10	16*	13*
4	22*	29*	32*

*Based on Table 14, page 122 of the submission (Report No. 100667; MRID No. 41867201). On days 14 and 35, 5 rats/group were used in the determination of BChE activity and on day 56, the remaining 15 rats/group were used. Acetylthiocholine was used as the substrate in these determinations. For BChE activities, reported as IU/g of brain tissue, see Attachment II.

*Significantly different from control at $p \leq 0.05$.

At the lowest level of methamidophos tested (0.5ppm), the following statistically significant ($p \leq 0.05$) inhibitions of cholinesterase activities, relative to the control values, were observed:

Plasma ChE: In females, 17% and 14% on sampling days 14 and 28, respectively.

Erythrocyte ChE: In females, 3% on sampling day 42.

Brain ChE: In females, 5% on study day 35 and in males, 3% on study day 56.

At other doses of methamidophos, statistically significant ($p \leq 0.05$), dose-related inhibitions of cholinesterase activities were as follows:

Activity Measured	Sex	Percent Inhibition*	Observed at Sampling Day(s)
At 1ppm: PChE	M F	10 14-20	28 All
BPChE	M F	13 12-19	28 All
RChE	M F	4-5 3-4	28, 42, 51 42,51
BChE	M F	7 6-12	All All
At 2 ppm: PChE	M F	8-13 19-35	All All
BPChE	M F	19-27 20-30	14, 28, 42 All
RChE	M F	8-12 9-11	28, 42, 51 28, 42, 51
BChE	M F	11-14 10-16	All All
At 4 ppm: PChe	M F	14-20 31-41	All All
BPChE	M F	25-31 25-34	All All
RChE	M F	16-25 17-27	All All
BChE	M F	22-26 22-32	All All

*Based on Tables 11-14; pages 119-122, of the submission (Project No. 100667; MRID No. 41867201).

COMMENTS

This study was well planned, conducted and clearly reported, especially the cholinesterase activities. Procedures used in the determination of cholinesterase activities (other than BPChE, where a commercial kit was used) were not only referenced but also briefly described. A detailed procedure was also reported for the determination of methamidophos in rat diets.

The following statements were included in the submission:
1) No Claim of Data Confidentiality, signed and dated 8/2/90;
2) Good Laboratory Practice Compliance, signed and dated 3/19/91;

and 2) Quality Assurance Statement, showing that this study was inspected 27 times, starting on 1/8/90 (Protocol Checklist) and ending on 1/11/91 (Final Report Review).

According to this submission, 0.5 ppm (0.03 mg/kg/day), the lowest dose of methamidophos tested, was a NOEL for the inhibition of cholinesterase activities in plasma (both PChE and BPChE), erythrocytes and brain, in both sexes. Statistically significant inhibitions ($p \leq 0.05$) of cholinesterase activities observed at this level (PChE, RChE and BChE) were considered to be of no toxicological significance. Toxicology Branch/HED disagrees, in certain instances, with this interpretation of cholinesterase data.

According to our interpretation of the currently submitted cholinesterase activities data, 0.5 ppm of methamidophos was a NOEL for the inhibition of BPChE (plasma cholinesterase with butyrylthiocholine as the substrate), in both sexes. Although this enzyme was inhibited in the male rats on sampling days 28 (13%) and 42 (6%), and in the female rats on each sampling day (3-11%), none of these inhibitions was statistically significant.

Regarding the inhibitions of cholinesterase activities in plasma (with acetylthiocholine as the substrate), PChE, 0.5 ppm of methamidophos was a NOEL only for the male rats. In the case of the female rats, statistically significant ($p \leq 0.05$) inhibitions (17 and 14%) at two sampling times (that is, in 50% of the determinations) can hardly be regarded as toxicologically insignificant.

Regarding the inhibitions of cholinesterase activities in erythrocytes, 0.5 ppm of methamidophos was a NOEL only for the male rats. In the case of the female rats, a small (3%) but statistically significant ($p \leq 0.05$) inhibition of RChE activity was observed on sampling day 42 (that is, in 25% of the determinations). Because of this inhibition, 0.5 ppm of methamidophos should probably be regarded as a borderline NOEL for the female rats.

Regarding the inhibitions of cholinesterase activities in brain tissue, 0.5 ppm of methamidophos significantly ($p \leq 0.05$) inhibited BChE activity in males on sampling day 56 (3%) and in females on sampling day 35 (5%), or in 33% of the determinations. Because of these inhibitions, a NOEL for BChE was < 0.5 ppm of methamidophos, for both sexes. Because of the importance of BChE in neurological processes, it is difficult to determine of an inhibition is of "the inconsequential magnitude" and "not of a toxicological significance" (expressions used in this submission to characterize these inhibitions).

In summary, the NOELs, based on the inhibitions of cholinesterase activities, were as follows:

Plasma acetyl cholinesterase (PChE): 0.5 ppm; males*
< 0.5 ppm; females

Plasma butyryl cholinesterase (BPChE): 0.5 ppm; males and females

Erythrocyte acetyl cholinesterase (RChE): 0.5 ppm; males
≤ 0.5 ppm; females

Brain acetyl cholinesterase (BChE): < 0.5 ppm; males and females

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*Based on the daily consumption of methamidophos data (page 6 of this review), 0.5 ppm of methamidophos = 0.03 mg/kg b.w. (male rats) and 0.06 mg/kg b.w. (female rats).

Attachment I

RIN 1651-99

~~FEMA~~

Page 16 is not included in this copy.

Pages _____ through _____ are not included in this copy.

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.

✓ 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.

Attachment II

RIN 1651-99

Page _____ is not included in this copy.

Pages 15 through 29 are not included in this copy.

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.

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_____ 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.

GUIDELINE: None

Primary Review by: Krystyna K. Locke, Review Section I, Toxicology Branch I/HED Krystyna K. Locke 11/15/91

Secondary Review by: Roger Gardner, Section Head, Review Section I, Toxicology Branch I/HED Roger Gardner 11-15-91

DATA EVALUATION RECORD

STUDY TYPE: Position Paper

EPA IDENTIFICATION NOS: Tox. Chem. No.: 378A
MRID No.: None

Test Material: Technical grade methamidophos (O,S-Dimethyl Phosphoramidothioate); Purity (a.i.): 62-72.4%

SYNONYMS: Monitor, Tamaron

STUDY NUMBER: None

TITLE OF REPORT: Discussion of the Toxicological Basis for Revising the Reference Dose (RfD) for Chronic Dietary Exposure to MONITOR (Methamidophos)

AUTHORS: D.L. Van Goethem, Mobay Corporation
J.H. Kinzell, Chevron
R.A. Zimmerman, Valent

REPORT ISSUED: April 16, 1991

CONCLUSION:

This Position Paper, regarded by the registrants as an administrative document rather than a formal data submission, is being submitted, along with the new 8-week rat feeding (cholinesterase) study and other relevant studies, to the Agency's RfD Committee which is responsible for the establishing of the RfDs.

COMMENTS:

This 31-page Position Paper is concerned with the establishing of the Reference Dose (RfD; ADI) for methamidophos, based on the inhibition of cholinesterase (ChE) activities in plasma, erythrocytes and brain. Since the NOELs for ChE inhibition were not established in the 2-year rat feeding/oncogenicity study (dated 11/13/84; MRID No.: 00148452) and in the 1-year dog feeding study (dated 6/26/84; MRID No.: 00147938), the LEL (LDT) of 2 ppm (0.05 mg/kg) from the 1-year dog feeding study and the Uncertainty Factor (UF; SF=Safety Factor) of 1000 were used to establish the Provisional RfD (PADI) of 0.00005 mg/kg. The PADI was established by the EPA's RfD Committee in 1987. The

published tolerances represent 5254% of the PADI.

In order to establish a ChE NOEL and subsequently a RfD for methamidophos, the registrants (Chevron Chemical Company/Valent USA and Mobay Corporation) submitted in 1989 a protocol for a 4-week oral feeding (ChE) study in the rat. Toxicology Branch/HED approved this protocol, with modifications, on November 2, 1989.

The proposed ChE study, submitted with the Position Paper, was actually conducted for 8 weeks (Project No.: 100667; MRID No.: 41867201). According the Toxicology Branch (TB)/HED's interpretation of the reported results, the NOELs for the inhibition of ChE activities were as follows:

Plasma acetyl cholinesterase (PChE): 0.5 ppm (LDT); males
< 0.5 ppm; females

Plasma butyryl cholinesterase (BPChE): 0.5 ppm; males and females

Erythrocyte acetyl cholinesterase (RChE): 0.5 ppm; males
≤ 0.5 ppm; females

Brain acetyl cholinesterase (BChE): < 0.5 ppm; males and females

According to the Position Paper, the 8-week study clearly defines a NOEL of 0.5 ppm (0.03 mg/kg/day; males and females) for ChE inhibition in plasma, erythrocytes and brain, and allows calculation of a RfD even in the absence of a final Agency Policy on cholinesterase inhibition. Using this value and an UF of 15, the registrants proposed a RfD of 0.002 mg/kg/day. The UF of 15 was regarded as realistic and the RfD of 0.002 mg/kg/day as conservative and appropriate. The following studies were used (discussed) in support of the proposed UF and RfD:

1. Subchronic (ChE) study with humans; it is a valid (1973) IBT study, classified as Supplementary.

2. Two-year rat chronic feeding/oncogenicity study in which ChE NOEL for brain, plasma and erythrocytes was not determined.

3. One-year dog feeding study in which ChE NOEL for brain, plasma and erythrocytes was not determined.

4. Mouse oncogenicity study.

5. Two-generation rat reproduction study.

6. Developmental studies with rats and rabbits.

All of the above studies had already been evaluated by TB/HED and were submitted to the EPA's RfD Committee when the PADI was established.

Besides the results of the above studies and the currently submitted 8-week ChE study with rats, the Position Paper also contains 1) a brief history of the RfDs for methamidophos established by EPA; 2) reasons for selecting a rat rather than a dog as the most appropriate species for the critical (8-week) ChE study; 3) conclusions regarding cholinesterases in animals and humans; and 4) discussions of the RfD of 0.002 mg/kg/day and of the margins of safety (MOS) provided by this RfD. For details, see Attachment I (Position Paper).

Attachment I

RIN 1651-99

Page _____ is not included in this copy.

Pages 34 through 64 are not included in this copy.

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.

✓ FIFRA registration data.

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

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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.