4-2-85

004284

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

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Monocrotophos (AZODRIN) RS: Toxicology Chapter.

FROM: Irving Mauer, Ph.D.
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769) 3-22-85

TO: Willa Garner
Science Integration Staff/HED (TS-769)

THRU: Jane E. Harris, Ph.D.
Section Head, Section VI
Toxicology Branch/HED (TS-769) JEH 4/2/85

THRU: Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769) TMF 4-2-85

Attached find subject document, organized in the following sequence of sections:

I. Summary of available toxicological studies ("one-liners")

II. Discussion of test data base relative to satisfying regulatory requirements ("areas of concern")

III. Summary of additional data required ("data gaps")

IV. Tolerance re-assessment

V. Summary of data requirements under FIFRA 3(c)(2)(B) (Harrison Tables A/B)

VI. Other toxicological concerns

VII. References (but only those not included in Sequence Bibliographies provided by PMSD)

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Please note Toxicology Branch's concerns:

(i) Previously established tolerances (40 CFR 180.296) were based upon a NOEL of 1.6 ppm (0.040 mg/kg) for cholinesterase inhibition from an older chronic dog study (Woodard, 1967); the TMRC (0.0357 mg/day) thus occupied about 15% of the ADI (0.0040 mg/kg/day). A more recently submitted rat

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MONOCROTOPHOS
(AZODRIN)

Toxicology Chapter

- For -

The Registration Standard

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chronic study (Tunstall, 1982), however, suggests the rat is more sensitive, since the NOEL for this biochemical effect in this later study was determined to be 0.03 ppm (0.0015 mg/kg), thus increasing the occupancy of the consequent ADI for these published tolerances to nearly 400% (396.67%).

(ii) Inadequate studies, insufficient reporting and/or lack of data (and consequent requirements) exist for assessments of inhalation, rabbit teratology, mouse oncogenicity, metabolism and dermal sensitization.

(iii) Trimethyl phosphate (TMP) is a minor contaminant in AZODRIN formulations. At high doses, TMP is weakly mutagenic, and possibly carcinogenic, since endometrial tumors were found in treated B6C3F1 mice, but not in concurrent controls, nor in 100 historical controls.

OPP:HED:TOX:I.MAUER:sb 3/8/85 X77395 cw#17

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Carcinogenic Risk Assessment for the trimethylphosphate contaminant of Azodrin (Monocrotophos)

TO: Willa Garner
SIS/HED (TS-769)

FROM: Jane E. Harris, Ph.D. JEH 5/23/85
Section Head Review Section 6
Toxicology Branch/HED (TS-769)

The potential carcinogenic risk of the trimethylphosphate (TMP) contaminant of Azodrin (monocrotophos) was determined by linear extrapolation of the combined incidence of adenocarcinoma or squamous cell carcinoma [14/37 (38%) at 100 mg/kg/da and 7/40 (18%) at 50 mg/kg/da TMP] of the endometrium of the uterus in the B6C3F1 mouse. The slope or potency for TMP was estimated to be 8×10^{-4}. Assuming a maximal (1%) contamination by TMP of Azodrin, the potential exposure to TMP from foods is about 6×10^{-6} mg/kg/day [1% of TMRC (.0357 mg/da/60 kg)] of Azodrin. Therefore, the potential carcinogenic risk of TMP from exposure of food is approximately 5×10^{-9} [8×10^{-4} (slope) x 6×10^{-6} mg/kg/day (exposure)].

Additional exposure to TMP may occur to farm workers by mixer/loader and sprayer exposures for tobacco, cotton and peanut crops. Total exposure to farm workers was estimated by EAB (May 6, 1985 memorandum to Willa Garner from J. Reinert) to be approximately 5.2×10^{-5} mg/kg/da for tobacco crop, 7.9×10^{-4} mg/kg/day for cotton crop and 1.2×10^{-4} mg/kg/da for peanut crop. For examples, the carcinogenic risk of TMP for cotton workers is estimated over half a lifetime to be 35/70 yr. x 7.9×10^{-4} mg/kg/da x 8.0×10^{-4} (slope) or 3×10^{-7}. In view of the lower exposure to TMP from tobacco and peanut crops, the carcinogenic risks would be lower for these farm workers than those for cotton farm workers.

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Executive Summary

The available data indicate monocrotophos is a potent organophosphate chemical on an acute oral basis (Toxicity Category I). Potentiation of its acute toxicity by Ronnel (and possibly other organophosphates) precludes their combined use.

Repeated exposures of rats for 2 years produce significant cholinesterase inhibition at 0.9 ppm, with minor depressive trends at 0.09 (equivalent to 0.005 mg/kg/day). Evidence of minor systemic toxicity was present at 9 ppm (0.45 mg/kg/day).

Monocrotophos produces reproductive, parental and offspring toxicity in rats by the dietary route at 9 ppm (0.45 mg/kg/day). Although no frank terata were reported in oral rat teratology (gavage) studies at the highest dose tested (2 mg/kg/day), fetotoxicity (as evidenced by runting, reduced fetal weight and length) was observed at 2 mg/kg/day, a dosage level which is also maternally toxic (maternal LEL = 1 mg/kg/day, producing reduced weight gain).

The chemical was apparently not oncogenic in rats and mice at the highest dietary dose tested (10 ppm).

Studies suggest that monocrotophos demonstrates mutagenic activity as evidenced by positive results but only at levels close to or within the cytotoxic range in gene mutation studies *in vitro* (in both bacterial and mammalian cells), as well as by DNA damage/repair assays in yeast and mammalian cell systems *in vitro*. Although negative in a mammalian *in vivo* chromosome aberration assay (micronucleus test) and in a sex-linked recessive lethal test in *Drosophila*, it is positive for inducing sister chromatid exchanges *in vitro* (mammalian cells).

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I. "One-Liners"

Tox Chem No. 377 (monocrotophos) File Last Updated 9/7/84 Current Date 3/20/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50} - rat SRI #97, Project #B1008 March 19, 1963	Technical (77% a.i.)	090560 MRID 00053703	LD_{50} = 23 (21-25) mg/kg (males)	I	000098 000101 Supplementary 004284
Acute oral LD_{50} - mouse SRI #97, Project # B1008, March 19, 1963	Technical (77% a.i.)	MRID 00053703	LD_{50} = 15 (14-17) mg/kg (males)	I	000098 Supplementary 004284
Acute oral LD_{50} - rat SRI #5, Project # B4843, March 19, 1965	3.2 lb/gal (39.1% a.i.) in acetone	090560 MRID 00053705	LD_{50} = 59 mg/kg (males) = 23 mg/kg (a.i.) LD_{50} = 46 mg/kg (females) = 18 mg/kg (a.i.)	I	000098 000101 Minimum 004284
Acute oral LD_{50} - rabbit Shell SRI #3 Project #B4843, March 10, 1965	3.2 lb/gal (39.1% a.i.)	MRID 00053701	LD_{50} = 3.2-3.6 mg/kg (males)	I	000104 Supplementary 004284
Acute oral LD_{50} - rat Shell TLTR #0005.68, 1968	5 lb/gal (55% a.i.) in acetone	MRID 00005115	LD_{50} = 10.2 mg/kg (= 5.8 mg/kg a.i for both sexes)	I	000098 000099 Minimum 0004284
Acute dermal LD_{50} - rabbit SRI #97 and 111, Project # B1008, March 19, 1963, and June 24, 1964	Technical (77% a.i.)	090560 MRID 00099917 00053703	LD_{50} = 354 (154-760) mg/kg	II	000098 000101 Minimum 004284
Acute dermal LD_{50} - rabbit SRI #2, Project # B4843, December 8, 1961	3.2 lb/gal (39.1% a.i.) in acetone	090560 MRID 00053704	LD_{50} = 845 mg/kg = 342 mg/kg (a.i.)	II	000098 000099 Minimum 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rat Shell #TLTR. 0005.68, 1968	5 lb/gal (55% a.i.) in acetone	MRID 00005115	LD_{50} = 140-170 mg/kg (=80-100 mg/kg a.i. for both sexes)	II	000098 Minimum 004284
Acute dermal LD_{50} - rabbit IBT#601-07485, October 27, 1975	Azodrin-5 (55% a.i.)	MRID 00102499	LD_{50} (males) greater than 200 mg/kg (HDT)	II	Supplementary 004284
Acute dermal LD_{50} - rat Carnegie-Mellon #33-15, February 17, 1970	Azodrin-5 (56% a.i.)	MRID 00035378	LD_{50} = 0.700 (0.429 - 1.14) ml/kg (males) = 392 mg/kg.	II	Minimum 004284
Acute inhalation LC_{50} - rat SRI #2, Project # B4843, December 8, 1964	Technical (77% a.i.)	090560 MRID 00053704	No effect in "saturated vapors for 1 hr" (only level tested).	-	000098 000099 000101 Supplementary 004284
Acute inhalation LC_{50} - rat IBT #663-07360, October 8, 1975	5 lb/gal (55% a.i.)	MRID 00069332	Only dose tested = "295.5" mg/l (nominal). Actual chamber concentration not determined.	IV	Supplementary 004284
Potentiation - rat SRI #9, Project # B4843, October 19, 1964	Technical (77% a.i.)	091487 MRID 00053707	Slight potentiation with Ronnel	-	000098 000104 Supplementary 004284
Antidotal - guinea pig Tunstall #20/64, September 2, 1964 (Natoff, 1976)	Technical (77% a.i.)	091487 MRID 00064115 00005122	Atropine + P-2S gave more protection than atropine alone.	-	000104 Supplementary 004284
Acute delayed neurotoxicity - hen Tunstall #TLGR.0066.78, May, 1978	5 lb/gal (55% a.i.)	MRID 00102503	Doses tested = 6.7 mg/kg a.i. (ODT = the reported LD_{50}). 5/14 survivors had no clinical signs, nor histological lesions. Deficient reporting	-	Minimum 000105 Supplementary 000107 Supplementary 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation - rabbit IBT #8530-10808, June 29, 1977 (reported July 28, 1977)	Analytical (99.5% a.i.)	MRID 00050956	PIS = 1.0/0.8. Slightly irritating @ 250 mg/kg (ODT)	IV	Supplementary 000103 Supplementary 004284
Primary dermal irritation - rabbit. SRI #5, Project # B4843, March 19, 1965	3.2 lb/gal (39.1% a.i.) in acetone	090560 MRID 00053705	PIS - 1.0. Slightly irritating	IV	000098 Minimum 004284
Primary dermal irritation - rabbit. Westhollow #61533, May 12, 1981	5 lb/gal (55% a.i.) in acetone	071345 MRID GS015401	PII = 0.6 (/8.0). Slightly irritating. Erythema and edema evident at 24 hr. reversed by 72 hr.	IV	Minimum 004284
Primary eye irritation - rabbit. IBT #8530-10808, June 29, 1977	Analytical (99.5% a.i.)	MRID 05054021 00050957	Dose tested = 70 mg/kg (ODT) produced hyperapnea hyperactivity and miosis 30 min. post treatment. Recovery complete at 2-22 hr.	III	Supplementary 000103 Supplementary 004284
Primary eye irritation - rabbit. SRI #2, Project #B4843, December 8, 1964	3.2 lb/gal (39.1% a.i.) in acetone	090560 MRID 00053704	Slight to moderate irritant. Slight opacity reversible at 8 hr.	III	000098 000099 000104 Minimum 004284
Primary eye irritation - rabbit. Westhollow #61533, May 12, 1981	5 lb/gal (55% a.i.) in acetone	071345 MRID GS015402	PIS = 63.7-64.7 (/110). Corneal opacity, iritic reaction and conjunctival irritation produced at 48 hr. reversed by day 14.	II	Minimum 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subchronic oral (12-wk feeding) - rat SRI# B4843, December 9, 1963	Technical (77% a.i.)	091487 MRID 00005118	Doses tested = 0.5, 1.5, 4.5, 15, 45, 135 ppm. ChEI-NOEL = 0.5 ppm (LDT) ChEI-LEL = 1.5 ppm (brain, whole blood) Systemic - NOEL = 15 ppm Systemic - LEL = 45 ppm (HDT) (Body wt. reduction, tremors; increased rel. liver/kidney wts.)		000098 000099 Minimum 000104 000103 Minimum 004284
Subchronic oral (13-wk feeding) reversibility study - rat Tunstall #TGLR.79.154, Experiment No. 1720, June 9, 1981	Technical (77% a.i.)	071345 MRID GS015403	Doses tested = 0, 0.1, 0.25, 0.5, 2.0, 8.0 ppm in the diet to 3 groups: for 8-wks; 13-wks; and, 8-wks plus 5 wks no treatment. ChEI-NOEL (8 or 13-wk) < 0.1 ppm ChEI-LEL (males) = 0.1 ppm Systemic-NOEL = 2.0 ppm Systemic-LEL = 8.0 ppm (HDT; decreased wt. gain and food intake).		Minimum 004284
Subchronic (3-wk) dermal - rabbits Hilltop Res., # P-44, August 17, 1965	"Azodrin-5" (4.8 lb/gal) (55% a.i.)	MRID 00005117	Doses tested = 0, 36, 72 mg/kg/day. No adverse clinical signs or symptoms at either dose; no abnormal hematological, or gross or microscopic pathological findings. Slight atonia at HDT. NOEL = 72 mg/kg/day		000099 Minimum 000104 Minimum 004284

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subchronic oral (4-wk feeding) neurotoxicity - hen SRI #7, Project #B4843, July 29, 1965	Technical (77% a.i.)	091487 MRID 00053708	Doses tested= 0, 1, 10, 100 ppm. NOEL not determined (egg production 40% of control at 1 ppm) Inadequate reporting of lesions.		000098 Supplementary 0000104 Supplementary 004284
Subchronic oral (14-day capsule) neurotoxicity - hen FDRL #6535-I, July 11, 1980	Technical (77% a.i.)	246436 MRID 00087766	Doses tested = 0, 0.03, 0.10, 0.30, 1.0 mg/kg/day ChEI (plasma) NOEL = 0.03 mg/kg/day (LDT) ChEI (plasma) LEL = 0.10 mg/kg/day ChEI (brain) NOEL = 0.10 mg/kg/day ChEI (brain) LEL = 0.30 mg/kg/day (18% body wt. loss) Egg production NOEL = 0.03 mg/kg/day (LDT) Egg production LEL = 0.10 mg/kg/day		Supplementary (range-finding study). 002992 Supplementary 004284
Subchronic oral (90-day capsule neurotoxicity - hen FDRL #6535-II April 2, 1981	Technical (77% a.i.)	246436 MRID 00087765	Doses tested = 0, 0.03, 0.10, 0.30, 1.0 mg/kg/day. ChEI (plasma) NOEL = 0.03 mg/kg/day. ChEI (plasma) LEL = 0.10 mg/kg/day. Systemic NOEL = 0.10 mg/kg/day Sytemic LEL = 0.30 mg/kg/day (body wt. loss; relative brain wt. increase). Egg production NOEL = 0.10 mg/kg/day. Egg production LEL = 0.30 mg/kg/day No neurological lesions reported at any dose (including no demyelination).		Minimum 002992 Minimum 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subchronic oral (12-wk. feeding) - dog SRI #B4843, December 9, 1964	Technical (77% a.i.)	091487 MRID 00005118	Doses tested = 0, 0.5, 1.5, 15, 45, 135 ppm. (HDT increased to: 270 ppm at wk-8, to 540 at wk-10, 1080 ppm at wk-12) ChEI-NOEL = 0.5 ppm (LDT) ChEI-LEL = 1.5 ppm (RBC) Systemic-NOEL = 15 ppm Systemic-LEL = 45 ppm (~~wt. loss~~ decr. wt gain in males). Only 2 dogs/sex/group examined histologically.		000098 000099 Supplementary 000104 Supplementary 004284
Chronic oral (2-yr feeding) - rat Woodard #(?), July 10, 1967	3.2 lb/gal (39.1% a.i.)	091487 MRID 00005121 00005123 00029424 00046303	Doses tested = 0, 1, 10, 100 ppm of a.i. Systemic-NOEL = 10 ppm. Systemic-LEL = 100 ppm (reduced food intake, and body wt.). NOEL for ChEI not determined (<1 ppm, the LDT). Excessive mortality among control males. Inadequate to evaluate oncogenicity. Technical not used, but doses based on a.i.		Invalid for oncogenicity 000104 000100 Minimum for chronic 000108 Minimum for chronic; Supplementary for oncogenicity 004284
Chronic oral (2-yr feeding) - dog Woodard #[?], July 10, 1967	3.2 lb/gal. (39.1% a.i.)	091487 MRID 00005121 00005124 00029425	Doses tested = 0, 1.6, and 16 ppm to 3 Beagles/sex/group for 2 yr; 100 ppm to 2 dogs/sex/group for 1 yr. ChEI-NOEL = 1.6 ppm. ChEI-LEL = 16 ppm (plasma, RBC, brain) Systemic NOEL = 16 ppm. Systemic LEL = 100 (salivation and tremors) Technical not used, but doses based on a.i.		000100 Minimum 000104 Minimum 004284

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Tox Chem No. 377 (Azodrin)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Catetory	CORE Grade/ Doc. No.
Chronic oral (2-year feeding) oncogenic-mouse Shell Res. Ltd. Project No. 194/82 (AIA 1680) Group Res. Rpt# SBGR.81.218 March, 1982	Technical (78.7% a.i.)	071346 071347 071348 071349 071350 071351 MRID GS015404	Doses tested = 0, 1, 2, 5 and 10 ppm in the diet. Not oncogenic at 10 ppm (HDT). ChEI = 1 ppm (LDT) (brain, RBC and plasma). Strain of mouse not specified.		Supplementary 004284
Chronic oral (2-yr feeding) combined/oncogenicity - rat Shell Res. Ltd. #SBGR.82.062, September, 1982	Technical (78.7% a.i.)	(Petition #6F1851, 090794) 071875 071876 071878 071879 071880 MRID GS015405	Doses tested = 0, 0.01, 0.03, 0.1, 1.0 and 10 ppm in the diet (but analyzed as 85-90% of nominal). NOEL ChEI = 0.03 ppm LEL ChEI = 0.09 ppm (RBC and brain) Systemic NOEL = 0.9 ppm Systemic LEL = 9 ppm (body weight reduction in males; survival in females). Not oncogenic at HDT.		Minimum for chronic and oncogenicity. 004284
Reproduction oral (2-generation feeding) - rat Sittingbourne #SBGR.81.143, (Experiment #1752) November, 1983	Technical (78.7% a.i.)	071345 MRID GS015406	Doses tested = 0, 0.1, 0.3, 1, 3 and 10 ppm in the diet, nominal; actual doses = 0, 0.09, 0.27, 0.9, 2.7 and 9.0 ppm. Reproductive, parental and offspring toxicity: NOEL = 2.7 ppm LOEL = 9.0 ppm (Decreased fertility; decreased pup viability; depressed lactation; decreased pup weight).		Minimum 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Reproduction oral (3-generation feeding) - rat. Hine Lab #M-54-66, March, 1966	Technical (77% a.i.)	091487 MRID 00005119 00005120 00029426 00029427	Doses tested = 0, 2, 5, 12, 30 ppm. Reproduction NOEL = 2 ppm (LDT). Reproduction LEL = 5 ppm (reduced litter size). No feed analyses to establish "2 ppm" NOEL.		Supplementary 000103 000098 000099 000104 Minimum 000108 Supplementary 004284
Teratology - rabbit. Tunstall #TLGR.00031.72, October, 1972	Technical (77% a.i.)	093609 112253 112255 MRID 00040236 00040239	Doses tested = 0, 0.7, 2.0 mg/kg/day by gavage. NOEL-maternal toxicity=0.7 mg/kg LEL-maternal toxicity=2.0 mg/kg (decreased body wt.) NOEL-fetotoxicity = 0.7 mg/kg LEL-fetotoxicity = 2.0 mg/kg (increased resorptions) Teratogenic NOEL > 2.0 mg/kg (HDT). Only 2 animals/sex/group.		000098 000101 Supplementary 004284
Teratology - rat. ToxiGenics #450-1248, November 16, 1983	Technical (77% a.i.)	252075 MRID GS015407	Doses tested = 0, 0.3, 1.0, 2.0 mg/kg/day by gavage. Maternal NOEL = 0.3 mg/kg Maternal LEL = 1.0 mg/kg (reduced body wt. gain) Fetal NOEL = 1.0 mg/kg Fetal LEL = 2.0 mg/kg (runting; reduced fetal wt./length). No Terata at the HDT.		Minimum 004284

Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity - reverse gene mutation in bacterial cells (E. coli) Tunstall #TLGR. 0034.71, August, 1971	24% w/v solution	MRID 00072170	Negative in spot tests at unstated doses. Not tested with metabolic activation (MA) Technical not used.		Unacceptable 004284
Mutagenicity - gene mutation in bacterial cells (Ames) Tunstall #TLGR. 00030.74, July, 1974	Analytical (99% a.i.) - and - Technical (77% a.i.)	MRID 00102479	Negative in spot tests with Salmonella typhimurium strains and Serratia marescens. Not tested with metabolic activation (MA)		Minimum 000102 Unacceptable 004284
Mutagenicity - gene mutation in bacterial cells (Ames) Simmon (1977)	Azodrin-5 (55% a.i.)	MRID 00114210	Negative up to 1,000 ug/plate w/without MA; No reported toxicity or solubility limits. Technical not used.		Unacceptable 004284
Mutagenicity - gene mutation in bacteria (Ames) Simmon (1977)/SRI (1980).	Technical	MRID 00114210 GS015410	Levels tested: 500 to 20,000 ug/plate. Positive in TA 100 with/without MA at concentrations of 4,000 ug/plate and above; negative in TA 98 and TA 1535.		Acceptable 004284
Mutagenicity - gene mutation in bacteria (E. coli) Simmon (1977)	Azodrin-5 (55% a.i.)	MRID 00114210	Negative in spot test at 1,000 ug/plate, w/without MA; but no reported toxicity or solubility limits. Technical not used.		Unacceptable 004284
Mutagenicity - DNA damage/repair in bacteria (E. coli and B. subtilus rec assays) Simmon (1977) Mortelmans (1980)	Azodrin-5 (55% a.i.)	MRID 00114210 GS015410	Negative in spot tests at 1,000 ug in both assays. Controls inappropriate. Technical not used.		Unacceptable 0004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity - DNA damage/repair in yeast (mitotic recombination in S. cerevisiae - D3) Simmon (1977)/US - EPA, SCP-II (1975)	Azodrin-5 (55% a.i.)	MRID 00114210 GS015412	Positive in duplicate experiments at 5% w/v, w/without MA. Technical not used.		Acceptable 004284
Mutagenicity - DNA damage/ repair in WI-38 cells (Unscheduled DNA Synthesis in vitro) Mitchell (1975); Simmon (1977)	Azodrin-5 (55% a.i.)	MRID 00043657 00114210	Levels tested = 1.2 to 100 M x 10^{-4}. Positive only with MA in two tests into cytotoxic/inhibiting range (HDT).		Acceptable 004284
Mutagenicity - DNA damage/repair in yeast cells (gene conversion in vitro) Tunstall #TLGR.0030.74 July, 1974	Analytical (99% a.i.) and Technical (77% a.i.)	MRID 00102479	Doses tested = 0, 4, 5, 8, 10, 50 mg/ml (analytical); 25, 39, 50 mg/ml (technical). Positive at 5 mg/ml and above in dose-dependent manner for the analytical, into cytotoxic range (HDT). Positive at all doses for the technical.		Minimum 000102 Acceptable 004284
Mutagenicity - DNA damage repair in yeast (gene conversion in Host-Mediated Assay). Tunstall #TLGR.0030.74, July, 1974	Analytical (99% a.i.)	MRID 00102476 00102479	Doses tested in host = 0, 2, 4 8 mg/kg as a single oral dose to male mice. Negative for gene conversion in Saccharomyces cerevisiae D4 indicator cells.		Minimum 00010202 Acceptable 0043284

Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity - gene mutation in mammalian cells (L5178Y in vitro) Simmon (1977), SRI (1980)	Azodrin - 5 (55% a.i.)	MRID 00114210 GS015408	Weakly positive with/without MA in a dose-related manner into cytotoxic range.		Acceptable 004284
Mutagenicity - chromosome damage in mouse bone marrow cells. Tunstall #TLGR.0014.73, June, 1973	Analytical (99% a.i.)	MRID 00102477	Doses tested = 0, 2, 4 mg/kg orally to 8 animals/sex/group as a single dose (Only 4 animals/sex/group analyzed). Negative at the HDT. No justification for dose selection; no systemic or cytological effects at the HDT. No positive controls.		Minimum 000102 Unacceptable 004284
Mutagenicity - dominant lethal assay in mice Tunstall #TLGR.0027.73, September, 1973	Analtyical (99% a.i.)	MRID 00102478	Doses tested = 0, 1, 4 mg/kg orally as a single dose. Negative at the HDT. No positive controls; MTD not employed.		Minimum 000102 Unacceptable 004284
Mutagenicity - dominant lethal assay in mice. SRI (1977)	Azodrin - 5 (55% a.i.)	MRID 00114210 GS015409	Doses tested = 0, 15, 30, 60 mg/kg in the diet for 7 wk. Negative up to the HDT. No adverse clinical effects. Actual intake not determined. Technical not used.		Unacceptable 004284
Mutagenicity - micronucleus assay in mice Kirkhart (1980)	Azodrin - 5 (55% a.i.)	MRID GS015411	Doses tested = 0, 4, 8, 16 mg/kg (split doses ip, 24 hr apart). Negative in male mice. No deaths, no body wt. changes, no toxicity at HDT, but PCE/NCE ratios altered.		Acceptable 004284

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Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity - DNA damage/ repair and reverse mutation in yeast (S. cerevisiae D7) Mortelmans (1980)	Azodrin - 5 (55% a.i.)	MRID GS015410	Positive at non-toxic concentrations (up to 3%) with/without MA, for all genetic endpoints.		Acceptable 004284
Mutagenicity - sister-chromatid exchange in vitro (CHO cells) Simmon (1977)/SRI (1977)	Azodrin - 5 (55% a.i.)	MRID 00114210 GS015410	Levels tested = 0.0025 to 0.2%. Positive with/without MA at cytotoxic doses, 0.1% and 0.02%, respectively.		Acceptable 004284
Mutagenicity - gene mutation in Drosophila (SLRL) U.S. - EPA Substitute Chem. Prog. - II (1975)	Azodrin - 5 (% purity not stated)	MRID GS015412	Negative in male adult feeding tests (14 lethals/8276 chromosomes tested).		Acceptable 004284
Mutagenicity - Dominant lethal assay in mice of contaminant. U.S. - EPA Substitute Chem. Prog.-II (1975)	Trimethyl phosphate	MRID GS015412	Positive at high single oral doses (2500, 3500 mg/kg), and repeat dosage schedule (750 mg/kg/day).		Acceptable 004284
Metabolism - rat Menzer (1964)	SD-9129 (unstated % a.i.) -and- (^{32}P/N-Me-^{14}C-labeled)	MRID 00013505	50 males and females intubated with 1 mg/kg resulted in average 63-71% of label (^{32}P) in urine within 48 hr, and 5% in feces; "mostly unchanged Azodrin". No tissue distribution reported.		Supplementary 004284

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004284

Tox Chem No. 377 (monocrotophos)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Human studies-percutaneous absorption. Feldmann (1974)	^{14}C-labeled "Azodrin" of unstated purity	MRID 00031050	4 ug/cm^2 labeled material applied to 1-2 mm^2 forearm skin (in rings) for 24 hr. to unstated number of volunteers resulted in 14% of label appearing in urine by 120 hr. (5 days).		Supplementary 004284
Human exposure - Delta & Pine, July 28, 1964	"Azodrin"	MRID 00013500	One of three applicators (0.4-0.6 lb/A) previously exposed to methylparathion and endrin exhibited significant plasma and RBC-ChE reduction (>20%)		000099 000104
Human exposure - 2 incidents; May 27, 1964, June 18, 1964	"SD9129"	MRID 00013500	Two entomologists received multiple exposures in a sprayed area, but only one exhibited slightly reduced ChE level (<20%).		000104
Human exposure - one incident (no date)	(?Azodrin)	MRID 00013500	One college student hand-applicator manifested "OP poisoning" after 2 days' spraying, although both plasma and RBC-ChE levels were "normal." Atropine + 2-PAM treatment effected rapid recovery within 2 days.		000104
Human exposure (Shell, 1968)	Azodrin - 5 (55% a.i.)	MRID 00102444	Of 10 ground operators with no protective equipment monitored during and after aerial application (dermal patches), all 5 sampled for ChE had normal (pre-exposure) plasma and RBC values.		004284

II. DISCUSSION

Acute Toxicity

Monocrotophos (technical AZODRIN, 77% ai) is a potent organophosphate (OP) orally (Toxicity Category I), with an acute LD_{50} of 23 mg/kg in male rats and 18 mg/kg in females (MRIDs 00053703, 00053705). One of its formulations (AZODRIN-5, 55% ai) is even more toxic in this species, with a reported oral LD_{50} of 10.2 mg/kg, or 5.8 mg/kg ai for both sexes (MRID 00005115). Mice are also sensitive to the toxic effects of monocrotophos, with a reported oral LD_{50} in males of 15 mg/kg (MRID 00053703). Since adequate studies have been submitted, no further test data are required for acute oral toxicity at this time.

Technical AZODRIN is moderately toxic by the dermal route in rabbits (Toxicity Category II), with an LD_{50} of 354 mg/kg (MRIDs 00053703, 00099917). A 3.2 lb/gal formulation (39% ai) registered a dermal LD_{50} of 845 mg/kg (equivalent to 342 mg/kg ai) in this species (MRID 00053704), whereas the 5 lb/gal formulation (AZODRIN-5) was again more toxic, with a reported LD_{50} of 140 to 170 mg/kg for male and female rats, equivalent to 80-100 mg/kg ai for both sexes (MRID 00005115). Since adequate studies have been submitted to satisfy acute dermal toxicity, no further test data are required at this time.

Neither of the acute inhalation studies are adequate (MRIDs 00053704 and 00069332, both evaluated as SUPPLEMENTARY DATA), and additional data in the rat must be submitted to satisfy this requirement (LC_{50}). On the other hand, while the single acute delayed neurotoxicity study in hens (MRID 00012503) is considered deficient in design and reporting (SUPPLEMENTARY DATA), subchronic (90-day) neurotoxicity studies in both chickens and rats (see below) satisfy this test data requirement, and no additional studies need be submitted at this time.

Since the manufacturing-use product (MP) is the same as the technical (TGAI), the same studies satisfy both requirements (Personal communication, G. Otakie to I. Mauer, March 7, 1985). Thus, no additional data are required for acute oral toxicity or acute dermal toxicity, but there remains a data gap for acute inhalation. Adequate studies are also available for the formulations AZODRIN-5 and 3.2-AZODRIN to satisfy the label requirements to consider AZODRIN slightly irritating (Toxicity Category IV) dermally (MRID 00053705, GS015401), as well as slightly-to-moderately toxic (Toxicity Category III) as a primary eye irritant (MRID 00053704, GS015402). On the other

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hand, no studies have been submitted to assay dermal sensitization for any formulation of monocrotophos, and these data are required, using guinea pigs as the test animal.

Monocrotophos has been tested acutely for potentiation in oral combinations with a large number of other OP's (MRID 00053707), and only the AZODRIN-Ronnel combination has been demonstrated to be more toxic (lower acute LD_{50}) than expected by additive calculation. As commonly found with the effects of over-exposure to other OP's, atropine and 2-PAM are antidotal, as demonstrated in the guinea pig with the technical, and a combination of atropine and P-2S (2-hydroxyamino-methyl-N-methyl pyridinium methanesulfonate) gave more protection than atropine alone (MRIDs 00064115, 00005112).

Subchronic Studies

Ninety-day oral studies in both the rat (MRIDs 00005118, GS015403) and hen (MRID 00087765) are judged adequate for both short-term toxicity assessment and neurotoxicity (CORE-MINIMUM DATA). Although one available 12-week feeding study in the dog (MRID 00005118) is considered inadequate (SUPPLEMENTARY), this requirement has been satisfied by a 2-year dog feeding study (MRID 00005121/00005124/00029425 - SEE BELOW).

Both feeding studies in rats (SRI, 1963; Tunstall, 1981) reported a NOEL for cholinesterase inhibition (ChEI) at less than 1 ppm, but whereas the earlier reported an LEL for ChEI at 1.5 ppm (as evidenced in brain and whole blood), the later Tunstall study reported minor depression of ChEI at 0.1 ppm after both 8 weeks and 13 weeks exposure. The latter, however, also reported partial "recovery" at 13 weeks in one group fed for 8 weeks but not treated for the ensuing 5 weeks, i.e., a level of cholinesterase insignificantly different from controls at 0.5 ppm.

The dosage at which systemic effects were observed also differed between these two rat studies, the SRI (1963) registered body weight reductions, tremors and increased relative liver and kidney weights at 45 ppm (NOEL = 15 ppm), whereas Tunstall (1981) reported decreased weight gains and food intake at 8 ppm, the highest level tested (NOEL = 2 ppm).

The subchronic dog study performed by SRI in 1964 (in MRID 00005118) reported a NOEL of 0.5 ppm (the lowest dose tested) for ChEI and a systemic NOEL of 15 ppm, but has been faulted for inadequate reporting, plus the fact that only 2 of the 4 dogs per sex per group were examined for histopathology.

One of the three available subchronic hen studies (in which monocrotophos was given by capsule) is acceptable (MRID 00087765), reporting plasma ChEI at 0.10 mg/kg/day (and above) and a NOEL of 0.03 mg/kg, systemic effects (body weight loss, relative brain weight increase) at 0.3 mg/kg (NOEL = 0.10 mg/kg), and decreased egg production at 0.30 mg/kg (NOEL = 0.10 mg/kg). No neurohistopathological lesions including demyelination were observed here or in the acute delayed neurotoxicity study (MRID 00012503) in which only 5 of 14 hens survived at 6.7 mg/kg (ai), the reported LD_{50}.

Only one subchronic dermal study (in rabbits) was available (MRID 00005117), in which dermal application of 36 and 72 mg/kg AZODRIN-5 for three weeks produced no adverse clinical signs, hematological or chemical changes, nor gross or histopathological findings. Although slight atonia was observed at the higher dose, this is not considered toxicologically significant, and the NOEL for such short-term dermal exposure has been set as 72 mg/kg. This study is acceptable (Core-MINIMUM), and no further studies are required to satisfy this requirement at this time.

Chronic Oral Studies

As indicated above, inadequate assessment of the subchronic toxicity study in the dog (MRID 00005118) is satisfied by an adequate chronic two-year feeding study performed in 1967 by Woodard (MRID 00005121/00005124/00029425). This study was previously used to support regulatory requirements for food uses (40 CFR 180.296) based upon a NOEL for cholinesterase inhibition of 1.6 ppm, equivalent to 0.04 mg/kg/day; ADI = 0.004 mg/kg/day; TMRC for peanuts, tomatoes, cottonseed oil, and cane/beet sugar occupying 14.85% of the ADI. [See, however, TOLERANCE RE-ASSESSMENT section, below.] Although the 3.2 lb/gal formulation was used in that older study (rather than the technical), the dosages used to derive safety requirements were based on the active ingredient. Reduction in plasma, RBC and brain ChEI occurred at 16 ppm (= LEL), and systemic effects (salivation and tremors) at 100 ppm (systemic NOEL = 16 ppm). No additional data need be submitted for non-rodent chronic assessment at this time.

Both the older study with 3.2-AZODRIN (Woodard, 1967 - MRIDs 00005121, 00005123, 00029424, 00046306), as well as the more recent study in rats using technical AZODRIN (Tunstall, 1982 - MRID GS015405), are considered adequate for regulatory purposes (Core-MINIMUM DATA). Although a NOEL for ChEI was not firmly established in the Woodard assay (less than the LDT, 1.0 ppm), that for the later study has been set by TB at 0.03 ppm. Systemic effects (body weight decreases, reduced food intakes) were observed at a dose level of 100 ppm (the LEL) in the Woodard study, but at 9 ppm in the Tunstall study (nominally

10 ppm, but allowing for 85-90% loss in the diet), leading to a 10-fold discrepancy in systemic NOEL's between these studies (10 ppm, Woodard vs 0.9 ppm, Tunstall). TB prefers the more recent study to set tolerances (SEE BELOW).

Oncogenicity.

Of the two rat studies available for review, the earlier (Woodard, 1967 - MRIDs 00005121, 00005124, 00029424, 00046303) is inadequate (Core-INVALID) because of excessive mortality among control males, starting halfway through the study. The more recent Tunstall (1982) study submitted for combined assessment of chronic toxicity and oncogenicity (MRID GS015405) initially failed to meet minimal criteria for lack of reporting historical control data for the strain of rat used to offset the high control values for pituitary tumors observed, (initially Core-SUPPLEMENTARY DATA); the recent provision of historical data has permitted upgrading the study to MINIMUM.

The mouse oncogenicity study (MRID GS015404) was assigned a Core-SUPPLEMENTARY grade, because the strain used was not specified, and presented an unusually high "spontaneous" incidence of convulsions (stated to be an "inborn trait"). Additionally, the moderately increased frequency of optic problems (retinopathy and lenticular opacity) in both control and treated groups was not satisfactorily explained. Hence additional data must be submitted for the mouse to satisfy the oncogenicity requirement.

Reproduction and Teratology Studies

Of the two dietary rat reproduction studies available (MRIDs 00005119/00005120/00029246/00029247; and GS015406), only the more recent (Tunstall, 1983) is acceptable (Core-MINIMUM DATA) generating a reproductive (and offspring) NOEL of 2.7 ppm and an LEL of 9.0 ppm (as evidenced by decreased fertility, pup viability and weight, partly attributed to depressed maternal lactation). The earlier Hine study (1966) reported a reproductive NOEL of 2.0 ppm which could not be supported because no feed analyses were conducted (Core-SUPPLEMENTARY). This study also reported a reduced litter size at 5 ppm (=LEL), equivalent to an actual intake of 0.25 mg/kg/day). No further reproduction data are required under FIFRA 3(c)(2)(B) at this time.

The teratology requirement that at least two species be tested has been only partially fulfilled by submitted data. A rat gavage study conducted for Shell by ToxiGenics (reported in November, 1983 - MRID GS015407) found fetotoxic effects at 2 mg/kg, consisting of runting, reduced fetal weight and length (NOEL = 1.0 mg/kg), and maternal toxicity in the form of reduced body weight gain at 1.0 mg/kg (NOEL = 0.3 mg/kg). No teratogenic effect was observed at the HDT (2.0 mg/kg/day).

An earlier (Tunstall, 1972) intubation study in rabbits (MRID 00040236/00040239) is inadequate (Core-SUPPLEMENTARY) according to recently promulgated criteria (1982 FIFRA Guidelines), because only 2 animals per sex per group were treated at doses between 0.7 and 2 mg/kg. Thus, this constitutes a data gap, and a new study in rabbits is required.

Mutagenicity

A total of 19 studies evaluating monocrotophos for mutagenicity are available, but only 10 are adequate (ACCEPTABLE). Since all of the genetic end-points requiring adequate data have been satisfied (gene mutation, chromosome aberrations, DNA damage/repair), no additional data need be submitted at this time. [N.B. Thirteen of these studies were performed and evaluated by Stanford Research Institute (SRI) under contract to the Office of Research and Development of the Agency at Research Triangle Park (U.S. EPA/ORD-RTP). These studies by SRI have not been reviewed by the Toxicology Branch and therefore, the scientific conclusions reached do not necessarily represent those of the EPA.

Monocrotophos (as the analytical grade, the technical, or several of its formulations) is weakly mutagenic, as determined mainly from studies assessing DNA damage/repair. Thus positive results have been generated in assays for mitotic recombination and gene conversion in yeasts (MRIDs 00114210, 00102479, 00102476, GS015410, GS015412), and for unscheduled DNA synthesis (UDS) in vitro (MRIDs 00043657, 00114210) and sister-chromatid exchange (SCE) in vitro (MRIDs 00114210 and GS05410) in mammalian cells.

Whether monocrotophos induces gene (point) mutation is equivocal. Positive results for reverse mutation at specific gene loci have been reported, but only in studies involving strain TA100 of Salmonella typhimurium (MRID GS015410) and the mouse lymphoma mammalian cell line, L5178Y (MRID 00114210, GS015408), and only at highly cytotoxic concentrations. In vivo gene mutational studies in Drosophila (sex-linked recessive lethal induction) were negative (MRID GS015412), and a number of studies in bacterial cells (Escherichia coli), Ames Assays, Bacillus subtilis) although judged UNACCEPTABLE, support the contention that, if mutagenic, the chemical is at best a "weak mutagen."

Among the four chromosome assays available, only one is ACCEPTABLE, and that reported negative results for the induction of micronuclei in male mice treated at 2x the i.p. LD_{50} (MRID GS015411). In contrast, positive results for SCE were reported in vitro (indicated above - MRIDs 00114210, GS015410). In vivo studies for chromosome damage in mouse bone marrow cells (MRID 00102477) and dominant lethal assays in mice (MRID 00102478 and 00114209) have reported negative results, but these have

been judged UNACCEPTABLE, because of major deficiencies in design, procedure and reporting. Thus, although satisfied for regulatory purposes, TB recommends the submission of adequate studies for chromosomal damage (including aneuploidy) to properly assess the clastogenic potential of AZODRIN.

Consistent with previously published data [see REFERENCES], a contaminant of AZODRIN formulations, the alkylating agent trimethyl phosphate (TMP) is "weakly" positive for dominant lethals in vivo at high single oral doses (2,500 and 3,500 mg/kg), as well as following repeat oral dosage schedules (750 mg/kg/day) (MRID GS015412).

Metabolism

The metabolic fate of AZODRIN had been more or less defined in a 1964 unpublished paper by Menzer and Casida (MRID 00013505), especially with regards to the excretory products. Briefly, their study concerned the administration by intubation of P^{32} and N-methyl-C^{14} labeled technical AZODRIN (SD 9129) or Bidrin (the "parent" molecule) to adult male and female rats (total of 50 animals) at 1 mg/kg (single dose), and characterizing the urinary and fecal radioactive compounds at several time periods up to 48 hr post-treatment. The authors reported that 63-71% of the P^{32} activity in urine and 5% in feces was unchanged AZODRIN, and the balance hydrolysis and/or oxidation products of splitting the molecule at the P-O-vinyl (P^{32} activity) and/or the P-O-methyl bonds. The products of the first type of hydrolysis were dimethyl phosphate, monomethyl phosphate and phosphoric acid, leaving the 3-OH-N-methyl-cis crotonamide; N-methyl oxidation results in the 3-OH-cis crotonamide (SD 11319), found only in animals. P-O-methyl hydrolysis followed by N-methyl-oxidation apparently yields the 3-OH-N-OH-methyl-cis derivative (SD 12657), which is rapidly complexed to glucose only in plants (SD-13311). Presumably, this glucoside derivative can regenerate OP-active compounds if ingested.

This study has been graded Core-SUPPLEMENTARY because no tissue distribution for derivative products of AZODRIN was reported, to account for over 30% of the administered radioactivity. In addition, the study did not determine effects of repeated doses as well as a high dose on metabolism. Thus, additional data will be required to satisfy 3(c)(2)(B) re-registration.

III. SUMMARY OF ADDITIONAL DATA REQUIRED ("Data Gaps")

Based upon TB review and evaluation of the available toxicological data submitted and/or located, the following additional information or new studies are required under FIFRA 3(c)(2)(B):

1. Inhalation studies in the rat, specifically to determine a LC_{50} and a 21-day inhalation study among other studies may be required depending on the amount and nature of residue in tobacco.

2. Dermal sensitization study in the guinea pig.

3. Teratology study in the rabbit.

4. Additional information on the strain of mouse used in the oncogenicity study.

5. General metabolism of low dose, repeated low dose and high dose in the rat to assess tissue distribution and fate of radioactive AZODRIN and/or metabolites (especially OP-active derivatives).

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IV. TOLERANCE REASSESSMENT

Published tolerances have existed since 1975 for AZODRIN use on peanuts, tomatoes, cottonseed (including oil), potatoes and sugar (cane and beet), with a TMRC on these raw agricultural commodities (rac) of 0.0357 mg/day based on a 1.5 kg diet (40 CFR 180.296). Previous evaluations by TB of Section 18 requests for emergency use of the pesticide on field corn in Texas and New Mexico have been granted (Memos: Spencer to Housenger, June 26, 1981; Spencer to Stubbs, June 16, 1981, and May 26, 1983). These actions were based upon accepting a NOEL of 2 ppm from a 1966 rat reproduction study (MRIDs 00005119/00005120/ 00029426/00029427), supporting an ADI of 0.001 mg/kg/day and an MPI of 0.06 mg/kg (based on 60-kg body weight). This resulted in the TMRC occupying 59.42% of the ADI (printouts attached).

On the other hand, requests for a permanent tolerance on sweet corn and field corn at 0.3 ppm, and corn forage and fodder at 2 ppm (PP #6F1851), have been repeatedly denied because of deficiencies in the then submitted toxicology data base (Memos: Spencer to Gee, December 7, 1977, and September 2, 1980). In considering action on these previously submitted petitions, TB had based margins of safety upon a 1967 chronic dog study (MRIDs 00005121/00005124/00029425), providing a NOEL of 1.6 ppm (0.04 mg/kg/day) for cholinesterase inhibition (16 ppm for systemic effects), resulting in an ADI of 0.0040 mg/kg/day and an MPI of 0.2400 (60 kg), which results in the published TMRC occupying only 14.85% of the ADI for established tolerances, which would have been increased by about 4% if the requested additional tolerances on corn were granted (printout attached).

More recent submissions in support of requests for additional tolerances on corn, PP #6F1851 (MRIDs GS015404, GS015405, GS015406) indicate that the chronic rat feeding study (MRID GS015406) provides the basis for a more appropriate margin of safety. In that study, the NOEL for cholinesterase inhibition has been set at 0.03 ppm (and for systemic effects at 0.9 ppm), generating an ADI of 0.00015 mg/kg/day (systemically, 0.0045 mg/kg/day), which results in the TMRC for previously published tolerances occupying 396.67% of the ADI (132.22% based on systemic effects). Thus, on either basis (ChEI or systemic), the margins of safety have been exceeded for those tolerances already published, and precludes granting any new requests.

TB has taken a conservative position in setting the NOEL for cholinesterase inhibition at the 0.03 ppm level in the rat chronic study based on minor depressive trends in ChE at 0.09 ppm. This position is supported by the 8- and 13-week rat feeding study (GS015403) which indicated minor but consistently depressed cholinesterase inhibition in blood and brain at 0.1 ppm. (see Table 7 from that report, attached.)

It might be advantageous to the registrant to conduct a new short-term cholinesterase study in the rat to delineate more exactly this biochemical effect (in the crucial dose range, 0.03 to 0.1 ppm).

In addition, TB is concerned about the following (and requests from the appropriate HED branches information on):

1. Actual residues in or on rac, since published tolerances need to be re-evaluated because the TMRC exceeds the ADI.

2. Processed foods need to be evaluated for residues of AZODRIN.

3. Residues of AZODRIN in milk, meat, eggs and poultry need to be evaluated and/or re-evaluated (as follows from item 2).

4. Leaching and/or run-off of AZODRIN and its derivatives into waters used for human consumption, irrigation, or food-producing animals, as well as the preparation of feed.

5. Actual residues of AZODRIN on or in tobacco.

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Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
$$$$$$$$$	$$$$$$$$	$$$$	$$$$$$$$$$	$$$$$$$$$$

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Peanuts(115)	0.050	0.36	0.00027
Tomatoes(163)	0.500	2.87	0.02156
Cottonseed(41)	0.100	0.15	0.00022
Potatoes(127)	0.100	5.43	0.00814
Sugar,cane&beet(154)	0.100	3.64	0.00546

MPI	THEC	% ADI
$$$$$$$$$$ mg/day/60kg	0.0357 mg/day/1.5kg	0.00

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Chem 150.296 [illegible] 6/5/91

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Acceptable Daily Intake Data

RfD, Older	MOEL	S.F.	ADI	PAD
mg/kg	ppm		mg/kg/day	mg/day(60kg)
0.100	2.50	100	0.0010	0.0600

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Peanuts(115)	0.050	0.36	0.00027
Tomatoes(163)	0.500	2.87	0.02150
Cottonseed(41)	0.100	0.15	0.00022
Potatoes(127)	0.100	5.43	0.00814
Sugar,canebeet(154)	0.100	3.64	0.00546

PAD	TMRC	% ADI
0.0600 mg/day(60kg)	0.0357 mg/day(1.5kg)	59.42

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Current Action Section 18

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Corn,all types(36)	0.200	2.51	0.00753

PAD	TMRC	% ADI
0.0600 mg/day(60kg)	0.0432 mg/day(1.5kg)	71.97

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Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

NOEL change not recorded per

DOS mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
0.040	1.60	10	0.0040	0.2400

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Peanuts(115)	0.050	0.36	0.00027
Tomatoes(163)	0.500	2.87	0.02156
Cottonseed (Oil)(41)	0.100	0.15	0.00022
Potatoes(127)	0.100	5.43	0.00814
Sugar,cane&beet(154)	0.100	3.64	0.00546

MPI	TMRC	% ADI
0.2400 mg/day(60kg)	0.0357 mg/day(1.5kg)	14.85

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Current Action Section 18

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn,grain(68)	0.200	1.00	0.00300

MPI	TMRC	% ADI
0.2400 mg/day(60kg)	0.0387 mg/day(1.5kg)	16.10

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Table 7 - Mean cholinesterase values of rats fed diets containing AZODRIN for 8 weeks and then killed at that time (Group A), fed diets containing AZODRIN for 13 weeks (Group B) or fed diets containing AZODRIN for 8 weeks and then control diet for a subsequent 5 weeks (Group C)

Dietary concentration (ppm)	Number of rats	Mean cholinesterase values Males			Mean cholinesterase values Females		
		Plasma i.u.	Erythrocyte i.u.	Brain i.u.	Plasma i.u.	Erythrocyte i.u.	Brain i.u.
Group A							
0	20	0.43	1.27[6]	10.13	1.66	1.31	10.54
0.1	10	0.41	1.22	9.68**	1.53	1.14**	10.09**
0.25	10	0.41	1.09**	9.30**	1.43*	1.06**	9.44**
0.5	10	0.41	0.91**	8.36**	1.20**	1.06**	8.61**
2.0	10	0.34**	0.52**	5.49**	0.95**	0.51**	6.01**
8.0	10	0.21**	0.21**	2.80**	0.35**	0.18**	2.63**
Standard deviation of a single observation		0.037	0.152	0.321	0.197	0.118	0.328
Group B							
0	20	0.47	1.20[4]	11.12	2.03	1.27	11.71
0.1	10	0.49	1.19[2]	10.63**	1.58**	1.11**	11.36*
0.25	10	0.44	0.98**[1]	10.31**	1.61**	0.95**	10.50**
0.5	10	0.42**	0.83**[1]	9.22**	1.50**	0.80**	9.93**
2.0	10	0.34**	0.47**[2]	6.33**	1.11**	0.45**	6.78**
8.0	10	0.23**	0.24**[1]	3.17**	0.47**	0.21**	3.48**
Standard deviation of a single observation		0.040	0.153	0.328	0.302	0.100	0.368
Group C							
0	20	0.43	1.36[5]	11.10	1.75	1.30	11.51
0.1	10	0.47	1.27[2]	10.71**	1.91	1.31	11.29
0.25	10	0.43	1.10**[3]	10.72**	1.98	1.06**	11.35
0.5	10	0.44	1.22**	10.53**	2.01	1.16**	11.22*
2.0	10	0.47	1.06**[2]	9.93**	2.16*	1.08**	10.37**
8.0	10	0.45	0.94**[3]	9.16**	2.01*[1]	0.97**[1]	9.84**[1]
Standard deviation of a single observation		0.046	0.143	0.325	0.340	0.147	0.314

* Significantly different ($P \leq 0.05$) from mean control value
** Significantly different ($P \leq 0.01$) from mean control value

1 - number of observations = 9
2 - number of observations = 8
3 - number of observations = 7
4 - number of observations = 16
5 - number of observations = 15
6 - number of observations = 19

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VI. OTHER TOXICOLOGICAL CONCERNS

AZODRIN had previously been referred for consideration as an RPAR candidate (currently, "Special Review"), because of the presence of the contaminant, trimethyl phophate (TMP), at levels up to 1% (Memo: Spencer to P.S.O., December 7, 1977), but apparently no action was taken on this referral.

TMP is a mutagen (often used as a positive control substance in gene-tox testing), as indicated by positive results in both *in vitro* and *in vivo* studies (Adler, 1971; Bruce, 1979; Epstein, 1970; Newell, 1977).

A 1978 NCI bioassay (NCI-CG-TR-81) reported TMP was oncogenic in female (but not male) B6C3F1 mice, inducing adenocarcinomas of the uterine endometrium at high doses (500 mg/kg by gavage 3X weekly for 103 weeks), with a significant dose-related trend. This tumor type had not previously been observed among 100 historical control females at this laboratory (and was absent in concurrent controls). Additionally, AZODRIN treatment was associated with the induction of benign fibromas of subcutaneous tissue in male (but not female) Fisher 344 rats at the HDT (100 mg/kg by gavage 3X weekly for 104 weeks), which also showed significant dose-related trend.

However, TB does not consider that AZODRIN, even in the presence of minor amounts of this TMP contaminant, constitutes a dietary carcinogenic hazard in its registered uses, because of the following:

1. The potency of the technical monocrotophos in inhibiting cholinesterase provides its use on crops at minimal levels. (All tolerances were 0.5 ppm monocrotophos or less.)

2. TMP represents only a minor contaminant of the technical (up to 1%), and thus any contaminated residues from the use of end-use formulations would be at fractions of this level. This potential contamination of TMP would represent a "de minimis" amount of intake with a maximum TMRC of 0.3 microgram/day or 0.005 microgram/kg/day based upon published tolerances for monocrotophos.

3. At feeding levels up to 10 ppm monocrotophos with a potentially maximum amount of TMP of 0.1 ppm or 5 microgram/kg/day for two years, no carcinogenicity was evidenced in the rat or mouse. Thus, the amounts of TMP tested in the oncogenicity studies of monocrotophos are approximately 1000-fold higher than the potential exposure from foods (0.005 microgram/kg/day).

On the other hand, TB would like more information about levels of exposure to those persons involved in the manufacture, formulation, mixing and loading, as well as application of AZODRIN products. In addition, TB requests information concerning possible dietary exposure to the TMP contaminant.

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VII. REFERENCES
(NO MRID Included)

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TABLE A
GENERIC DATA REQUIREMENTS FOR ~~CHEMICAL X~~

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/
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: - Rodent, and	TGAI		YES	MRID 00105121, 00105123, 00129424, 00146303, G5015405	NO
- Non-rodent			YES	MRID 00105121, 00105124, 00129425	NO
83-2 - Oncogenicity - 2 species: - Rat (preferred), and	TGAI		~~YES NO~~	G5015405	~~YES~~ NO
- Mouse (preferred)			NO		YES
83-3 - Teratogenicity - 2 species: - Rat	TGAI		YES	MRID-G5015407	NO
- Rabbit			NO	—	YES
83-4 - Reproduction - Rat 2-generation	TGAI		YES	MRID-G5015406	NO
MUTAGENICITY TESTING				00114210 [redacted] MRID-G5015408 -G5015412	
84-2 - Gene Mutation	TGAI		YES		NO
84-2 - Structural Chromosomal Aberration	TGAI		YES	MRID-G5015411	NO
84-4 - Other Genotoxic Effects	TGAI		YES	MRID 00114210, 00143657, G5015412, 00102179, 00112476	NO

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TABLE A
GENERIC DATA REQUIREMENTS FOR ~~CHEMICAL X~~

§158.135 Toxicology
(continued)

TGAI = Technical grade of active ingredient;

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aqautic, 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/ Satisfied by 90-day neurotoxicity studies ©
5/ Satisfied by the chronic dog studies ©
~~6/ The NOEL for cholinesterase inhibition has not been formally established. A short term rat study is required at the following dose levels: by gavage: 0, 0.0005, 0.005, 0.015, 0.025, 0.037, and 0.05 mg/kg/day~~

6) A 21-day inhalation may be required depending on the residues in tobacco.

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TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING ~~CHEMICAL X~~ Monocrotophos

Data Requirement	Composition 1/ 3/	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)? 2/
§158.135 Toxicology				
ACUTE TESTING				
81-1 - Acute Oral Toxicity - Rat	MP	YES	MRID 00053705 MRID 00005115	NO
81-2 - Acute Dermal Toxicity - Rabbit	MP	YES	MRID 00099917 MRID 00053703 MRID 00053709	NO
81-3 - Acute Inhalation Toxicity - Rat	MP	NO		YES
81-4 - Primary Eye Irritation - Rabbit	MP	YES	MRID 00053704 MRID 65015402	NO
81-5 - Primary Dermal Irritation - Rabbit	MP	YES	MRID 00053705 MRID 65015401	NO
81-6 - Dermal Sensitization - Guinea Pig	MP	NO		YES

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TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING CHEMICAL X

§158.135 Toxicology
(continued)

1/ Composition: MP = Manufacturing-use product.
2/ Data must be submitted no later than _____.
3/ The MP is the same as the TGAI, and hence the same studies satisfy both requirements (G. Otakie, personal communication).

FINAL: 3/8/85

Corrections (????) 3-14-85

TABLE A
GENERIC DATA REQUIREMENTS FOR ~~CHEMICAL X~~ MONOCROTOPHOS

Data Requirement	Composition 1/	Use Patterns 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/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral Toxicity - Rat	TGAI		YES	MRID 00053705 MRID 00005115	NO
81-2 - Acute Dermal Toxicity - Rabbit	TGAI		YES	MRID 00099917 MRID 00053703 MRID 00053704	NO
81-3 - Acute Inhalation Toxicity - Rat	TGAI		NO		YES
81-7 - Delayed Neurotoxicity - Hen	TGAI		YES 4/		NO 4/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding: - Rodent, and	TGAI		~~YES~~	MRID 00005118 MRID GS015403	NO
- Non-rodent			YES 5/		NO 5/
82-2 - 21-Day Dermal - Rabbit	TGAI		YES	MRID 00005117	NO
82-3 - 90-Day Dermal - Rabbit	TGAI		NO		NO
82-4 - 90-Day Inhalation: - Rat	TGAI		NO		NO Yes 6/
82-5 - 90-Day Neurotoxicity: - Hen	TGAI		YES	MRID 00087765	NO
- Mammal			YES	MRID 00005118 MRID GS015403	NO

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TABLE A

GENERIC DATA REQUIREMENTS FOR ~~CHEMICAL "R"~~

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/
§158.135 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA		NO		YES
85-2 - Dermal Penetration	Choice		NO		YES
86-1 - Domestic Animal Safety	Choice		NO		YES

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TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING ~~CHEMICAL X~~ Monocrotophos.

Data Requirement	Composition 1/3/	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)?2/
§158.135 Toxicology				
ACUTE TESTING				
81-1 - Acute Oral Toxicity - Rat	MP	YES	MRID 00053705 MRID 00005115	NO
81-2 - Acute Dermal Toxicity - Rabbit	MP	YES	MRID 00119917 MRID 00053703 MRID 00053704	NO
81-3 - Acute Inhalation Toxicity - Rat	MP	NO		YES
81-4 - Primary Eye Irritation - Rabbit	MP	YES	MRID 00053704 MRID GS015402	NO
81-5 - Primary Dermal Irritation - Rabbit	MP	YES	MRID 00053705 MRID GS015401	NO
81-6 - Dermal Sensitization - Guinea Pig	MP	NO		YES

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