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

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NOV 12 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 627. Dyfonate. Review of Rabbit Developmental Toxicity Study.

Tox. Chem. No. 454B
Project No. 1-1025

TO: Joanne Edwards, PM Team #72
Special Review and
Reregistration Division (H7508C)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 10/16/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I Roger L. Gardner 11-5-91 KB 11/5/91
Health Effects Division (H7509C)

Record No(s). S404325

Background and Request:

A developmental toxicity study on dyfonate in rabbits was submitted by Stauffer Chemical Company as a generic data submission in support of reregistration (FIFRA '88). The Toxicology Branch (TB-I) was asked to review and comment on the study.

Toxicology Branch Response:

The Toxicology Branch (TB-I) has reviewed the developmental toxicity study in rabbits. At the present time, the study is classified as Core Supplementary Data pending submission of the maternal individual clinical signs data and the complete range-finding study. The Agency is requesting these additional data in order to clarify the no-effect levels (NOEL's) and the lowest adverse effect levels (LOAEL's) for both maternal toxicity and developmental toxicity for the developmental toxicity study reviewed in this action. In this study, there is an apparent increase in resorptions in the high dose group. This is mainly due to the fact that one doe resorbed her entire litter. The Agency wants to see the range-finding study in order to verify that the increase in resorptions is not toxicologically significant for this particular chemical. In addition, the

Agency wants to examine the individual clinical signs data, particularly for the one doe which resorbed her litter. Furthermore, the clinical signs seen in this study are not the signs expected for a known cholinesterase inhibitor, and therefore may not be toxicologically significant. The individual clinical signs data are needed in order to clarify this issue.

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EPA No.: 68D80056
DYNAMAC No.: 367-C
TASK No.: 3-67C
October 16, 1991

DATA EVALUATION RECORD

DYFONATE TECHNICAL

Developmental Toxicity Study in Rabbits

STUDY IDENTIFICATION: Sauerhoff, M.W. A teratology study in rabbits with dyfonate technical. (Unpublished study No. WIL-27027 conducted by WIL Research Laboratories, Inc., Ashland, OH, and submitted by Stauffer Chemical Company, Farmington, CT; dated February 23, 1987.) MRID No. 401501-22.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: October 16, 1991

DATA EVALUATION RECORD

1. CHEMICAL: O-Ethyl-S-phenylethylphosphonodithioate.

2. TEST MATERIAL: Dyfonate technical, 94% pure; amber liquid; lot No. EHC-0586-32.

3. STUDY/ACTION TYPE: Developmental toxicity study in rabbits.

4. STUDY IDENTIFICATION: Sauerhoff, M.W. A teratology study in rabbits with dyfonate technical. (Unpublished study No. WIL-27027 conducted by WIL Research Laboratories, Inc., Ashland, OH, and submitted by Stauffer Chemical Company, Farmington, CT; dated February 23, 1987.) MRID No. 401501-22.

5. REVIEWED BY:

Pia Lindström, DPH
Principal Reviewer
Dynamac Corporation

Signature: Pia Lindström
Date: October 16, 1991

James R. Plautz, M.S.
Independent Reviewer
Dynamac Corporation

Signature: James R. Plautz
Date: Oct. 16, 1991

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation

Signature:
Date:

Esther Saito, Ph.D.
Section Head
Science Administration Section
Science Analysis and Coordination Branch
(H-7509C)

Signature:
Date:

STUDY TYPE: Developmental toxicity. Guideline §83-3.

MRID NUMBER: 401501-22.

TEST MATERIAL: Dyfonate technical, 94% pure; amber liquid; lot No. EHC-0586-32.

SYNONYMS: Fonofos, BSI, ISO.

STUDY NUMBER: WIL-27027.

SPONSOR: Stauffer Chemical Company, Farmington, CT.

TESTING FACILITY: WIL Research Laboratories, Inc., Ashland, OH.

TITLE OF REPORT: A Teratology Study in Rabbits with Dyfonate Technical.

AUTHOR: Sauerhoff, M.W.

REPORT ISSUED: February 23, 1987.

CONCLUSIONS: A developmental toxicity study was conducted in which New Zealand White rabbits were administered dyfonate technical via gavage at 0, 0.2, 0.5, or 1.5 mg/kg/day during gestational days (GD) 7 through 19. Slightly increased incidences of maternal clinical signs (the only maternal effects observed) were noted at 0.5 and 1.5 mg/kg/day. However, these signs were not typical for a cholinesterase inhibitor and may not have been compound-related. An evaluation of clinical signs in the range-finding study is recommended prior to determination of the maternal NOEL and LOEL.

Developmental toxicity may have been manifested as an increased number of resorptions at 1.5 mg/kg/day. However, a more careful comparison between results from the present study and those from the range-finding study is recommended prior to determination of the developmental NOEL and LOEL.

Classification: CORE Supplemental Data. This study does not meet the minimum requirements set forth under EPA Guideline §83-3 for a developmental toxicity study in rabbits, since the highest dose tested (1.5 mg/kg/day) did not elicit unambiguous maternal toxicity. If data on individual maternal clinical observations are submitted along with a detailed protocol and results for the range-finding study, a determination of the maternal and developmental NOELs and/or LOELs may be possible and the study may consequently be upgraded to Minimum.

A. MATERIALS:

Test Compound:	Purity:	94%.
	Description:	Amber liquid.
	Lot No.:	EHC-0586-32.
	Contaminants:	Not reported.
Vehicle:	Mazola corn oil (source: Best Foods, CPC International, lot No. Apr 02, 1986).	
Test Animals:	Species:	Rabbit.
	Strain:	New Zealand White.
	Source:	Hazleton-Dutchland, Inc., Denver, PA.
	Age:	Approximately 5.5 months at study initiation.
	Weight:	3190-4202 g on GD 0.

B. STUDY DESIGN:

This study was designed to assess the potential of dyfonate technical to cause developmental toxicity in rabbits when administered daily via gavage from GD 7 through 19, inclusive.

Mating: Following a minimum of 42 days of acclimation, females were artificially inseminated using semen from four males of the same strain and from the same supplier. Sperm motility (>50%) and concentration (>3 million motile sperm/mL) were determined before insemination. The diluted semen from each male was used to inseminate an equal number of females in each group. To ensure ovulation, each doe was given an iv injection of 100 U.S.P units of human chorionic gonadotropin (A.P.L. Ayerst Laboratories, Inc., NY) immediately after the insemination. The day of insemination was designated GD 0.

Group Arrangement: Animals were randomly assigned to dose groups using a stratified block design based on body weight as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	18
Low dose	0.2	18
Mid dose	0.5	18
High dose	1.5	18

Dosing: Doses were administered daily via gavage on GD 7 through 19 in a volume of 0.5 mL/kg. The most recently recorded individual body weights were used to provide the correct mg/kg/day dose. Dose suspensions were prepared in corn oil once before the start of the study and stored in amber glass jars at room temperature. Analyses for stability, homogeneity, and concentrations were carried out prior to, at midpoint, and after termination of the dosing period.

The selection of dose levels was based on the results of a range-finding study in which rabbits were administered dyfonate technical at 2, 4, 6, 8, and 10 mg/kg/day. In this study, maternal and developmental toxicity were observed at all dose levels.

Observations: Animals were observed daily for mortality and overt signs of toxicity. Females that aborted and/or died were necropsied, and gross findings and fetuses from these animals were preserved in 10% neutral buffered formalin for possible microscopic examination. Body weight was recorded on GD 0, 7, 10, 13, 19, 24, and 29. Food consumption was recorded daily during the entire gestation. Females were sacrificed on GD 29 by an injection of T-61 Euthanasia solution (American Hoechst Corporation, Sommerville, NJ), and litters were delivered by

cesarean section. Examination of the dams at sacrifice included the following:

- Gross pathological observations;
- Number of corpora lutea;
- Gravid uterine weight;
- Number of implantation sites; and
- Number and location of resorptions (early and late) and live and dead fetuses.

Uteri from apparently nonpregnant animals were stained with 10% ammonium sulfide to detect early embryonic death.

Fetuses were examined in the following manner:

- All fetuses were weighed and sexed;
- External anomalies were recorded for all fetuses and included palate, eyes, and external orifices;
- Visceral anomalies were evaluated (including the heart and major vessels) using Staples' fresh dissection technique. Half of the fetal heads were fixed and subsequently examined using Wilson's serial-sectioning technique,while the other half were examined by a midcoronal slice; and
- All fetuses were evaluated for skeletal anomalies after staining with Alizarin Red S using a modification of Dawson's technique.

Statistical Analysis: The following methods were used.

- Maternal body weight, body weight gain, food consumption, numbers of viable fetuses, implantations, and corpora lutea, and fetal body weight--ANOVA and Dunnett's test;
- Fetal sex ratios--Chi-square test with Yates' correction factor;
- Numbers of early and late resorptions, dead fetuses, and postimplantation losses--Mann-Whitney U-test; and
- Fetal and litter incidences of malformations and variations--Fisher's Exact test.

The level of significance was set at $p \leq 0.05$.

Compliance:

- A Statement of No Data Confidentiality Claim, dated February 23, 1987, was provided;

- A signed Statement of Compliance with EPA and OECD GLPs, dated February 23, 1987, was provided; and

- A signed Quality Assurance Statement, dated January 4, 1986, was provided.

C. RESULTS:

The following results were reported by the study author:

1. Test Material Analysis: Analyses for homogeneity of the test material in corn oil revealed sample homogeneity and concentration values between 99.5 and 109.4% of nominal concentrations; analysis for stability of the test material in corn oil on the last day of dosing revealed values between 104.2 and 105.0% of nominal concentrations.

2. Maternal Toxicity:

Mortality: One animal died in the 0.2-mg/kg/day group on GD 22; necropsy revealed congestion of lungs, liver, kidneys, stomach and intestines, and hemorrhagic uterus and meningeal hemorrhage of the brain. A second animal died in the 1.5-mg/kg/day group on GD 21; necropsy revealed meningeal congestion of the brain, congested lungs, pale kidneys, biliary stasis of the liver, stomach ulceration, loss of epithelium of the stomach/intestine, and a reddened trachea with bright red fluid.

Abortion: One animal in the 0.2-mg/kg/day group aborted on GD 26; necropsy revealed diffuse necrosis of the liver, and congested and consolidated lungs. A second animal in the 1.5-mg/kg/day aborted on GD 29; necropsy revealed no gross findings.

Clinical Observations: Selected clinical observations are presented in Table 1. Clinical signs were observed in all study groups and included alopecia and scabs (data not shown), decreased excreta, stained excreta, and/or mucoid feces. (See Reviewers' Discussion/Conclusions for further comment.)

Body Weight: A summary of maternal body weight gain and corrected weight gain data is presented in Table 2. Body weight (data not shown), body weight gain, and corrected

TABLE 1. Summary of Selected Clinical Observations[a]

Finding	Dose Level (mg/kg/day)			
	0	0.2	0.5	1.5
Soft stool	1/ 1[b]	1/ 1	3/ 3	8/ 1
Decreased defecation	24/ 7	26/ 7	34/10	48/13
Decreased urination	19/ 7	21/ 6	34/10	52/12
Dried brown anogenital matting	0/ 0	0/ 0	8/ 1	10/ 3
Wet brown anogenital matting	1/ 1	0/ 0	2/ 1	7/ 3
Mucoid feces	0/ 0	0/ 0	1/ 1	3/ 1
Wet yellow urogenital matting	0/ 0	0/ 0	1/ 1	2/ 1
Red material found on cage paper	0/ 0	1/ 1	0/ 0	2/ 1
Diarrhea	0/ 0	0/ 0	2/ 1	0/ 0

[a]Data were extracted from Study No. WIL-27027, Table 2.

[b]Represents total incidence/No. animals.

TABLE 2. Mean Body Weight Gain (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-dosing Period (GD 19-29)	Entire Gestation Period (GD 0-29)	Corrected Body Weight Gain[b]
0	199 ± 112	102 ± 145	60 ± 169	360 ± 222	-138 ± 227
0.2	172 ± 160	92 ± 135	152 ± 91	433 ± 208	27 ± 283
0.5	221 ± 169	128 ± 163	112 ± 199	461 ± 217	- 28 ± 266
1.5	250 ± 166	47 ± 398	67 ± 283	445 ± 317	90 ± 240

[a]Data were extracted from Study No. WIL-27027, Tables 4 and 14.

[b]Calculated as GD 29 body weight - GD 0 body weight - gravid uterine weight.

TABLE 3. Mean Food Consumption (g/kg/day ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-7)	Dosing Period (GD 7-19)	Post-dosing Period (GD 19-29)	Entire Gestation Period (GD 0-29)
0	47 ± 7	39 ± 9	31 ± 6	38 ± 6
0.2	47 ± 6	38 ± 7	37 ± 9	39 ± 6
0.5	45 ± 6	40 ± 9	30 ± 8	38 ± 6
1.5	50 ± 7	39 ± 12	32 ± 10	40 ± 7

[a]Data were extracted from Study No. WIL-27027, Table 6.

weight were similar in all dose groups, including the control group.

Food Consumption: A summary of food consumption is presented in Table 3. Food consumption was similar in all dose groups (including the control group), with the exception of a significant increase ($p < 0.01$) in the 0.2-mg/kg/day group on GD 24-29 (data not shown).

Gross Pathological Observations: The following observations were occasionally noted in all dose groups, including the control group: soft spleen, accentuation of the lobular markings of the liver, pitted kidneys, congested lungs, and small gallbladder.

Cesarean Section Observations: A summary of cesarean section data is presented in Table 4. A slight increase in number of resorptions/doe was noted in the 1.5-mg/kg/day group (0.5/doe for controls versus 1.3/doe for high-dose animals). (See Reviewers' Discussion/Conclusions for further comment.)

3. Developmental Toxicity:

A summary of incidences of malformations is presented in Table 5.

External Examinations: One fetus in the 0.2-mg/kg/day group exhibited gastroschisis; one fetus in the 0.5-mg/kg/day group exhibited carpal and/or tarsal flexure. One fetus in the 1.5-mg/kg/day group had an absent tail in addition to gastroschisis and carpal and/or tarsal flexure. No variations were noted.

Visceral Examinations: Hydrocephaly was evident in two (one litter), one, one, and one fetus in the control, 0.2-, 0.5-, and 1.5-mg/kg/day groups, respectively. Kidney and ureter were absent in two fetuses (two litters) in the 1.5-mg/kg/day group. Other visceral malformations, occurring as single events, included heart and/or great vessel anomaly, iris bombe, and absent adrenal. Variations, evident in all dose groups, included major blood vessels, retrocaval ureter, and absent/small gallbladder (data not shown).

Skeletal Examinations: Vertebral anomaly with or without associated rib anomaly was observed in two (two litters), one, three (three litters), and five (three litters) fetuses in the control, 0.2-, 0.5-, and 1.5-mg/kg/day groups, respectively. Rib anomaly was observed in one fetus in the 0.2-mg/kg/day group and in two fetuses (one litter) in the 0.5-mg/kg/day group. Other skeletal

TABLE 4. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	0.2	0.5	1.5
No. animals assigned	18	18	18	18
No. animals pregnant	15	16	14	16
Pregnancy rate (%)	83	89	78	89
Maternal wastage				
No. died/pregnant	0	1	0	1
No. died/nonpregnant	0	0	0	0
No. nonpregnant	3	2	4	2
No. aborted	0	1	0	1
Uterine weight/doe (g)	498 ± 87[b]	406 ± 172	489 ± 126	410 ± 184
Total No. corpora lutea	166	137	158	146
Corpora lutea/doe	11.1 ± 1.8	9.8 ± 2.5	11.3 ± 2.4	10.4 ± 2.7
Total No. implantations	130	98	132	112
Implantations/doe	8.7 ± 1.9	7.0 ± 3.5	9.4 ± 2.6	8.0 ± 2.2
Total No. live fetuses	123	93	125	94
Live fetuses/doe	8.2 ± 1.8	6.6 ± 3.4	8.9 ± 2.8	6.7 ± 3.0
Total No. resorptions	7	5	7	18
Early	3	5	4	16
Late	4	0	3	2
Resorptions/doe	0.5 ± 0.5	0.4 ± 0.8	0.5 ± 0.7	1.3 ± 1.7
Total No. dead fetuses	0	0	0	0
Fetal weight/litter (g)	42.7 ± 5.2	45.4 ± 7.9	39.5 ± 5.7	41.3 ± 5.7
Preimplantation loss (%)[c]	20.7	29.3	15.9	21.8
Postimplantation loss (%)[c]	5.1	4.8	5.9	18.2
Sex ratio (% male)[c]	52	45	44	49

[a]Data were extracted from Study No. WIL-27027, Tables 1, 7 and 14.

[b]Mean ± S.D.

[c]Calculated by the reviewers.

TABLE 5. Summary of Fetal Malformations[a]

Finding[b]	Dose Level (mg/kg/day) 0	0.2	0.5	1.5
No. fetuses (litters)	123 (15)	93 (14)	125 (14)	94 (13)
EXTERNAL OBSERVATIONS:				
Carpal and/or tarsal flexure	0	0	1	1
Gastroschisis	0	1	0	1
Absent tail	0	0	0	1
Total No. fetuses (litters) with external malformations	0	1	1	1
VISCERAL OBSERVATIONS:				
Heart and/or great vessel anomaly	0	0	1	1
Iris bombe	1	0	0	0
Kidney and ureter absent	0	0	0	2 (2)
Adrenal absent	0	0	0	1
Hydrocephaly	2 (1)	1	1	1
Total No. fetuses (litters) with visceral malformations	3 (2)	1	2 (2)	4 (4)
SKELETAL OBSERVATIONS:				
Rib anomaly	0	1	2 (1)	0
Vertebral anomaly with/without associated rib anomaly	2 (2)	1	3 (3)	5 (3)
Sternebrae fused	0	0	1	1
Vertebral centra anomaly	1	0	1	0
Costal cartilage anomaly	0	0	1	0
Sternebra(e) malaligned	1	0	0	0
Appendicular skeletal anomaly	0	0	0	1
Total No. fetuses (litters) with skeletal malformations	4 (3)	2 (2)	7 (4)	6 (4)
TOTAL NO. FETUSES (LITTERS) WITH MALFORMATIONS	7 (5)	4 (3)	10 (6)	8 (5)

[a]Data were extracted from Study No. WIL-27027, Table 8.

[b]More than one finding may be observed in one fetus.

malformations, occurring as single events, included sternebrae fused or malaligned, vertebral centra anomaly, costal cartilage anomaly, and appendicular skeletal anomaly. Variations, evident in all dose groups, included malaligned and/or unossified sternebrae, 13th rudimentary or 13th full ribs, bent hyoid arch(es), and 27 presacral vertebrae (data not shown).

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Acceptance Criteria: The reviewers have completed an Acceptance Criteria checklist (Attachment I) that is included with this evaluation. Criterion 3 (maternal toxicity) may not be fulfilled (see discussion below); criterion 7 was only partially fulfilled, since no individual daily observation data were submitted.

2. Test Material Analyses: Homogeneity and stability of the test material in the vehicle were confirmed. Concentrations of the dosing suspensions were within ±10% of nominal values.

3. Maternal Toxicity: Maternal effects were indicated by increased incidences of clinical signs at 0.5 and 1.5 mg/kg/day. Incidences of decreased defecation and urination increased by 43% in the 0.5-mg/kg/day group and by 78% in the 1.5-mg/kg/day group; brown anogenital matting was also observed in three animals in the 1.5-mg/kg/day group versus none in the control group. These signs are not typical signs caused by cholinesterase inhibitors and would not support the conclusion that these effects are compound-related. On the other hand, the range-finding study reported maternal toxicity as decreased weight gain and food consumption at 2 mg/kg/day (the lowest dose used). The dose-response for maternal toxicity appears to increase dramatically somewhere between 1.5 and 2.0 mg/kg/day, and the increased clinical signs at 0.5 and 1.5 mg/kg/day may be a compound-related response at the lowest adverse effect levels.

Until more detailed evaluations of the individual clinical signs data in the present study and the individual animal data in the range-finding study have been conducted, the maternal NOEL and LOEL cannot be determined.

4. Developmental Toxicity:

a. Deaths/Resorptions: The number of resorptions/doe was increased in the 1.5-mg/kg/day group (1.3) when compared to the control group (0.5), which also caused the postimplantation loss to increase from 5% to 18% at

this dose level. This increase is still within the historical range (0.3-1.9) and it is largely due to one doe that experienced 100% resorptions (six embryos), which may indicate that it is not a compound-related effect. On the other hand, when considered in light of the results from the range-finding study (decreased intrauterine survival at 2.0 mg/kg/day, the lowest dose tested), it may represent a compound-related response at the lowest adverse effect level. As was noted for maternal toxicity, there seems to be a sharp increase in developmental toxicity somewhere between 1.5 and 2.0 mg/kg/day.

b. Altered Growth: No compound-related effects were observed.

c. Developmental Anomalies: Slight increases were observed in % fetuses and litters with any malformation in the 0.5- and 1.5-mg/kg/day. However, all fetal and litter incidences of both malformations and variations were within the historical control range and any differences from controls were therefore considered to be within the normal range.

Until a more detailed evaluation has been conducted on the individual animal data (resorptions) in the range-finding study, the developmental NOEL and LOEL cannot be determined.

5. Reporting Deficiency:

No individual clinical observations were submitted.

E. CLASSIFICATION: CORE Supplementary Data.

Maternal NOEL = Not determined.
Maternal LOEL = Not determined.
Developmental Toxicity NOEL = Not determined.
Developmental Toxicity LOEL = Not determined.

F. RISK ASSESSMENT: Not applicable.

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	YES	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	Y/N	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	YES	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	Y/N	Individual daily observations.
8.	YES	Individual body weights.
9.	YES	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	YES	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with an asterisk (*) are supplemental; they may not be required for every study.

Tox. Chem No. 454B File Last Updated _____ Current Date 10/16/91

Study/Lab/Study #/Date	Material	MRID No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Oncogenicity - mouse/Stauffer Chem. Co./#T-11995;3/12/87	Dyfonate 94.0% pure	401501-21	Dose levels tested: 0, 5, 25, 100 ppm for 18 months. Not oncogenic. Systemic LOEL 25 ppm; NOEL 5 ppm based on cholinesterase inhibition (brain, erythrocyte and serum). Hyperplasia and hypertrophy of duodenum. Reductions in body weights and gains and food consumption also observed.	N/A	Guideline
Chronic/Oncogenicity - rat/ICI Americas, Inc./# T:11997;5/2/88	Dyfonate 94.0% pure	406179-01	Dose levels tested: 0, 4, 16, 60 ppm for 24 months. Not oncogenic. Systemic LOEL 60 ppm; NOEL 15 ppm based on cholinesterase inhibition (brain, serum and erythrocyte) and on decreases in body weights and body weight gains.	N/A	Minimum
Developmental Toxicity - Rabbits/WIL Research Labs/# WIL-27027; 2/23/87	Dyfonate 94% pure	401501-22	Dose levels tested: 0, 0.2, 0.5, 1.5 mg/kg/day during GD 7-19. No NOEL's or LOEL's established for maternal or developmental toxicity. Need individual animal data for clinical signs and range-finding study to clarify issues.	N/A	Supplement ary