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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

#154B

MEMORANDUM

SUBJECT: Pesticide Use Classification of Fonofos (Dyfonate) 20%G
Pesticide Use Restriction 44 FR 45218; ID Notification
OPP-30029

FROM: Ray Landolt, Pharmacologist
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TO: Walter I. Waldrop
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THRU: William Burnam, Acting Chief
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THRU: Peter E. McGrath, Director
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Conclusion

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).

Background Information

The Agency published in 44 FR 45218, August 1, 1979 proposed rules to amend 40 CFR 162.31 by adding the uses of eight granular formulations for restricted use classification. With respect to human safety, previous non-domestic use classifications were based on the acute dermal and acute inhalation toxicity of the formulations under consideration. Acute oral toxicity was the criterion used with the present proposal to classify the non-domestic uses of these granular formulations for restricted use. Paragraph 162.11(c)(2)(ii)(A) provides that a non-domestic use of a previously registered product shall be a candidate for restricted use if the formulation meets the criterion for Toxicity Category I. The acute oral toxicity criterion for Toxicity Category I is an acute oral LD_{50} less than or equal to 50 mg/kg. The granular formulations under consideration have an acute oral LD_{50} less than or equal to 50 mg/kg.

The use of the acute oral toxicity as a criterion to classify these granular formulations was influenced by several factors. First, there was concern for the potential for inadvertant ingestion of the granular formulations by the user during loading, application, equipment calibration, equipment maintenance, and cleaning, and handling of containers during disposal. Second, there was concern for possible accidental ingestion by children, pets and farm animals during storage of the granular formulations. Generally, the farm environment is considered to be non-domestic but obviously children living on the farm, pets and farm animals often have access to stored pesticides. In assessing the hazard of non-domestic uses the Agency has considered the reports of farm animals dying from ingestion of the stored granular formulation as well as ingestion of feed contaminated with these granular formulations.

Stauffer Chemical Co. has challenged (1) the use of acute oral toxicity as a criterion for identifying the Dyfonate 20 granular formulation for restricted use classification (2) that the Dyfonate 20 granular formulation is highly toxic (in Toxicity Category I) when administered orally to experimental animals, and (3) that Dyfonate granular formulations cause adverse efforts to man or farm animals when used in accordance with label directions. In support of its position. Stauffer Chemical Co. presented on October 26, 1979 its rationale and data for reconsideration of these issue by the Agency. These issues raised by Stauffer Chemical Co. along with an evaluation of the acute oral toxicity studies were addressed with my memo of December 20, 1979, (copy enclosed) with the following Conclusions:

(1) The acute oral LD_{50} is a valid trigger for classification of non-domestic uses. The rat is the preferred species for determining acute oral LD_{50} values.

(2) The rat has been shown to be the most sensitive species to the oral toxicity of Dyfonate and the basis for classifying the 20 granular for restricted use. When there is a question of safety in extrapolation of experimental data to man the Agency consistently uses the most sensitive species.

(3) The acute oral toxicity studies on the rat and rabbit reported in Appendix 3B are not adequate to determine the toxicity category for either the technical or 20 granular formulation of Dyfonate. These animals were observed for 7 days rather than the required 14-day observation period.

(4) The incidents of death among farm animals from ingesting feed contaminated with the granular formulations of Dyfonate demonstrates the lack of understanding by the user of the high toxicity of the Dyfonate 20 granular to cattle.

Current Considerations

On October 23, 1980 Stauffer Chemical Co. submitted additional toxicity data and comments reiterating their position presented in their letter of October 29, 1979. This memo has addressed the three issues raised by Stauffer with their submission of October 23, 1980 that are pertinent to the toxicology review of Dyfonate 20 granular for restricted use classification.

I. In the covering letter Stauffer expressed the view that:

> "It is not appropriate to use acute oral mammalian toxicology as a basis for classification of restricted use and general use."

Acute oral toxicity is applicable to restricted use classification of those formulations that meet the criteria for Toxicity Category I. Refer to 40 CFR 162.11(c)(2)(ii).

Non-domestic applications:

> A pesticide use(s) intended for non-domestic application shall be a candidate for general use classification if the pesticide formulation:
>
> (A) Does not meet the criteria of Toxicity Category I.

The acute oral toxicity criteria for Toxicity Category I is an acute oral LD_{50} less than or equal to 50 mg/kg. This level can be equated to the probable lethal dose from ingestion of less than one teaspoonful by a 70 kg (150 lb) adult* or to the volume of one swallow by a 15 kg (30 lb) child.** This comparison assumes the toxicity of a formulation to be the same for man as it is to the rat. Those formulations that meet the criteria for Toxicity Category I, an acute rat oral LD_{50} less than or equal to 50 mg/kg, shall be a candidate for restricted use classification.

*Clinical Toxicology of Commercial Product
Marvin N. Gleason, Robert E. Gosselin, Harold C. Hodge and Roger R. Smith
The Williams and Walkins Co.

**Volume of a Swallow
Daniel V. Jones and Charles E. Work
Diseases of Children 102:427, 1961

II. In their letter of October 23, 1980 Stauffer concluded from a review of all available scientific evidence that the proposed restricted use classification of Dyfonate granular products is not appropriate since:

> "Field use experience with Dyfonate granular products demonstrate that these products do not cause harm to man or farm animals when used according to label directions"

Stauffer Chemical Co. has overlooked Appendix eight of its October 23, 1980 submission. Appendix eight summarizes all incidents involving Dyfonate granular insecticide formulations as of October, 1980. Fourteen episodes were reported by Stauffer involving the ingestion of the granular formulations of Dyfonate by cattle. Of the fourteen episodes eleven resulted in the death of 225 cattle from either improper storage and disposal or feeding contaminated feed to cattle. Improper storage and disposal accounted for the death of 2, 6, 6, 26 and 10 cattle in each of five respective episodes from ingestion of the Dyfonate granular formulations. Ingestion of contaminated feed accounted for another six episodes with the death of 1, 28, 5, 25, 5 and 111 cattle, respectively. Three episodes resulted in no ill effects from cattle ingesting the granular formulations during storage and disposal or feeding contaminated feed to farm animals. That cattle do ingest the granular formulations was the concern of the Agency's Pesticide Classification Meeting held February 13, 1979 in Rosemont, Illinois with USDA Cooperative Extension Service personnel and State regulatory officials from states where granular formulations are widely used. The participants of this meeting documented incidents involving the granular formulations and discussed use patterns and associated hazards. During the discussion of the granular formulations of Dyfonate they expressed concern that the "Acute hazard to the applicator appears to be low, however, storage and disposal presents a significant hazard to livestock and pets."

These granular formulations are labeled with the precautionary statements:

> "Do not transport or store Dyfonate 20G with any food or feed intended for human or animal consumption."
>
> "Do not contaminate food or feed."
>
> "Completely empty the contents of bag and bury unused chemical at least 18 inches deep in an isolated location away from water supplier. Bury bag with wastes."

"Do not apply or allow to drift to areas occupied by unprotected humans or beneficial animals or adjoining food, fiber or pasture crop."

Dyfonate 20 granular is registered and marketed with the signal word Danger for products that are in Toxicity Category I along with the symbols of high toxicity of Poison and the skull amd crossbones. Neither the symbols of high toxicity nor the above use directions for proper storage and disposal have been adequate to minimize the economic loss incurred by the death of cattle from ingesting these granular formulations. It is clear from the incidents of death among farm animals from ingesting the granular formulations of Dyfonate that the users of these products are not aware of the toxicity of this pesticide to farm animals. With Section 3d of FIFRA as amended 1972, it was the intent of Congress to strengthen the regulatory control on the use and misuses of pesticides through the classification of uses for general or restricted use. Congress recognized that the long standing label requirements had not been adequate standing alone to protect the pesticide user or other persons from the adverse effects of exposure to acutely toxic pesticides. Dyfonate 20 granular does not meet the criteria of 162.11(c)(3) Adequacy of label and labeling. Failure to follow the use directions for proper storage and disposal have resulted in discernible adverse effects from careless handling of a toxic material.

III. Toxicity Data Review

The following observations and conclusions are related by Stauffer in their letter of October 16, 1980.

"Stauffer in an effort to contribute to the scientific literature and advance the state of the art implemented a series of research, programs to determine an appropriate means of conducting acute oral LD_{50} studies using intact granular products.

In this research we found that while intact granulars can be administered to rats by capsule, the data are equivocal because the animals were stressed and traumatized. In considering another animal to conduct acute oral LD_{50} studies we found that rabbits easily handled capsules without stress or trauma. In addition, we found that in comparative studies, the male and female rabbit were as sensitive to Dyfonate as the female rat (most sensitive species and sex). The acute oral LD_{50} of intact granules of Dyfonate 20G for male rabbits is 59 mg/kg and 66 mg/kg for female rabbits. On the basis of these data Dyfonate 20G is in category II toxicity."

The following chronology of toxicity data evaluation on the Dyfonate granular formulations has been developed.

In November, 1967 Stauffer Chemical Co. registered its 5, 10, 12, 15 and 20% granular Dyfonate formulations with highly toxic (category I) labeling. Then in January, 1970 Stauffer submitted acute rat oral toxicity studies on the 10, 12, 15 and 20% granular formulations of Dyfonate with the request to change the precautionary labeling of these formulations from Toxicity Category I to Toxicity Category II. The reported LD_{50} values were determined by administering the granular formulations in gelatin capsules orally to male and female rats. In the covering letter submitted by Stauffer, for this request, the following observation was related.

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

This data was reviewed independently by the pesticide Regulation Division of the USDA and the Division of Pesticide Chemistry and Toxicology of the Bureau of Food and Pesticides, FDA. Both agencies independently concluded that the 5, 10, 12, and 15% granular formulations could be reclassified Toxicity Category II and the 20% granular must remain in Toxicity Category I (Refer to Table one). Products that are in Toxicity Category I because of their acute oral toxicity (LD_{50} of 50 mg/kg or less) are required to be labeled with the signal word Danger, the word Poison and the skull and crossbones.

Subsequent to this determination, in 1977 Stauffer submitted acute oral LD_{50} values for the 20% granular formulation administered orally as a suspension in 1.0% tragacanth to male and female rats. With reference to table one these studies support the Toxicity Category I labeling for the 20% granular formulation of Dyfonate with acute oral LD_{50} values of 44 mg/kg for male rats and 28 mg/kg for female rats.

On October 26, 1979 Stauffer Chemical Co. submitted additional toxicity data in support of Toxicity category I labeling for the 20% granular formulation of Dyfonate. The acute oral LD_{50} values for the 20% granular formulation administered as a powder suspended in corn oil, for male and female rats were 100 and 43 mg/kg, respectively (Refer to table one). In conjunction with this up dating of the toxicity profile on the 20% granular Dyfonate formulation, Stauffer submitted the results of an extensive testing program to show by the oral administration of these granular formulations to rats and rabbits that the rabbit is as acceptable a test animal as the rat for determining acute oral LD_{50} values. In pursuit of this objective, attempts were made to determine acute oral LD_{50} values in male and female rats and rabbits for the technical material and the 20% and 10% granular Dyfonate formulations. The rabbit studies consisted of the oral administration of the 20 granular in capsules, capsules plus corn oil, powdered granules in capsules and powdered granules in corn oil suspension (Refer to Table 2). In addition, the 10 granular was administered orally in capsules to male and female

rabbits. For comparison of the suitability of the rabbit for testing of the granular formulations, acute oral LD_{50} values were determined in male and female rats for the 20 granular formulation in corn oil suspension and the 10 granular formulation in a corn oil, 1% carboxymethyl cellulose and water suspensions. All of these studies were reviewed and evaluated for their scientific quality by comparing the test parameters of these studies with those parameters of the acute oral toxicity testing guidelines and the parameters for the minimum data criteria. All of the acute rat oral toxicity studies submitted for the 20 and 10 granular formulations were judged to meet the acute oral guideline standards and would support regulatory actions for labeling and classification of pesticide uses. All of the acute rabbit oral toxicity studies submitted for the technical, 20 and 10 granular formulation as well as the rat oral toxicity study on the technical material did not meet the parameters for minimum data criteria. These studies were deficient in the following parameters (1) the study was terminated on day seven rather than carried to a 14 day observation period (2) pharmacotoxic signs were not reported (3) gross necropsy was not performed at the conclusions of the study.

It is recognized that the purpose of the rabbit study is to show the suitability of the rabbit for oral administration of the granular formulations as compared to the rat. However, it is likely at some future date these rabbit studies would be used to support a regulatory action or referred to in support of a regulatory action. In either case they must be of the same quality as any other study being considered for regulatory action. Stauffer has sought to compare acute rat oral toxicity studies which meet the guideline standards to acute rabbit oral toxicity studies which do not meet the minimum data criteria. If the deficiencies in the acute rabbit oral toxicity studies can be set aside consideration should be directed to the conclusions drawn by Stauffer in their discussion of the data.

First, in comparative studies the male and female rabbit were as sensitive to Dyfonate as the female rat (more toxic to the to the female rat than to the male rat as reported in earlier oral toxicity studies).

Second, that Dyfonate 20 granular was found to be equally toxic to male and female rabbits when administered orally either as intact granular or powder in capsules or in a corn oil suspension.

Third, that Dyfonate 20 granular formulation is in Toxicity Category II when administered orally either in a corn oil suspension or in capsules to rabbits (Refer to table two).

If corn oil did not alter the toxicity of Dyfonate and the corn oil suspension of Dyfonate was no more toxic than either the intact granules or powdered form when administered orally in capsules to male or female rabbits, then the acute oral LD_{50} values from the oral administration of the 20 granular formulation either as a corn oil suspension or in capsule to rats is an equitable indicator of the acute oral toxicity of Dyfonate. Dyfonate 20 granular is in Toxicity Category I and is equally toxic to rats when administered orally either as a corn oil suspension or in capsules. With reference to table one, the comparative acute oral LD_{50} values of the 20 granular in rats, whether administered as a liquid suspension in corn oil or in capsules, indicates lack of trauma and stress to the rat from the oral administration of capsules. The acute oral LD_{50} values for the 20% granular formulation suspended in corn oil for male and female rats are 100 and 43 mg/kg respectively as compared to the acute oral LD_{50} values for the 20% granular administered in capsules to male and female rats of 93 and 43 mg/kg respectively. Dyfonate 20 granular requires Toxicity Category I labeling and is classified for restricted use.

The acute rat oral LD_{50} values for Dyfonate 20G whether administered in corn oil suspension or by capsule are in Toxicity Category I as compared to the rabbit acute oral LD_{50} values in Toxicity Category II. Extrapolating the responses of different species calls for the assumption that man is at least as sensitive as the most sensitive species studied. By inspection of the acute oral toxicity data for the granular formulations on table one, the female rat is consistently the most sensitive indicator of toxicity to either of the liquid suspensions or dry formulations of Dyfonate. To consider an alternate to the rat for acute oral testing the alternate should be more sensitive than the female rat. This is not the case for testing formulations of Dyfonate in the rabbit. The rabbit is not a suitable alternate to the rat for assessing the ingestion hazard of the Dyfonate granular formulations.

Table I
Acute Oral Toxicity in Rat of Dyfonate

Test Material	Form	Vehicle	LD50 mg/kg Male	LD50 mg/kg Female	Toxicity Category	Study Ref.
Tech. 95.4%	Liquid	Corn Oil	24.5	10.8	I	6461
20G	Powder	1% Tragacanth 0.05% Tween 20	68	17	I	1057
20G	Powder	1% Tragacanth	44	28	I	5612
20G	Powder	Polyethylene Glycol 300	68	32	I	1251
20G	Granular	Capsule	58	23	I	1743
20G	Granular	Capsule	93	43	I	1251
20G	Powder	Corn Oil	100	43	I	6774
10G	Powder	1% Tragacanth 0.05% Tween 20	68	37	I	989
10G	Powder	1% Tragacanth 0.05% Tween 20	79	58	II	991
10G	Powder	Polyethylene Glycol 300	147	79	II	1251
10G	Granular	Capsule	200	126	II	1251
10G	Powder	Corn Oil	188	84	II	6738A
10G	Powder	Water	115	39	I	6738A
10G	Powder	1% Carboxylmethylcellulose	87	38	I	6738A

Table II
Acute Oral Toxicity in Rabbit of Dyfonate

Test Material	Form	Vehicle	LD50 mg/kg Male	LD50 mg/kg Female	Toxicity Category	Study Ref.
Tech. 95.6%	Liquid	Corn Oil	14.2	12.7	I	6883 6384
20G	Granular	Capsule	59	66	II	6384
20G	Granular	Capsule + 2 ml/kg Corn Oil	79	83	II	6384
20G	Powder	Capsule	73	59	II	6384
20G	Powder	Corn Oil	59	58	II	6384
10G	Granular	Capsule	135	158	II	6883