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

JUL 21 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTAN

MEMORANDUM

DATE: ~~JUL 9 1981~~

454 B

SUBJECT: Pesticide Use Classification of Fonofos (Dyfonate) 20G
Pesticide Use Restrictions 44FR 45218 ID Notification
OPP 30029 February 17, 1981
Addendum to October 26, 1979 and October 23, 1980 Comments

FROM: Ray Landolt, Pharmacologist
Review Section #1
Toxicology Branch/HED (TS-769)

MLG for R.G. Zaeger 7/14/81

TO: William Miller, PM 16
Insecticide Rodenticide Branch
Registration Division (TS-767)

Registrant: Stauffer Chemical Co.

Conclusions: This data was reviewed with my memo of April 29, 1981, (copy attached) and is on file in 454B. This data is identified with Accession No. 244376.

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MEMORANDUM

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SUBJECT: Pesticide Use Classification of Fonofos (Dyfonate) 20G
Pesticide Use Restrictions 44FR 45218 ID Notification
OPP-30029
Addendum to October 26, 1979 and October 23, 1980 Comments

FROM: Ray Landolt, Pharmacologist
Review Section #1
Toxicology Branch/HED (TS-769)

TO: Waler Waldrop
Policy and Liaison Staff
Registration Division (TS-767)

THRU: Christine Chaisson, Acting Chief
Toxicology Branch/HED (TS-769)

Peter E. McGrath, Director
Hazard Evaluation Division (TS-769)

Conclusion:

1. The acute oral toxicity of Dyfonate 20% granular is in toxicity category I (less than 50 mg/kg) and exceeds the criteria for restricted use classification as specified in 40 CFR 162.11(c)(2)(ii)(A).

2. Stauffer Chemical Company has expended a great deal of time, effort, and expense in this and subsequent presentations on this subject. However, no effort has been directed by Stauffer to produce a safer product.

3. Stauffer should correct the deficiencies of the following toxicity studies by submitting the observations of toxicity, the rationale for terminating the study at seven days and gross necropsy observations.

   a. The acute rat oral toxicity study T-6461 on the technical material.

   b. The acute rabbit oral toxicity study T-6384 Dyfonate 20G in capsules (calculated as active ingredient).

Background Information:

This memorandum will deal with those items in this February 17, 1981 letter from Stauffer Chemical Company that have evolved from the subsequent memorandum from R. Landolt to W. Waldrop of February 5, 1981. It is not necessary to reiterate the Agency's concern over the restricted use classification of Dyfonate 20G.

Current Considerations:

Stauffer Chemical Company has voluntarily submitted this document to:

1. Question the reliability of their study T-1251 used by the Agency to originally classify Dyfonate 20% granular for restricted use.

2. Reiterate their rational for administering the intact granule to rabbits to determine the acute oral toxicity of Dyfonate 20% G.

3. Amend the acute rabbit oral toxicity studies found deficient for Dyfonate technical, 20% G and 10% G formulations submitted October 1979 and October 1980.

Item one of the February 17, 1981 letter from Stauffer Chemical Co.

1. Stauffer Chemical Company has taken this opportunity to question the reliability of their acute rat oral toxicity study T-1251 reported in 1968. In this study capsules of the 20, 15, 12 and 10% granular formulations of Dyfonate were administered orally to rats. Stauffer Chemical Co. has reported the following deficiencies in the T-1251 study.

   a. Stress and trauma were involved in dosing rats with intact granules in capsules.

   b. Controls were not used.

   c. Inadequate dose levels.

In 1968 when the study in question was submitted for review Stauffer embraced the concept of administering gelatin capsules to rats with this comment in their letter to the Agency.

> "These values should be considered therefore as being most reliable in evaluating the acute oral toxicity of Dyfonate".

At this time Stauffer shared their proficiency in administering gelatin capsules to rats with a number of other independent testing laboratories. The stress and trauma alluded by Stauffer in dosing rats with intact granules in capsules is not apparent when considering the LD_{50} values of the recent acute rat oral toxicity studies submitted October 1979 (T-6774 and T-6738A) using various vehicles to administer the 20% G and 10% G formulations.

Table I

Acute Oral Toxicity in Rat of Dyfonate

Test Material	Form	Vehicle	LD_{50} mg/kg Male	LD_{50} mg/kg Female	Toxicity Category	Stauffer Report
20G	Intact	Capsule	93	43	I	T-1251
20G	Ground	Corn oil	100	43	I	T-6774
20G	Ground	Polyethylene glycol 300	68	32	I	T-1251
10G	Intact	Capsule	200	126	II	T-1251
10G	Ground	Corn oil	188	84	II	T-6738A
10G	Ground	Polyethylene glycol 300	147	79	II	T-1251
10G	Ground	Water	115	39	I	T-6738A
10G	Ground	Carboxylmethyl cellulose	87	38	I	T-6738A

The stress and trauma reported for the capsules administration are not apparent with the comparison of the LD_{50} value for the 20% G Dyfonate formulation whether administered in capsule or in corn oil suspension. In both of these studies T-1251 or T-6774 the female rat is more sensitive to the toxicity of Dyfonate 20% G than the male rat and is in toxicity Category I by either vehicle of oral administration.

Concurrent vehicle control groups were administered orally to rats at 10 ml/kg with T-6774 and T-6738A studies. In these studies fifty male and fifty female rats dosed orally with 10 ml/kg of corn oil appeared normal throughout the study and had no visible lesions at necropsy on day 14. These studies would reinforce the acceptability of corn oil as the preferred vehicle for oral administeration of granules to rats.

Concurrent vehicle controls were not required at the time T-1251 was reported. If the lack of control vehicle groups were used to determine the reliability of an acute oral toxicity study then approximately 97% of all acute oral toxicity studies conducted over the last thirty years would not be acceptable. Stauffer Chemical Company has failed to report concurrent vehicle control groups for rabbit oral studies T-6383 and T-6384 submitted October 1979 and October 1980.

Stauffer Chemical Company has been overly critical of a study preformed in 1968 for which they did not have the benefit of the 1978 proposed testing guidelines before this study was initiated. The purpose of the testing guidelines is to establish a more reliable data base in support of regulatory actions. When evaluating the quality of a study submitted prior to 1978, it is not the policy of the Agency to arbitrarily down grade the quality of scientific study, but to determine whether the study contains useful information. To repeat a study, when the end point of an acute toxicity study would apparently not change, would be a waste of our animal resources.

Item two of the February 17, 1981 letter from Stauffer Chemical Co.

2. Stauffer Chemical Company is of the opinion that their product should be tested as it is formulated as intact granules. To accomplish this they have presented the following acute oral toxicity data on the rabbit in support of the oral administeration of the intact granules to rabbits.

Table II
Acute Oral Toxicity in Rabbits of Dyfonate

Test Material	Form	Vehicle	LD_{50} mg/kg Male	LD_{50} mg/kg Female	Toxicity Category	Stauffer Report
20G	Intact	Capsule	59	66	II	6384
20G	Intact	Capsule + 2 ml/kg corn oil	79	83	II	6384
20G	Ground	Capsule	73	59	II	6384
20G	Ground	Corn oil	59	58	II	6384
10G	Intact	Capsule	135	158	II	6383

On examination of this table it is apparent that the vehicle whether corn oil or gelatin capsule, is of little consequence in determing the LD_{50} value of Dyfonate 20% granular.. The same observation can be made for the preceeding rat oral (Table I) study for using either capsules or corn oil to determine the LD_{50} of Dyfonate 20% granular. It is not the physical form of the granules nor the vehicle, i.e. capsule or corn oil, but the sensitivity of the species tested. Namely, the female rat is the most sensitive indication of the toxicity of Dyfonate 20% granular.

Item three of the February 17, 1981 letter from Stauffer Chemical Co.

3. The acute rabbit oral toxicity studies on the technical, 20% G and 10% G submitted October 1979 and October 1980 were determined to be inadequate by the present standards. The acute rat oral toxicity studies on the technical formulation of Dyfonate submitted October 1979 were also determined to be inadequate. These acute oral toxicity studies were deficient in that the studies were terminated at 7 days, toxic signs were not reported and none of the animals were necopsied. Stauffer has submitted the following addendums to the acute rabbit oral studies T-6384 and T-6883. The addendum of toxic signs and the rational for terminating these studies at 7 days will upgrade studies T-6384 and T-6883 from supplementary to core minimum. However, Stauffer Chemical Report T-6461 acute rat oral toxicity for the technical formulation of Dyfonate is still deficient.

The following observations for the acute rat oral toxicity study T-6774 on Dyfonate 20% G and 10% G are added to the record for comparison with the rabbit studies. The male survivors on the next to highest level receiving Dyfonate 20% G in corn oil did not return to normal until day 11. Necropsy finds were reported on day 14 for both male and female survivors of the middle dose. The female survivors on the next to highest level receiving 10% G in corn oil did not return to normal until day 8.

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Toxicity Data
Addendum to
Pesticide Use Restrictions 44 FR 45218
I.D. Notification OPP - 30029
1979 - 1980

Acute Oral Toxicity in Rats and Rabbits
(1979-1980)
Technical Dyfonate
-2-

Study	Material	Vehicle	EPA Asscession No.	Results	Toxicity Category	Core Grade	Study Reference
Acute oral LD50 male rabbit	95.6%	corn oil	243640	14.2 mg/kg	I	Minimum	T-6384
Acute oral LD50 female rabbit	95.6%	corn oil	243640	12.7 mg/kg	I	Minimum	T-6883
Acute oral LD50 male rat	95.4%	corn oil	243640	24.5 mg/kg		Supplementary	T-6461
Acute oral LD50 female rat	95.4%	corn oil	243640	10.8 mg/kg		Supplementary	T-6461

Technical Dyfonate

I. Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report T-6384. October 3, 1979

A. Procedure

Thirty male New Zealand rabbits weighing 1.3 to 2.4 kg were divided into five groups of 10 animals per group dosed at 25, 18.7 12.5, 9.4 and 6.3 mg/kg. One group of four animals received 50 mg/kg. The animals were fasted 18 hours prior to treament. The technical material (95.6%) was administered by intubation at a constant volume of 2 ml/kg in corn oil. All animals were observed daily for mortality for a total of 7 days.

B. Results

1. LD50 14.2 mg/kg (10.7-18.8)

2. Pharmcotoxic signs include clonic convulsions, salivation tremors, inactivity and diarrhea at the approximate LD_{50} level. Survivors appeared normal within 72 hours. Deaths occured within 48 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: I

Technical Dyfonate

II. Acute Female Rabbit Oral Toxicity
Stauffer Chemical Co. Report T-6883. April 16, 1980

A. Procedure

One hundred and thirty young adult albino rabbits weighing between 1.46 to 2.52 kg were divided into the following eight dosage levels (number of animals per level in parenthesis) 22.4(10), 20(20), 17.8(10), 15.8(20), 12.6(30), 11.9(10), 11.2(20), and 10(10) mg/kg. Animals were fasted overnight prior to treatment. The technical material (95.6%) was administered at a constant volume of 2 ml/kg in corn oil by oral gavage using a 16 gauge dosing needle. All animals were observed for mortality for 7 days.

B. Results

1. LD50 12.7 mg/kg (11.4-14.11)

2. Pharmacotoxic signs include salivation, tremors, polypnea, convulsions, diarrhea and ataxia at the approximate LD_{50} level. Survivors appeared normal by day 2. Deaths occurred within 24 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported.

2. Toxicity Category: I

Technical Dyfonate

III. Acute Male Rat Oral Toxicity
Stauffer Chemical Co. Report T-6461. October 3, 1979

A. Procedure

Sixty male Charles River rats weighing between 150-200 gram were divided into six groups of 10 animals per group. Animals were fasted for 18 hours prior to treatment. The technical material (95.4%) at dosages of 39.9, 35.6, 31.7, 25.2, 20.0 and 14.1 was administered at a constant volume of 2 ml/kg in corn oil by intubation. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 24.5 mg/kg (21.4-28.0)

2. Pharmacotoxic signs

3. Necropsy.

C. Conclusion

1. Classification of Data - Core Supplementary
   a. Deficiency of Data

      1. Animals were not observed for 14 days

      2. Pharmcotoxic signs not reported

      3. No gross pathology reported.

2. Toxicity category:

Technical Dyfonate

IV. Acute Female Rat Oral Toxicity
Stauffer Chemical Co. Report T-6461. October 3, 1979

A. Procedure

Eighty female Charles River rats were divided into seven groups of 10 animals per group dosed at 20, 15.8, 12.6, 11.2, 10.6 mg/kg and 15 animals per group dosed at 10.0 and 7.9 mg/kg. Animals were fasted for 18 hours prior to treatment. The technical material (95.4%) was given by intubation at a constant volume of 2 ml/kg in corn oil. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 10.8 mg/kg (9.6-12.2)

2. Pharmacotoxic signs

3. Necropsy

C. Conclusion

1. Classification of Data - Core Supplementary
   a. Deficiency of Data
      1. Animals weights were not recorded.
      2. Animals were not observed for 14 days.
      3. Pharmacotoxic signs were not reported.
      4. No gross pathology reported.

2. Toxicity category:

Acute Oral Toxicity in Rats and Rabbits
(1979-1980)
Dyfonate 20 Granular
-7-

Study	Material	Vehicle	EPA Accession No.	Results	Toxicity Category	Core Grade	Study Reference
Acute oral LD50 male rabbit	20 G	capsules	243640	59 mg/kg	II	Minimum	T-6384
Acute oral LD50 female rabbit	20 G	capsules	243640	66 mg/kg	II	Minimum	T-6384
Acute oral LD50 male rabbit	20 G	capsules plus corn oil	243640	79 mg/kg	II	Minimum	T-6384
Acute oral LD50 female rabbit	20 G	capsules plus corn oil	243640	83 mg/kg	II	Minimum	T-6384
Acute oral LD50 male rabbit	20 G	powdered in capsules	243640	73 mg/kg	II	Minimum	T-6384
Acute oral LD50 female rabbit	20 G	powdered in capsules	243640	59 mg/kg	II	Minimum	T-6384
Acute oral LD50 male rabbit	20 G	powdered in corn oil	243640	59 mg/kg	II	Minimum	T-6384
Acute oral LD50 female rabbit	20 G	powdered in corn oil	243640	58 mg/kg	II	Minimum	T-6384
Acute oral LD50 male rabbit	20 G	capsules	243640	12.7 mg/kg*		Supplementary	T-6384
Acute oral LD50 female rabbit	20 G	capsules	243640	15.8 mg/kg*		Supplementary	T-6384
Acute oral LD50 male rat	20 G	powdered in corn oil	243640	100 mg/kg	II	Guideline	T-6774
Acute oral LD50 female rat	20 G	powdered in corn oil	243640	43 mg/kg	I	Guideline	T-6774

*Calculated as active ingredient

Dyfonate 20 G in capsules

Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report T-6384. October 3, 1979

A. Procedure

Sixty-nine male New Zealand rabbits weighing between 1.3-2.4 kg were divided into six groups of 10 animals per group dosed at 125, 100, 80, 63, 50, 40 mg/kg and another group of 9 animals received 32 mg/kg. The granules were weighed and packed in No. 4 gelatin capsules and administered with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 59 mg/kg (47-73)

2. Pharmacotoxic signs include inactivity, salivation, tremors, diarrhea and grinding of teeth at the approximate LD_{50} level. All animals appeared normal by day 2 except one animal exhibited diarrhea until termination on day 7. Deaths occurred within 24 to 48 hours.

3. Necropsy

C. Conclusion

1. Classification of Date - Minimum
   a. Deficiencey - No gross pathology reported.

2. Toxicity Category: II

Dyfonate 20 G in capsules

Acute Female Rabbit Oral Toxicity
Stauffer Chemial Co. Report No. T-6394. October 3, 1979

A. Procedure

Sixty female New Zealand rabbits weighing 1.3 to 2.4 kg were divided into six groups of 10 animals per group. Doses of 125, 100, 80, 63, 50, 40 mg/kg were administered to each of the six respective groups. The granules were weighed and packed in No. 4 gelatin capsules and administered with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 66 mg/kg (55-79)

2. Pharmacotoxic signs include salivation, ataxia inactivity, diarrhea and grinding of teeth at the approximate LD_{50} level. Miosis was observed at the next to highest level. All animals appeared normal by day 3. Deaths occurred within 24 hours.

3. Necropsy

C. Conclusion

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II

Dyfonate 20 G in Capsules Plus Corn Oil

Acute Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Two groups of 40 males and 40 females New Zealand rabbits weighing between 1.3-2.4 kg were divided into four dosage levels of 10 animals per level per sex. Dosages of 200, 125, 80, and 50 mg/kg of the granules were administered orally in No. 4 gelatin capsules with a balling gun to both male and female rabbits. Prior to the administration of the capsules each rabbit received 2 ml/kg of corn oil by gastric gavage. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. a. Male LD50 79.0 mg/kg (58-107)
   b. Female LD50 83 mg/kg (64-108)

2. Pharmacotoxic signs include inactivity, diarrhea, salivation, tremors and grinding of teeth at the approximate LD_{50} level. Survivors appeared normal by day 3 for male and by day 4 for the females. Deaths occurred within 48 hours for male and within 24 hours for female rabbits.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II

Powdered Dyfonate 20 G in Capsules

Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Fourty-eight male New Zealand rabbits weighing between 1.3-2.4 kg were divided into three groups of 10 animals each dosed at 125, 80 and 50 mg/kg. Two levels of nine animals each were dosed at 100 and 40 mg/kg. The granular material was ground to a fine powder, packed into No. 4 gelatin capsules and then administered orally with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 73 mg/kg (59-90)

2. Pharmacotoxic signs include inactivity, tremors, salivation and polypnea at the approximate LD_{50} level. Survivors appeared normal by day 5. Deaths occurred with 96 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II

Powdered Dyfonate 20 G in Capsules

Acute Female Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Fifty female New Zealand rabbits weighing between 1.3-2.4 kg were divided into five groups of 10 animals per group. The dosage levels were 125, 100, 80, 50, and 40 mg/kg. The granular material was ground to a fine powder, packed into No. 4 gelatin capsules and then administered orally with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 59 mg/kg (39-89)

2. Pharmacotoxic signs include inactivity, diarrhea, ataxia, and salivation at the approximate LD_{50} level. Survivors appeared normal by day 3. Deaths occurred within 72 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II

Powdered Dyfonate 20 G in Corn Oil Suspension

Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Fifty-nine male New Zealand rabbits weighing between 1.3-2.4 kg were divided into three groups of 10 animals per group. The dosage levels were 125, 80, and 56 mg/kg. Two additional groups were tested, one with 20 animals at 63 mg/kg and another with nine animals at 50 mg/kg. The Dyfonate 20 granular was ground to a fine powder and suspended in corn oil so that a constant volume of 2 ml/kg could be administered by gastric gavage. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for a total of 7 days.

B. Results

1. LD50 59 mg/kg (52-67)

2. Pharmcotoxic signs include tremors salivation, prostration, polypnea ataxia, hypothermia and grinding of teeth at the approximate LD_{50} level. Survivors appeared normal by day 3. Death occurred within 24 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II

Powdered Dyfonate 20 G in Corn Oil Suspension

Acute Female Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Seventy-nine female New Zealand rabbits weighing between 1.3-2.4 kg were divided into five groups of 10 animals per group each dosed at 125, 80, 50, 40 and 35 mg/kg. Two additional groups were tested, one with 20 animals at 63 mg/kg and another with nine animals at 71 mg/kg. The Dyfonate 20 granular was ground to a fine powder and suspended in corn oil so that a constant volume of 2 ml/kg could be administered by gastric gavage. Animals were observed daily for mortality for a total of 7 days.

B. Results

1. LD50 58 mg/kg (50-67)

2. Pharmacotoxic signs include tremors, salivation, inactivity, polypnea and hyperreactivity at the approximate LD_{50} level. Survivors appeared normal by 2. Deaths occurred within 24 hours.

3. Necropsy

C. Conclusion

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported.

2. Toxicity Category: II

Dyfonate 20 G in Capsules (calculated as active ingredient)

Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Sixty-nine male New Zealand rabbits weighing between 1.3-2.4 kg were divided into six groups of 10 animals per group dosed at 27, 22, 17, 14, 11, 9 mg/kg. One additional group of nine animals were dosed at 7 mg/kg. The granules were weighted and packed in No. 4 gelatin capsules and administered with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

1. LD50 12.7 mg/kg (10.2-15.8) calculated as active ingredient (Estimated LD50 63.5 mg/kg on the 20 granular formulation)

2. Pharmacotoxic signs

3. Necropsy

C. Conclusions

1. Classification of Data - Core Supplementary
   a. Deficiency of Data

      1. Animals were not observed for 14 days.

      2. Pharmacotoxic signs were not reported.

      3. No gross pathology reported.

2. Toxicity Category:

Powdered Dyfonate 20 G in Capsules (calculated as active ingredient)

Acute Female Rabbit Oral Toxicity
Stauffer Chemical Co. Report No. T-6384. October 3, 1979

A. Procedure

Forthy-eight female New Zealand rabbits weighing between 1.3-2.4 kg were divided into three groups of 10 animals per group dosed at 27, 17, 11 mg/kg. Two other groups of nine animals per group were dosed at 22 and 9 mg/kg. The granules were ground to a fine powder, doses were weighed from the powder, packed into No. 4 capsules and administered with a balling gun. Animals were fasted for 18 hours prior to treatment. All animals were observed daily for mortality for 7 days.

B. Results

1. LD50 15.8 mg/kg (13.5-18.6) calculated as active ingredient (Estimated LD50 79 mg/kg on the 20 granular formulation)

2. Pharmacotoxic signs

3. Necropsy

C. Conclusions

1. Classification of Data - Core Supplementary
   a. Deficiency of Data

      1. Animals were not observed for 14 days.

      2. Pharmacotoxic signs were not reported.

      3. No gross pathology reported.

2. Toxicity Category:

Powdered Dyfonate 20 G in Corn Oil Suspension

Acute Rat Oral Toxicity
Stauffer Chemical Co. Report No. T-6774. October 21, 1979

A. Produce

Two groups of 120 males weighing between 163-287 grams and 90 females weighing 136-190 grams, Sprague-Dawley albino rats, were divided into seven male and six female dosage levels. There were 10 males per dosage level dosed at 151, 76 and 60 mg/kg, 20 males per level of 107, 96 and 85 mg/kg and one level of 30 males at 120 mg/kg. The females rats were divided into six dosage levels, of these three consisted of 10 females at 62, 55, and 44 mg/kg and twenty females at 49, 39 and 31 mg/kg. All animals were fasted for 24 hours prior to treatment. The granular material was ground, suspended in corn oil and administered orally in a constant volume of 10 ml/kg. All animals were observed twice daily for 14 days. Necropsies were performed on all animals that died during the study and on all survivors at 14 days. Controls: Thirty female and thirty males were treated orally with corn oil at 10 ml/kg.

B. Results

1. LD50 males 100 mg/kg (93.5-107)
   LD50 females 43 mg/kg (40.2-46)
   Corn oil control - no deaths

2. Pharmacotoxic signs
   Females and males at the LD50 dosage level showed depression, tremors, salivation and diarrhea
   Corn oil control - Normal

3. Necropsy
   Gross necropsy of males and females revealed possible hemorrhage in the small intestine and lungs on day 14.
   Corn oil control - no visable signs of gross pathology observed at 14 days.

C. Conclusions

1. Classification of Data - Core Guidelines

2. Toxicity Category I

Acute Oral Toxicity in Rats and Rabbits
(1979-1980)
Dyfonate 10 Granular
-18-

Study	Material	Vehicle	EPA Accession No.	Results	Toxicity Category	Core Grade	Study Reference
Acute oral LD50 male rat	10 G	powdered in corn oil	243640	188 mg/kg	II	Guideline	T-6738A
Acute oral LD50 female rat	10 G	powdered in corn oil	243640	84 mg/kg	II	Guideline	T-6738A
Acute oral LD50 male rat	10 G	powdered in water	243640	115 mg/kg	II	Guideline	T-6738A
Acute oral LD50 female rat	10 G	powdered in water	243640	39 mg/kg	I	Guideline	T-6738A
Acute oral LD50 male rat	10 G	powdered in carboxymethylcellulose	243640	87 mg/kg	II	Guideline	T-6738A
Acute oral LD50 female rat	10 G	powdered in carboxymethylcellulose	243640	38 mg/kg	I	Guideline	T-6738A
Acute oral LD50 male rabbit	10 G	capsule	243582	135 mg/kg	II	Minimum	T-6883
Acute oral LD50 female rabbit	10 G	capsule	243582	158 mg/kg	II	Minimum	T-6883

Powdered Dyfonate 10 G Corn Oil Suspension

Acute Rat Oral Toxicity
Stauffer Chemical Co. Report T-6738A. October 15, 1979

A. Procedure

Two groups of 70 males weighing between 174-223 grams and 60 females weighing between 160-189 gram Sprague Dawley Albino rats were divided into seven male and six female groups of 10 animals each. The males were dosed orally at 316, 282, 224, 178, 158, 141 and 112 mg/kg. The females were dosed orally at 158, 126, 100, 79, 63 and 50 mg/kg. All animals were fasted 24 hours prior to treatment. The granular material was ground, suspended in corn oil and administered orally in a contant volume of 10 ml/kg. All animals were observed twice daily for 14 days. Necropsies were performed on all animals that died during the study and on all survivors at 14 days. Controls: Twenty males and twenty females were treated orally with corn oil at 10 ml/kg.

B. Results

1. LD50 males 188 mg/kg (166-214)
   LD50 females 84 mg/kg (69-103)
   Corn oil control - no deaths.

2. Pharmacotoxic signs:

   Males at the approximate LD50 value showed severe tremors, slight to moderate depression, excessive salivation and diarrhea.

   Females at the approximate LD50 value showed moderate to severe depression, excessive salivation, matted fur, tremors, and blood like stains on the face.
   Corn oil controls - Normal

3. Necropsy

   Gross necropsy of males and females rats that died on test revealed small intestines which appeared opaque and yellow in appearance.

C. Conclusion

1. Classification of Data - Core Guideline

2. Toxicity Category II

Powdered Dyfonate 10 G in Water Suspension

Acute Rat Oral Toxicity
Stauffer Chemical Co. Report T-6738A. October 15, 1979.

A. Procedure

Sixty male Sprague-Dawley rats weighing between 162-231 grams were divided into six groups of 10 animals each and dosed at 316, 224, 158, 112, 100 and 79 mg/kg respectivily. One hundred and ten female Sprague-Dawley rats weighing between 142-200 grams were divided into four groups of 10 animals each and dosed at 100, 50, 32 and 25 mg/kg. Another four groups of 20 females per group were dosed at 79, 63, 40 and 35 mg/kg. All animals were fasted for 24 hours prior to treatment. The granular material was ground, suspended in deionized water and administered orally in a constant volume of 10 ml/kg. All animals were observed twice daily for 14 days. Necropsies were performed on all animals that died during the study and on all survivors at 14 days. Controls: Twenty male and forty female rats were treated orally with deionized water at 10 ml/kg.

B. Results

1. LD50 males 115 mg/kg (95-139)
   LD50 females 39 mg/kg (35-44)
   Water controls - no deaths.

2. Pharmacotoxic signs:

   Males at the approximate LD50 value showed tremors, excesive salivation and depression.

   Females at the approximate LD50 value showed marked depression, severe tremors and excessive salivation. Males and female animals dosed with water suspensions of Dyfonate 10 G died more rapidly than those male and female rats treated with the corn oil suspensions of the 10 granular.
   Water Controls - Normal.

3. Necropsy

   Gross necropsy of males and females rats that died during the revealed reddened intestines.

C. Conclusion

1. Classification of Data - Core Guideline

2. Toxicity Category I

Powdered Dyfonate 10 G in 1% Carboxymethylcellulose Suspension

Acute Rat Oral Toxicity
Stauffer Chemical Co. Report T-6738A. October 15, 1979

A. Procedure

One hundred and ten male Sprague-Dawley rats weighing between 158-240 grams were divided into two groups of 10 animals each dosed at 158 and 40 mg/kg and three groups of twenty rats each were dosed at 112, 100 and 56 mg/kg respectively. One addition group of thirty rats were dosed at 79 mg/kg. Seven groups of ten females rats per group weighing between 147-197 grams were dosed orally at 79, 63, 50, 40, 35, 32 and 25 mg/kg respectively. All animals were fasted for 24 hours prior to treatment. The granular material was ground, suspended in 1% (CMC) carboxymethycellulose and administered orally in a constant volume of 10 mg/kg. All animals were observed twice daily for 14 days. Necropsies were performed on all animals that died during the study and on all survivors at 14 days. Controls: Thirty males and twenty females were treated orally with 1% CMC 10 ml/kg.

B. Results

1. LD50 males 87 mg/kg (78-97)
   LD50 females 38 mg/kg (34-43)
   Carboxymethycellulose Controls - no death.

2. Pharmacotoxic signs:

   Males at the approximate LD50 value showed severe tremors, moderate depression and excessive salivation.

   Females at the approximate LD50 value showed moderate tremors, moderate to severe depression and excessive salivation. Male and female animals dosed with 1% CMC suspension of Dyfonate 10 granular died more rapidly than those animals treated with the corn oil suspension of Dyfonate 10 G.
   Carboxymethylcellulose controls appeared normal.

3. Necropsy

   Gross necropsy of males and females rats that died during the test revealed reddened intestines.

C. Conclusion

1. Classification of Data - Core Guideline

2. Toxicity Category I

Dyfonate 10 G in capsules

Acute Male Rabbit Oral Toxicity
Stauffer Chemical Co. Report T-6883. April 16, 1980

A. Procedure

One hundred and thirty young adult albino rabbits weighing between 1.62 to 2.46 kg were divided into the following nine dosage levels (number of animals per level in parenthesis) 200(10), 188(10), 178(10), 158(10), 141(20), 125(20), 119(20), 112(20) and 100(10) mg/kg. Animals were fasted overnight prior to treatment. The dosages of the granular material were administered orally in gelatin capsules by means of a small balling gun. Doses were prepared individually for each animal. All animals were observed for mortality for 7 days.

B. Results

1. LD50 135 mg/kg (121-151)

2. Pharmacotoxic signs include inactivity, prostration and salivation at the approximate LD_{50} level. Survivors appeared normal by day 6, except for one rabbit that was mildly inactive. This rabbit had gradually recovered from the severe toxic signs he exhibited after dosing. Deaths occurred within 24 hours.

3. Necropsy

C. Conclusions

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported.

2. Toxicity Category: II

Dyfonate 10 G in capsules

Acute Female Rabbit Oral Toxicity
Stauffer Chemical Co. Report T-6883. April 16, 1980

A. Procedure

One hundred and sixty-nine young adult albino rabbits weighing between 1.46 to 2.52 kg were divided into the following ten dosage levels (number of animals per level in parenthesis) 224(10), 200(30), 188(10), 178(30), 158(20), 141(10), 125(10), 119(10), 100(30) and 79(9) mg/kg. Animals were fasted overnight prior to treatment. The dosages of the granular material were prepared individually for each animal and administered orally in gelatin capsules by means of a small balling gun. All animals were observed for mortality for 7 days.

B. Results

1. LD50 158 mg/kg (144-174)

2. Pharmacotoxic signs include tremors, diarrhea, salivation, dyspnea, prostration and inactivity at the LD_{50} level. Survivors appeared normal by the end of day 3. Death occurred within 48 hours. Mild inactivity was reported on day 7 for one survivor on each of the 200 and 188 mg/kg dosage levels.

C. Conclusion

1. Classification of Data - Minimum
   a. Deficiency - No gross pathology reported

2. Toxicity Category: II