1-27-83

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

003640

MEMORANDUM

TO: Kyle Barbehenn

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

THRU: William Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Dimethoate Registration Standard

The discussion below addresses some of your concerns relating to the dimethoate registration standard.

1) Reason for Modification of the Mouse Strain for the Oncogenicity Study:

It was agreed by Burnam and Schneider of Toxicology Branch and the Dimethoate European Task Force that since the strain of mouse tested by Gibel was not easily available outside of East Germany, that a different strain could be used. Data were required to indicate that any new strain would have to be susceptable to the same type of tumors found by Gibel. The meeting where the agreement took place was chaired by Dr. Werdig of SPRD's Data Call- In Program.

2) Neurotoxicity Studies:

The RPAR PD-1 was critical of the American Cyanamid studies because:

a. Only 1/8 of the LD_{50} dose was administered.

b. The chemical was administered in the feed, which the PD-1 stated could compromise adequate dosing.

The repeat administration of a pesticide at lower doses in lieu of single doses near the LD_{50} in a delayed neurotoxicity test is considered acceptable, especially since the registrant had been unable to obtain protection by the use of atropine in the acute studies. This is consistent with our CORE Grading System. The hens were dosed with 1/8 the LD_{50} dose daily for

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one month, or 4 weeks, which we certainly would consider adequate exposure. Usually, 10 hens should be treated instead of just 6. However, when the negative results of the study are reviewed together with those of another study (Gaines), additional testing would not be necessary. This recommendation is consistent with the opinion of the EPA Science Advisory Panel.

Toxicology Branch has previously been on record discounting the need for additional neurotoxicity testing. In July-August, 1982 the Agency's Freedom of Information Office received a request from the University of Saskatchewan for data which would justify the need for additional demyelination studies to demonstrate the neurotoxicity potential (or lack thereof) of dimethoate. In consultation, the Registration Standard toxicologist (Gessert) and RPAR toxicologist (Burnam) determined the data available could be considered adequate and that it would be difficult to properly fill the FOI request. Subsequently, Dr. Geraldine Werdig (SPRD) notified the Dimethoate Task Force (Ms. Lynn Gregory, American Cyanamid), deferring a decision regarding a new hen neurotoxicity test.

3) Terata- Exposure Analysis:

In the PD-4, label warnings were not considered necessary. In the Registration Standard we are requesting two teratology studies on the technical chemical. We are definitely not requesting label warnings at this time since the new teratology studies aren't completed.

According to Paul Parsons, Dimethoate Project Manager, the Dimethoate Task Force have agreed to provide an exposure analysis. SPRD also are not requesting label warning changes until the exposure analysis is received and reviewed. So in answer to your question, we might say SPRD is "pushing exposure".

Other brief revisions suggested by you have been made in the document.

Roland A. Gessert

Roland A. Gessert, D.V.M.
Toxicology Branch/HED (TS-769)

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

TO: Paul Parsons, Product Manager
Special Pesticide Review Division (TS-791)

THRU: Henry Craven H.T. Craven
Registration Standards Coordinator
Ecological Effects Branch
Hazard Evaluation Division (TS-769)

Raymond W. Matheny RWM
Head, Review Section No. 1
Ecological Effects Branch
Hazard Evaluation Division (TS-769)

Clayton Bushong, Chief
Ecological Effects Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Dimethoate Registration Standard: Aquatic Organism Accumulation Study

An HED Registration Standard team meeting for dimethoate, called by the HED Science Integration Staff (SIS), was held on 1/5/83. At this meeting, Hudson Boyd of the Environmental Fate Branch (EFB) indicated that EFB no longer had a need for a fish accumulation study (Guideline Citation 165.4), due to a reported octanol/water partition coefficient of 0.5-3.2. This range is quite low and thus implies a low potential for bioaccumulation. However, environmental fate data (Task 3, Environmental Fate Profile, 8/25/82) are inadequate to determine the degree to which dimethoate reaches and persists in fish-bearing waters, especially in light of repeat applications. Pending completion of these information gaps (and results of outstanding EEB data requirements) an aquatic organism accumulation study may be needed in the future, as is already indicated in the Phase II Ecological Effects Data Requirements Table (9/21/82).

James D. Fokel
James D. Fokel, Wildlife Biologist
Ecological Effects Branch
Hazard Evaluation Division (TS-769)

cc: K. Barbehenn, SIS

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Effects on Beneficial Insects

The following studies received full review under this topic:

Author	ID
Fraser and Jenkins	00026489
Atkins et al.	00036935
Johansen et al.	00045046
Cole	00059971
Johansen and Hutt	00060625
Johansen and Eves	00060628
Johansen	05000837
Stevenson	05001991
Stevenson	05004151
Harris and Svec	05011163
Gorecki	05012881

Studies are outlined in Table 1.

Table 1. Toxicity studies on beneficial insects with dimethoate.

Species	Formulation	Results	Author	Date	MRID#
Honey bee (Apis mellifera)	Technical	0.1% solution caused 100% mort. (direct appl.)	Harris and Svec	1969	05011163
Honey bee	Technical	Highly toxic (oral and contact toxicity)	Stevenson	1968	05004151
Honey bee	Technical	Contact LD50= 0.12 micrograms per bee; oral LD50= 0.15 micrograms per bee (highly toxic)	Stevenson	1978	05001991
Honey bee	Technical	Contact LD50= 0.17 micrograms per bee; oral LD50= 0.083 micrograms per bee (highly toxic)	Cole	1974	00059971
Honey bee	Technical	Contact LD50= 0.16 micrograms per bee; oral LD50= 0.056 micrograms per bee (highly toxic)	Fraser and Jenkins	1972	00026489

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Table 1. (cont.)

Species	Formulation	Results	Author	Date	MRID#
Honey bee	Technical	Contact LD50= 0.188 micrograms per bee (highly toxic)	Atkins et al.	1975	00036935
Honey bee Alkali bee (Nomia melanderi) Leafcutter bee (Megachile rotundata)	2.67 lb EC	At 0.5 lb AI/A, 2-day residues low to moderate in tox. to all 3 species	Johansen	1972	05000837
Honey bee Alkali bee Leafcutter bee	2.67 lb EC	At 0.5 lb AI/A, 3-hr residues highly toxic, 2-day residues low to moderate in tox. to all 3 species	Johansen and Eves	1965	00060628
Honey bee Alkali bee Leafcutter bee	2.67 lb EC	At 0.5 lb AI/A, residues highly toxic through one day posttreatment	Johansen et al.	1975	00045046
Honey bee	4 lb E	At 0.5 lb AI/A, residues highly toxic through 2.5 hr	Johansen and Hutt	1962	00060625
Honey bee	37% EC	"Harmful" to bees	Gorecki	1973	05012881

There is sufficient information to characterize dimethoate as highly toxic to honey bees, alkali bees, and alfalfa leafcutter bees, when bees are exposed to direct application or to residues less than one day old. Data indicate that residual toxicity declines to low/moderate by two days posttreatment.

There are presently no guidelines requirements for evaluating toxicity to nontarget insects.

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Effects on Nontarget Soil and Surface Invertebrates

The following studies received full review under this topic:

Author	ID
Bartlett	05003978
Bartlett	05004148
Bartlett	05005640
Searle	05006416
Hoy et al.	05008360
Croft and Nelson	05009345
Harper	05012227
Niemczyk and Flessel	05012231
Teotia and Tiwari	05013372

Studies are outlined in Table 1.

Table 1. Toxicity studies on nontarget soil and surface invertebrates with dimethoate.

Species	Formulation	Results	Author	Date	MRID#
Parasitic wasp (Bathyplectes curculionis)	Technical	LC50= 0.0[illegible]43% solution (highly toxic)	Niemczyk and Flessel	1975	05012231
Eleven species of parasitic wasps and predaceous beetles	4 lb/gal EC	At .50 lb AI/100 gal, highly toxic to wasps, mod.-highly toxic to beetles	Bartlett	1963	05003978
Two species of parasitic wasps, two species of predaceous beetles	4 lb/gal EC	At .0477% conc., mod. to high tox. to beetles, high tox. to wasps; at .477% conc., high tox. to all species	Bartlett	1966	05005640
Predaceous mite (Amblyseius hibisci)	4 lb/gal EC	At 0.50 lb AI/100 gal, highly toxic	Bartlett	1964	05004148
Predaceous mite (Amblyseius fallacis)	2.67 EC	Azinphosmethyl resistant strain showed some resistance to dimethoate	Croft and Nelson	1972	05009345

Table 1. (cont.)

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Species	Formulation	Results	Author	Date	MRID#
Predaceous mite (*Metaseiulus occidentalis*)	25%WP	Susceptibility varied depending on life stage, exposure route, etc.	Hoy et al.	1979	05008360
Predaceous beetle (*Coccinella septempunctata*)	Formulated product	35% mort. after 24 hr when fed poisoned aphids. Mortality increased to 73.3% after 72 hr	Teotia and Tiwari	1972	05013372
Parasitic wasp (*Pauridia peregrina*)	Formulated product	Addition of oil did not reduce toxicity of dimethoate	Searle	1964	05006416
Lady beetles, syrphid flies, hemipteran predators, predaceous thrips	Formulated product	Pops. of all predators (except thrips) reduced at field rates	Harper	1978	05012227

There is sufficient information to characterize dimethoate as generally highly toxic to predaceous and parasitic insects, including parasitic wasps and predaceous beetles, mites, flies, and hemipterans.

There are presently no guidelines requirements for evaluating toxicity to nontarget insects.

Dimethoate Registration Standard - Nontarget Insects

The following studies received abbreviated reviews:

Author	ID
Johansen and Eves	00001361
Anon	00004409
Johansen	00008960
Atkins et al.	00014714
Sanford	00037812
Upjohn Co.	00040867
Clark	00045044
Atkins et al.	00066220
Johansen and Hutt	00074043
Harris and Svec	00078515
Anderson et al.	05003871
Singh and Malhotra	05004376
Attri and Sharma	05004597
Hameed et al.	05004909
Hain and Wallner	05008194
Johansen and Eves	05008989
Hamlen	05009588
Bartlett	05009955
Waddill	05009995
Glofke	05010079
Axtell	05011413
Torchio	05012786
Watve and Lienk	05014275
Karg	05020178

Statements for Disciplinary Review

Effects of dimethoate on beneficial insects

Dimethoate was shown to be highly toxic to honey bees, through oral and contact exposure routes, in a number of studies (Atkins et al. 1975, Cole 1974, Fraser and Jenkins 1972, Gorecki 1973, Harris and Svec 1969, Stevenson 1968 and 1978.) Data from residue exposure studies indicate that dimethoate residues less than one day old are highly toxic to honey bees, alkali bees, and alfalfa leafcutter bees, and that residual toxicity declines to low/moderate by two days posttreatment (Johansen 1972, Johansen and Hutt 1962, Johansen and Eves 1965, Johansen et al. 1975.)

Effects of dimethoate on nontarget soil and surface invertebrates

In laboratory studies, dimethoate was shown to be generally highly toxic to parasitic wasps, predaceous beetles, and predaceous mites (Bartlett 1963, 1964, and 1966, Niemczyk and Flessel 1975.) In one laboratory study (Croft and Nelson 1972) an azinphosmethyl-resistant strain of predaceous mite showed some resistance to dimethoate. Several other laboratory studies showed variability in responses of predaceous mites and beetles and parasitic wasps, depending on insect life stage, route of exposure to dimethoate, etc. (Hoy et al. 1979, Searle 1964, Teotia and Tiwari 1972.)

In one field study, application of dimethoate at field rates reduced populations of lady beetles, syrphid flies, and hemipteran predators (Harper 1978.)

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Dimethoate Registration Standard - Nontarget Insects

References (for Disciplinary Review)

Atkins, E.L., E.A. Greywood, and R.L. Macdonald. 1975. Toxicity of pesticides and other agricultural chemicals to honey bees: Laboratory studies. Univ. of California, Dept. of Entomology. Leaflet 2287. FICHE/MASTER ID 00036935.

Bartlett, B.R. 1963. The contact toxicity of some pesticide residues to hymenopterous parasites and coccinellid predators. J. Econ. Entomol. 56(5): 694-698. FICHE/MASTER ID 05003978.

Bartlett, B.R. 1964. The toxicity of some pesticide residues to adult Amblyseius hibisci with a compilation of the effects of pesticides upon phytoseiid mites. J. Econ. Entomol. 57(4): 559-563. FICHE/MASTER ID 05004148.

Bartlett, B.R. 1966. Toxicity and acceptance of some pesticides fed to parasitic hymenoptera and predatory coccinellids. J. Econ. Entomol. 59(5): 1142-1149. FICHE/MASTER ID 05005640.

Cole, J.H. 1974. The acute contact and oral toxicity to worker honey bees of technical Dowco 290: DWC 246/74726. (Unpublished study rec'd Nov 12, 1980 under 464-563; prepared by Huntingdon Research Centre, England, submitted by Dow Chemical U.S.A., Midland, Mich.; CDL: 099724-F) FICHE/MASTER ID 00059971.

Croft, B.A., and E.E. Nelson. 1972. Toxicity of apple orchard pesticides to Michigan populations of Amblyseius fallacis. Envir. Entomol. 1(5): 576-579. FICHE/MASTER ID 05009345.

Fraser, W.D., and G. Jenkins. 1972. The acute contact and oral toxicity of CP67573 and Mon 2139 to worker honey bees. (Unpublished study rec'd on unknown date under 4G1444; prepared by Huntingdon Research Centre, subm. by Monsanto Co.; Wash., D.C.; CDL: 093848-R) FICHE/MASTER ID 00026489.

Gorecki, K. 1973. Zatrucia Pszczoly Miodnej- - Apis mellifica L. (Hym., Apidae) Insektycydemi stosowanymi W Kraju. [Harmful effects of insecticides used in Poland on the honey bee - - Apis mellifica L. (Hym., Apidae.] Polskie Pismo Entomologiczne 43(1): 201-210. FICHE/MASTER ID 05012881.

Harper, A.M. 1978. Effect of insecticides on the pea aphid, Acyrthosiphon pisum (Hemiptera: Aphididae), and associated fauna on alfalfa. Can. Entomol. 110(8):891-894. FICHE/MASTER ID 05012227.

Harris, C.R., and H.J. Svec. 1969. Laboratory studies on the contact toxicity of some insecticides to honey bees. Pp. 165-167 In Proceedings of the Ent. Soc. of Ontario. Vol. 100. Guelph, Ont., Canada: Ent. Soc. of Ontario. (Research Institute, Canada Dept. of Agric., London, Ont., contribution No. 439) FICHE/MASTER ID 05011163.

Hoy, M.A., D. Flaherty, W. Peacock, and D. Culver. 1979. Vineyard and Laboratory evaluations of methomyl, dimethoate, and permethrin for a grape pest management program in the San Joaquin Valley of California. J. Econ. Entomol. 72(2): 250-255. FICHE/MASTER ID 05008360.

Johansen, C.A. 1972. Toxicity of field-weathered insecticide residues to four kinds of bees. Envir. Entomol. 1(3): 393-394. FICHE/MASTER ID 05000837.

Johansen, C.A., and J. Eves. 1965. Bee poisoning investigations, 1965. Report No. G-1705; Report No. 17338. (Unpublished study, incl. letter dated Jun 12, 1973 from C.A. Johansen to A.D. Cohick, rec'd Mar 27, 1974 under 4F1485. Prepared by Wash. St. Univ., Dept. of Entomology, subm. by Chemagro Corp. Kansas City, Mo.; CDL: 092011-I) FICHE/MASTER ID 00060628.

Johansen, C., and R. Hutt. 1962. Bee poisoning investigations, 1962. Report No. 10617. (Unpublished study rec'd. Mar 27, 1974 under 4F1485; prepared by Wash. St. Univ. subm. by Chemagro Corp., Kansas City, Mo.; CDL:092011-E) FICHE/MASTER ID 00060625.

Johansen, C., D. Mayer, R. Madsen, et al. 1975. Bee research investigations, 1975. (Unpublished study rec'd. Dec 20, 1976 under 100-EX-53; prepared by Wash. St. Univ., subm. by Ciba-Geigy Corp., Greensboro, NC; CDL=095990-E) FICHE/MASTER ID 00045046.

Niemczyk, H.D., and J.K. Flessel. 1975. Contact toxicity of 8 insecticides to adult Bathyplectes curculionis, a parasite of alfalfa weevil larvae. J. Econ. Entomol. 68(5):585-586. FICHE/MASTER ID 05012231.

Searle, C. M.S.L. 1964. The reduction in toxicity of some insecticides to a parasitic insect by the addition of oil. S. Afr. J. Agric. Sci. 7(2): 271-276. FICHE/MASTER ID 05006416.

Stevenson, J.H. 1968. Laboratory studies on the acute contact and oral toxicities of insecticides to honeybees. Annals of Appl. Biol. 61(3): 467-472. FICHE/MASTER ID 05004151.

Stevenson, J.H. 1978. The acute toxicity of unformulated pesticides to worker honey bees (Apis mellifera L.). Plant Path 27(1): 38-40. FICHE/MASTER ID 05001991.

Tectia, T.P.S., and G.C. Tiwari. 1972. Toxicity of some important insecticides to the coccinellid predator, Coccinella septempunctata Linn. Labdev, Part B 10(1): 17-18. FICHE/MASTER ID 05013372.

TABLE A
GENERIC DATA REQUIREMENTS FOR DIMETHOATE

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.155 Nontarget Insect					
NONTARGET INSECT TESTING - POLLINATORS:					
141-1 - Honey bee acute contact LD_{50}	TGAI	A,B,H	Yes	00026489 00036935 00057971 05001991	No
141-2 - Honey bee - toxicity of residues on foliage	TEP	A,B,H	Yes	00045046 00060635 00060628 05000837	No
141-3 - Wild bees important in alfalfa pollination - toxicity of residues on foliage	TEP	B 4/	Yes	00045046 00060628 05000837	No
141-4 - Honey bee subacute feeding study	[Reserved] 5/				
141-5 - Field testing for pollinators	TEP	No 6/	No	———	No

1/ Composition: TGAI = Technical grade of the active ingredient; TEP = Typical end-use product.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.
4/ Required only if product is intended for foliar application to seed alfalfa.
5/ Reserved pending development of test methodology.
6/ Required only on a case-by-case basis.
7/ Reserved pending decision as to whether these data requirements should be established.

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TABLE A
GENERIC DATA REQUIREMENTS FOR DIMETHOATE

Data Requirement	Composition	Use Pattern	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
158.155 Nontarget Insect (continued)					
NONTARGET INSECT TESTING - AQUATIC INSECTS:					
42-1 - Acute toxicity to aquatic insects	[Reserved] 1/				
42-2 - Aquatic insect life-cycle study	[Reserved] 1/				
42-3 - Simulated or actual field testing for aquatic insects	[Reserved] 1/				
43-1 - NONTARGET INSECT TESTING - PREDATORS AND PARASITES 43-3	[Reserved] 1/				

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

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MEMORANDUM:

DATE: August 31, 1982

SUBJECT: Dimethoate Registration Standard; Toxicology Assessment

FROM: Roland A. Gessert, D.V.M. Roland A. Gessert
Toxicology Branch, HED (TS-769) c. Trick for R.A.G. 8/31/82

THROUGH: Orrille E. Paynter, Ph.D. 8-31-82
Toxicology Branch Chief

TO: Paul Parsons; Project Manager;
Dimethoate Registration Standard

Attached is the Toxicology Section of the Registration Standard for Dimethoate, consisting of:

1. "One-liner" summaries of toxicology studies
2. Charts showing data gaps
3. Brief Toxicology Profile of Dimethoate

Page not updated _____ Current Date 08-06-82

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD50 -- Rat Cannon Laboratories, Inc. P.O. Box 3627 Reading, PA 19605 Project No. 1F-8317 11-30-81	Dimethoate.... .....43.5% Inerts...56.5% (EPA File Symbol:34704-ENT)	247669	Oral LD50(M)=428(366-501) mg/kg Oral LD50(F)=415(346-498)mg/kg Oral LD50(combined)=420(386-458)mg/kg	II	Guidelines
Acute Inhalation LC50-Rat Cannon Laboratories, Inc. P.O. Box 3627 Reading, PA 19605 Project No. 1F-8319 12-4-81	"	247668	4-hr LC50(M)=0.91(0.59-1.41)mg/L 4-hr LC50(F)=0.60(0.20-1.80)mg/L combined = 0.69(0.25-1.93)mg/L	(III)	Supplementary (needs particle size distribution data).
Acute Dermal LD50 - Rabbit Cannon Laboratories, Inc. P.O. Box 3627 Reading, PA 19605 Project No. 1F-8318 11-30-81	"	247667	LD50 above 2 g/kg	III	Minimum
Primary Dermal Irritation-Rabbit Cannon Laboratories, Inc. P.O. Box 3627 Reading, PA 19605 Project No. 1F-8320 11-19-81	"	247666	PDIS=0.29, with all sites clear at 72 hrs.	IV	Guidelines
Primary Eye Irritation-Rabbit Cannon Laboratories, Inc. P.O. Box 3627 Reading, PA 19605 Project No. 1F-8321 12-16-81	"	247665	Corneal involvement in all exposed eyes; persisting in 2/6 eyes after 7 days, 1/6 unwashed eyes after 21 days.	II	Guidelines

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Chemical No. _____ File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD50 - Rat. Consultex Labs., London, England for Industria Prodotti Chimica Italy. August 1974	95% technical dimethonate dissolved in methyl sulfoxide	EPA File Symbol 33660-U	LD50 = 389 mg/kg. (395 - 357)	II	Minimum (Quaife)
Acute Dermal LD50 - Rat Consultex Labs, London August 1974	95% technical chemical	File Symbol 33660-U	LD50 = 1555 mg/kg (1240 - 1938)	II	Minimum (Quaife)
Primary Dermal Irritation - Rabbit Consultex Labs, London August 1974	95% technical chemical	File Symbol 33660-U	Primary Dermal Irritation Score = 0 no irritation	IV	Minimum (Quaife)
Acute Inhalation LC50 - Rat Bazleton Labs, Vienna, VA April 1975	95% technical chemical	File Symbol 33660-U	LC50 less than 200 mg/L/hr LC50 greater than 2 mg/L/hr	III or IV	Minimum (Quaife)
(1) Primary Eye Irritation - Rabbit Bazleton Labs, Vienna, VA. 1975	95% technical chemical	MRID 0002 7098	72 hr Draize score = 28/110. Varying degrees of irritation at all observation intervals in at least 1 rabbit, including corneal damage. Study did not include washed eyes and observations did not carry through 7 days.	I or II	Supplementary
(2) Acute Oral Toxicity. From Fitcons Summary Data May 1959	Laboratory Grade	MRID 0005 5371	Rat LD50 = 300 - 350 mg/kg Mouse LD50 = 120 mg/kg Guinea Pig LD50 = 450 mg/kg	II	Supplementary. Only summary reports provided.
	Very highly purified chemical		Rat LD50 = 680 mg/kg		
	Technical chem.		Rat LD50 = 250 mg/kg		

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File last updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(3) Gaines; USPHS-CDC; rats 1969 Acute Oral Toxicity	43.5% technical chemical in emulsifiable spray conc.	MRID 00049330	1959 - LD50 = 28 mg/kg (males) 30 mg/kg (females) 1962 - LD50 = 215 mg/kg (males) 245 mg/kg (females)	I II	Supplementary Publication repor of studies with 98 pesticides
(4) Gaines; USPHS-CDC; rats 1969 Acute Dermal Toxicity	43.5% technical chemical in emulsifiable spray conc.	MRID 00049330	1959 - LD50 = 61 mg/kg (males) 55 mg/kg (females) 1962 - LD 50 = 610 mg/kg (males & females)	II II	Supplementary Publication repor of studies with 98 pesticides
(5) Acute Inhalation LC50 - rats & mice. Inst. Francais Recherches et Essais Biologics, France 1976	Formulation of 400 g/L tech chemical	MRID 00060719	Mice LC50 = 4.5 mg/m^3, or 1.8 mg dimethoate/liter All male mice died; all female mice survived. Reduced weight gain in surviving females. No lesions seen on necropsy. Rats: No deaths. Clonic spasms only symptoms. Full recovery within 24 hours.	II (mice) IV (rats)	Supplementary. Only 2 dose levels tested.
(6) Acute Inhalation LC50 - Rat Inhalation Labs. for Industria Prodotti Chimica, Italy. 1975	Technical chem. dimethoate	EPA File Symbol 33660-U	LC50 less than 200 mg/L/hr LC50 greater than 2 mg/L/hr	III or IV	Minimum (Quinfe)

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Tox Chem No. 358 File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(7) Acute Neurotoxicity (Demyelination) Hen American Cyanamid Report 6[illegible]-76. Levi Skan, et al 1965	technical chemical	MRID 0004 5817	Oral LD50 for hen was 50 mg/kg. Repeated treatment at ½, 1/8, LD50 and lower for 4 weeks in diet (65, 130, or 260 ppm) showed no adverse nerve effects. One hen at each dose level died. Hens on 260 ppm lost 13% body weight		Minimum, in spite of using only 6 hens per group
(6) Acute Neurotoxicity - Hen Gaines, USPHS-CDC, Atlanta 1969	technical chemical	MRID 0004 9330	Hens given oral atropine to protect from acute poisoning and then injected subcutaneously with dimethoate No paralysis resulted.		Supplementary. Only a study summary was given.
(9) Acute Neurotoxicity - Hen Study Report 22 by E.F.Edson Edsons Pest Control/American Cyanamid June 1958	95% technical chemical	MRID 0005 1679	Hens received 20-30 mg/kg dimethonte, the highest tolerated dose, weekly by crop intubation for 3 weeks. All hens showed anti ChE toxic signs, including weakness, unsteadiness, & dyspnea, but recovered in 1-3 days; then remained normal for 3 months. No signs of demyelination were seen.		Supplementary. Only summary report submitted. No necropsy nor histopath exam.
(10) [illegible]-day dog feeding. American Cyanamid report [illegible]-11 July 1959	95% technical chemical	MRID 0005 1676	Doses of 0, 2, 10, 50, or 1500 -3000 ppm. NOEL = 2 ppm (ChE) LEL = 10 ppm (rbc ChE depression) Plasma ChE scarcely affected at 50ppm No clinical signs seen at 1500 ppm except in female - occasional tremors & 10% food refusal. No pathology attributable to dimethoate was found		Minimum

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Tox Chem No. 358 File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(11) 90-Day Dog Feeding - American Cynamid Report # 68-76 August 1968	99.8% technical chemical	MRID 0007 5532	4 males & 4 females fed 0, 4, 6, or 9 ppm dimethoate for 14 weeks NOEL = 9 ppm for rbc & plasma ChE No effect on survival, appearance, behavior, food intake, body weight, hematology, or clinical chemistry		Supplementary. Study done primarily to further titrate ChE effect level
(12) 90-Day Rat Feeding. American Cynamid Report # 59-13. August 1959	95% technical dimethoate	MRID 0005 1675 MRID 0007 7532	NOEL = 32 ppm. 50 ppm produced decreased plasma, rbc, & brain ChE activity. 400 ppm depressed growth & food consumption also, & increased kidney & liver weight ratios. No abnormal gross or histo necropsy findings		Minimum
(13) 2-Year Rat Feeding. By CIN, East Germany for American Cynamid 1970	95% technical dimethoate	Accession 234501 MRID 0006 3995	ChE NOEL = 1.0 ppm. Lack of detailed tumor information & necropsy & histopath tables precludes setting onco and histopath NOEL.		Supplementary
(14) Oncogenicity - Mouse. By NCI, NIH 1976	Technical dimethoate	Accession 234501 MRID 0006 3997	Non carcinogenic NOEL = 500 ppm (HDT)		Minimum
(15) Oncogenicity - Rats. By NCI, NIH 1976	Technical dimethoate	MRID 0006 3997	Non carcinogenic NOEL = 250 ppm (HDT)		Minimum

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(16) Oncogenicity - Wister Rats By Thiel, et al., Germany (17) AB Mice 1973	Technical dimethoate	MRID 0007 5634	Hematopoeitic hyperplasia & splenic & hepatic myeloid hyperplasia in rat Increased tumors in high dose rats (30mg/kg 2 X weekly by p.o. gavage) Also similar myeloproliferative syndrome in mice. Possibly mildly oncogenic.		Supplementary. Information not sufficiently detailed.
(18) Teratogenicity - Wistar Rats. By Khera 1979	Cygon 4E formulation (47.3% dimeth.)	MRID 0501 8751	Decreased maternal weight gain at highest dose. At the two high doses saw increase in numbers of anomalous litters & wavy ribbed fetuses. NOEL = 6.0 mg/kg		Supplementary. Should retest to determine if effe is due to dimethoate per se.
(19) Teratogenicity - Cats By Khera (unpated)	47.3% dimethoate (Cygon 4E form.)		Increase in number of digits on the paws at 12 mg/kg formulation (5.7 mg/kg dimethoate), an anomaly. NOEL = 6 mg/kg Cygon 4E (2.8 mg/kg dimethoate)		Supplementary. Retest to determi if effect is due dimethoate per se
(20) 3-Generation Reproduction - Mice. American Cyanamid Report 65-65. 1965	98.3% technical chemical	MRID 0004 5816	No adverse effects on reproduction. No terata. NOEL = 50 ppm (HDT)		Minimum
(21) Human feeding studies. By E. F. Elson. Chelsford Park Research Station. Essex, England 1958; 1967	Dimethoate	MRID 0005 5381;5394 MRID 0007 5536	No ChE inhibition at doses of 2.5, 9, and 18 mg per day for 21 days or more At 0.4 mg/kg/day for 57 days, very slow decrease in whole-blood ChE activity. At 0.2 mg/kg/day and below no effect was seen. NOEL = 0.2 mg/kg/day LEL = 0.4 mg/kg/day		Supplementary Upgraded to Minimum Data.

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Study/Lab/Study #/Date	Material	EBA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(38) 3-Generation Reproduction Study in House. By Budreau & Singh 1972	95-99% technical dimethoate in drinking water		At 1/6 LD50 caused reduced mating success & increased reproduction time. Reduced survival rate in generations I, III, IV, & V. Reduced growth rate. Increased pup mortality.		Supplemental. (Tested only one level)
(33) Hematologic Studies in Rat. Stegelitz, Gilel, et al. CIB, Berlin, Germany. 1974	Technical dimethoate		Hyperplasia of hematopoietic parenchyma in bone marrow and extraosseous myeloid metaplasia		Supplemental information
(34) Embryotoxicity in Mouse. Horst Schuefler. Luther Univ. Med. School, Halle-Wittenberg, E. Germany 1975	dimethoate		Embryotoxicity but no teratogenicity seen. Preimplantation losses		Supplemental
(35) Mitotic Gene Conversion of Saccharomyces cerevisiae. By R. Fahrig. Germany 1973	dimethoate		At 7 doses (40 mM to 100 mM) induction of mitotic gene conversions were observed		Supplemental
(36) Ames Tests. By Hanna & Dyer. Australia. 1975	dimethoate		Positive in 2 E.coli strains. Negative in other E. coli and in all Salmonella strains.		Supplemental
(37) Mutagenic Activity of Organo phosphate Insecticides. By G. Holin, West Germany. 1973	dimethoate		Mutagenic in E. coli K-12/gal Rs 18. Dose responsive		Supplemental

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
(28) Mutagenicity Testing. By J.S. Allen, et al. American Cyan. Project 0-796. 1977 Ames plate test	technical dimethoate	Accession 234501 MRID 0006 3996	No positive mutagenic responses on any plates containing non toxic doses		Minimum (Dykstra)
(29) Ames disc test			Non mutagenic for Salmonella. Positive at high doses with E.coli, but at less than 0.01 revertants per nanamole: non mutagenic.		Minimum (Dykstra)
	isodimethoate	234501	Non mutagenic on plate and disc		Minimum
(30) Micronucleas test. Usha Rani et al. Osmania Univ., India 1980	51.7 mg/kg dimethoate in 2 doses to mice	MRID 0502 2182	0.85% polychromatic erythrocytes with micronuclei (Increase significant at 0.05)		Satisfactory
(31) Host Mediated Assay. Usha Rani, et al. Osmania Univ., India 1980	155 mg/kg dimethoate in 3 doses	MRID 0502 2182	Positive. Mutation factor of 3.4 ($p > 0.05$)		Satisfactory
(32) Toxicity with Other Pesticides P.S. Pramatao, et al. American Cyanamid Report 62-11. 1962	98% dimethoate tech chem.Co-Ral Delnav, Di-Syston, Ethion, Merphos, Ronnel, Behradan, Sevin	MRID 0005 1678	Dimethoate is additive but not synergistic with other pesticides		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity of Dimethoate. J. R. P. Gustafson, American Cyanamid Co. 1977	96% technical dimethoate		At doses of 20 to 100 ug/plate dimethoate was negative in Ames tests in 9 Salmonella and 1 E. coli strains		Supplemental

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Roland Gessert
TOX, HED (TS-769)

SUBJECT: Dimethoate Subchronic Toxicity Data Requirements

This is to confirm our discussion yesterday about subchronic data requirements for dimethoate.

First, a 21-day dermal study will be required, in accordance with proposed guideline requirements.

Second, a 90-day rat inhalation study will not be required, but 21-day study will, in accordance with proposed guideline requirements, since dimethoate has a tobacco use.

All other subchronic testing requirements will stay as they were in your toxicology chapter.

Paul N. Parsons, Project Manager
Chemical Review Branch #2
Special Pesticide Review Division

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A. Toxicology Profile

1. Acute Effects

Acute oral toxicity studies of dimethoate have been reviewed by Burnam in the RPAR process. The acute oral LD50 varies from 28 mg/kg in males (study by Gaines, 1969. MRID 00049330), to greater than 600 mg/kg. The Gaines study utilized dimethoate provided in a 43.5% emulsifiable spray formulation. Most LD50s are in the range of 150 - 400 mg/kg. Unfortunately, the purity of the chemical is not stated in most of the reports, but toxicity is generally associated with impurities; and, as exemplified by the low LD50 of the 43.5% formulation, toxicity may be associated with the "inert" components of the formulation.

Sanderson and Edson (MRID 00051671) further purified laboratory grade dimethoate by repeated recrystallizations from anhydrous ether with minimum exposure to atmospheric moisture. Although this did not in any known way effect the physico-chemical properties, the toxicity was reduced. This material reverted to laboratory grade on exposure to moist air.

In acute oral toxicity studies in rats, dimethoate was additive but not synergistic with other pesticides.

Dermal absorption, and thus acute dermal toxicity, of dimethoate is not great, except as influenced by carriers or solvents of the formulation.

Dimethoate per se is not irritating to the skin, but it is quite irritating to the eye. No dermal sensitization data are available on dimethoate.

Acute neurotoxicity data are available from three laboratories. One study was conducted by Edson, 1958 (MRID 00051679) in which hens received 20 - 30 mg by crop

intubation weekly for 3 weeks. The hens showed toxic signs of cholinesterase depression, but recovered in 1 to 3 days after each treatment and showed no signs of demyelination. They were not necropsied, nor was a histopathological examination performed. A second study conducted in 2 parts by American Cyanamid Co. gave aberrant results in controls in the first part, but was negative upon repeating. A third (screening) study conducted by T. B. Gaines at the U.S. National Communicable Disease Center Toxicology Laboratory was negative, although histopathology was not conducted. While none of these studies were conducted in strict accordance with the proposed guidelines, it is believed they adequately demonstrate dimethoate is not neurotoxic.

2. Subchronic Effects

Subchronic oral feeding studies in the rat and dog produce red blood cell cholinesterase depression as the most sensitive indicator of toxicity. The LEL for red blood cell cholinesterase depression is 10 ppm in the dog and 50 ppm in the rat. The highest dose in the dog, 3000 ppm, produced no observable effects other than the aforementioned cholinesterase effects. In human studies (MRID 00055394) 2.5 mg, 9 mg, and 18 mg daily for 3 weeks were without effect in producing cholinesterase depression.

3. Chronic Effects

A chronic rat feeding study conducted by the German Academy of Sciences Central Institute of Nutrition in Berlin (Accession 234501; MRID 00063995) established a cholinesterase NOEL of 1.0 ppm for 2 years. Lack of detailed data prevents establishment of a histopathological NOEL and oncogenicity.

Oncogenicity studies in Osborne-Mendel rats and B6C3F mice by NCI showed dimethoate to be non carcinogenic. However, German studies in Wistar rats by Zibel et al

(MRID 00071[illegible]) showed a significant increase in malignant tumors when all sites were combined among treated rats at the highest dose levels for both oral and intramuscular routes of administration. In AB mice treated percutaneously twice a week for 6 weeks Cibel observed metaplasia in the spleen with atrophy of white pulp and diffuse myeloid proliferation in the red pulp. Because of Cibel's findings additional oncogenicity studies are requested.

4. Reproduction

The American Cyanamid Co. conducted a 3-generation reproduction study in CFL strain albino mice and saw no adverse effects on reproduction and no terata. (1965. MRID 00045816). The NOEL was 50 ppm.

However, Budreau and Singh (1972, conducted a 5-generation reproduction study in Charles River CD-1 mice with dimethoate in drinking water. At 1/6 the LD50 dose they saw reduced mating success and increased reproduction time, and also a reduced survival rate in generations I, III, IV, AND V. They also observed reduced growth rate and increased pup mortality.

5. Teratogenicity

Embryotoxicity was seen in mouse studies by Scheufler (1975), apparently by pre-implantation interference with embryo development.

In teratogenicity studies with a 47.3% dimethoate formulation in Wistar rats, Khera (1979) observed decreased maternal weight gain with a 24 mg/kg formulation (11.3 mg/kg dimethoate). At 12 and 24 mg formulation/kg (5.7 and 11.3 mg/kg dimethoate) there observed an increase in numbers of anomalous litters and wavy ribbed fetuses. The NOEL was 6 mg/kg formulation (2.8 mg/kg dimethoate).

Since these tests were performed with the 47.3% dimethoate formulation, additional testing is indicated to determine if the effects were due to the dimethoate or to the inert ingredients of the formulation.

6. Mutagenicity

In mutagenic tests, dimethoate showed negative in the Ames test in Salmonella strains, but weakly positive in two E. coli strains. (Accession 234501; MRID 00063996). In a host-mediated assay conducted by Usha Rani et al, 1980 (MRID 05022182) dimethoate was positive with a mutation factor of 3.4. ($P > 0.05$).

A dominant lethal test in the mouse by Gerstengarbe (1975) showed an increased absorption rate and mutation index.

The following data gaps are considered to exist with dimethoate technical chemical:

1. Dermal sensitization
2. Oncogenicity Studies:
   a) 2-year rat - Wistar strain (because of Cibel study)
   b) 18-month mouse - of a strain susceptible to same tumor types as mice used in Cibel study
3. Teratology studies in 2 species of laboratory animals. Follow proposed guidelines.
4. Mutagenicity Studies:
   a) Spindle effects studies (in-vivo bone marrow cytogenetic study).
   b) Dominant lethal study in mice.
   c) Gene mutation study in mammalian system.

TOLERANCE REASSESSMENT:

Tolerances for dimethoate, including its oxygen analog, are established in 40 CFR 180.204, as listed in the attached computer printout. The Acceptable Daily Intake (ADI) is 0.0200 mg/kg/day, and is based on the human cholinesterase inhibition NOEL of 0.200 mg/kg/day (established by subchronic daily dosing) and a safety factor of 10. The Maximum Permissible Daily Intake (MPI) is 1.200 mg/day (based on a 60 kg body weight person). The Theoretical Maximum Residue Contribution (TMRC), based on

the value [illegible] tolerances is 0.0150 [illegible], assuming a 2.5 Cpk limit. This [illegible] tolerances utilize 10.00% of the AMI. Therefore, the established tolerances are acceptable and adequate.

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human				
mg/kg			mg/kg/day	mg/day (60kg)
0.200	.00	12	0.0200	1.2000

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Apples(2)	2.000	2.53	0.07590
Beans(4)	6.00	0.04	0.0240
Broccoli(19)	2.00	0.10	0.00300
Cabbage,Sauerkraut(22)	1.000	0.74	0.02220
Cauliflower(27)	2.000	0.07	0.00210
Celery(28)	2.000	0.09	0.00270
Collards(37)	2.00	0.00	0.00240
Escarole/Endive(54)	2.00	0.00	0.0000
Grapefruit(60)	2.000	0.05	0.00150
Kale(75)	2.000	0.03	0.00090
Lemons(82)	2.000	0.07	0.0021
Lettuce(84)	2.00	0.32	0.0096
Mustard Greens(97)	2.00	0.00	0.0000
Oranges(106)	2.000	0.22	0.0066
Pears(110)	2.000	0.06	0.00180
Peas(117)	2.00	0.09	0.00270
Peppers(120)	2.000	0.02	0.00060
Spinach(150)	2.00	0.05	0.0015
Swiss Chard(156)	2.000	0.03	0.00090
Tangerines(165)	2.00	0.00	0.00000
Tomatoes(169)	2.00	0.08	0.0024
Turnip Greens(180)	2.00	0.03	0.0009
Turnips(181)	2.000	0.05	0.00150
Grapes, Inc Raisins(66)	2.00	0.02	0.00060
Melons(91)	2.000	0.00	0.0000
Potatoes(134)	0.10	0.01	0.0003
Cottonseed (Oil)(42)	0.100	0.15	0.00022
Pecans(116)	0.100	0.03	0.00005
Soybeans(147)	0.10	0.03	0.00005
Sorghum(144)	0.100	0.03	0.0005
Corn,grain(46)	0.00	0.00	0.0000
Soybeans (oil)(147)	0.10	0.03	0.0060
Wheat(171)	0.40	13.30	0.0622
Eggs(54)	0.010	2.77	0.0083
Poultry (Fat)(54)	0.00	13.00	0.0000
Milkdairy products(95)	0.02	20.62	0.0086

ADI		TMRC
1.2000 mg/day(60kg)	0.06 mg/day(1.5kg)	42.50

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Unpublished,Tox Approved 1943

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Crop	Tolerance	Food Factor	mg/day(1.5kg)
Cherries(30)	2.00	0.15	0.0307

[illegible]
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[illegible]

[illegible]	[illegible]olerance [illegible]ood [illegible]actor		mg/day(1.5kg)
[illegible]s([illegible])	[illegible]	[illegible]	[illegible]3

[illegible]	[illegible]	[illegible]1
[illegible] mg/day[illegible]	[illegible] (1.5kg)	[illegible]

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Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Core Classification	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
TOXICOLOGY							
163.81-1	Acute Oral Toxicity	Yes	Technical Chemical	Yes	MRID00055377; 00051674; 00055371; 00049330; 00073757; 00073440; 00037597; 00044988; 00043996; 00071569; 00071504; 00051677; 00044982	Minimum	No
163.81-2	Acute Dermal Toxicity	Yes	Technical Chemical	Yes	MRID 00051674; 00049330	Minimum	No
163.81-3	Acute Inhalation Toxicity	Yes	Technical Chemical	Yes	MRID 00060719	Minimum	No
163.81-4	Primary Eye Irritation	Yes	Technical Chemical	Yes	MRID 00027078	Supplementary	No
163.81-5	Primary Dermal Irritation	Yes	Technical Chemical	Yes	MRID 00069150	Minimum	No
163.81-6	Dermal Sensitization	Yes	Technical Chemical	No			Yes
163.81-7	Acute Neurotoxicity	Yes	Technical Chemical	Yes	MRID 00051679; 00045817; 00049330	Supplementary	No
163.81-1	Subchronic Oral Toxicity	Yes	Technical Chemical	Yes	MRID 00051676; 00075532; 00051675; 00055374	Minimum	No
163.82-2	Subchronic 21 day Dermal Toxicity	No		No			No

Guideline Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement?	Bibliographic Citation	Core Classification	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of stand
163.82-3	Subchronic 90-day Dermal Toxicity	No		No			No
163.82-4	Subchronic Inhalation Toxicity	No		No			No
163.83-1	Chronic Feeding	Yes	Technical chemical	Yes	MRID 00063995	Supplementary	Yes (1)
163.83-2	Oncogenicity	Yes	Technical chemical	Yes	NCI-CG-TR 4 MRID 00063997	Minimum	Yes (2)
			Technical chemical		MRID 00075634	Supplementary	Yes
163.83-3	Teratogenicity	Yes	Technical chemical	Yes on rat & cat	MRID 05018751	Supplementary	Yes (3)
163.83-4	Reproduction	Yes	Technical chemical	Yes	MRID 00045816	Minimum	No
163.84-1 thru -4	Mutagenicity	Yes	Technical chemical	Yes			Yes - a) Gene mutation in mammalian system; b) Dominant lethal in mice; c) Aptitle effect. - in vivo bone marrow cytogenetic assay.
163.85-1	General metabolism	Yes	Radioactive pure dimethoate	Yes	MRID 00091682; 00044983	Supplementary	No

(1) A complete chronic toxicity study is needed in the rat (2-year feeding). A chronic feeding study is waived in the dog because 2 subchronic dog studies and the human studies show similar toxicity. Because we have human data we do not believe another dog study would contribute any meaningful data to the data base.
(2) Another oncogenicity study is requested using the Wistar rat and a mouse strain susceptible to the type of tumor found in the Gibel oncogenicity study.
(3) Studies were conducted with a 47.3% formulation; should be repeated using the technical chemical.