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

MEMORANDUM:

DATE: August 31, 1982

SUBJECT: Dimethoate Registration Standard; Toxicology Assessment

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

THROUGH: Orville E. Paynter, Ph.D.
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

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% elmusifiable 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 affect 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 <u>per se</u> 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

intoxication 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 Gibel et al

(MRID 00075634) 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 Gibel observed metaplasia in the spleen with atrophy of white pulp and diffuse myeloid proliferation in the red pulp. Because of Gibel's findings additional oncogenicity studies are requested.

4. Reproduction

The American Cyanamid Co. conducted a 3-generation reproduction study in CF1 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) Khera 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 [illegible]). 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 Gibel study)
   b) 18-month mouse - of a strain susceptible to same tumor types as mice used in Gibel 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 relevent food factors and published food tolerances is 0.5150 mg/day, assuming a 1.5 kg diet. The approved residue tolerances utilize 42.90% of the ADI. Therefore, the established tolerances are acceptable and adequate.

File last updated 6/17/92

ACCEPTABLE DAILY INTAKE DATA

Human	NOEL	S.F.	ADI	RfD
mg/kg	ppm		mg/kg/day	mg/day(60kg)
0.200	3.00	10	0.0200	1.2000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Apples(2)	2.000	2.53	0.07590
Beans(4)	2.000	2.04	0.06120
Broccoli(19)	2.000	0.10	0.00307
Cabbage,sauerkraut(22)	2.000	0.74	0.02207
Cauliflower(27)	2.000	0.07	0.00215
Celery(28)	2.000	0.29	0.00858
Collards(37)	2.000	0.08	0.00245
Escarole/endive(56)	2.000	0.03	0.00090
Grapefruit(65)	2.000	0.99	0.02974
Kale(75)	2.000	0.03	0.00090
Lemons(82)	2.000	0.17	0.00521
Lettuce(84)	2.000	1.31	0.03924
Mustard Greens(99)	2.000	0.06	0.00184
Oranges(103)	2.000	2.17	0.06500
Pears(116)	2.000	0.26	0.00766
Peas(117)	2.000	0.69	0.02085
Peppers(120)	2.000	0.12	0.00368
Spinach(150)	2.000	0.05	0.00153
Swiss Chard(158)	2.000	0.03	0.00090
Tangerines(160)	2.000	0.03	0.00090
Tomatoes(163)	2.000	2.87	0.08624
Turnip Greens(165)	2.000	0.03	0.00090
Turnips(165)	2.000	0.05	0.00153
Grapes, inc raisins(66)	1.000	0.49	0.00736
Melons(92)	1.000	2.00	0.03005
Potatoes(127)	0.200	5.43	0.01628
Cottonseed (oil)(41)	0.100	0.15	0.00022
Pecans(118)	0.100	0.03	0.00005
Safflower(141)	0.100	0.03	0.00005
Sorghum(147)	0.100	0.03	0.00005
Corn,grain(68)	0.100	1.00	0.00150
Soybeans (oil)(140)	0.050	0.14	0.00069
Wheat(170)	0.040	10.36	0.00622
Eggs(54)	0.020	2.77	0.00083
Meat,inc poultry(89)	0.020	13.85	0.00415
Milk&Dairy Products(95)	0.002	28.62	0.00086

ADI	TMRC	% ADI
1.2000 mg/day(60kg)	0.0008 mg/day(1.5kg)	42.56

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Unpublished,Tox Approved 7/31/1949

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cherries(30)	2.000	0.10	0.00307

1.2000 mg/day (60kg) 0.515 mg/day(1.5kg) 42.92

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Current Action Section 18

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Lentils(53)	2.000	0.14	0.00123

IPI	T.I.C	% ADI
1.2000 mg/day(60kg)	0.5150 mg/day(1.5kg)	42.92

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Guidelines 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 00027098	Supplementary	No
163.81-5	Primary Dermal Irritation	Yes	Technical Chemical	Yes	MRID 00069156	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
163.82-1	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) spindle effects - in vivo bone marrow cytogenetic study.
163.85-1	General metabolism	Yes	Radioactive pure dimethoate	Yes	MRID 00051682; 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.

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