Atrazine/Review #10/9 pages/8.30.77

8

Releasable

August 30, 1977

Atrazine Technical - Addition of Data to Files
Casewell #63
Shaughnessy #080803
Toxicology Branch
Registration Division

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Thru: O.E. Paynter, Ph.D.
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Recommendation

No action required.

Review

1. 28-Day Range Finding Study with Atrazine in Albino Mice - (Industrial Bio-Test, IBT # 8532-08868, 5/28/76, submitted by Ciba-Geigy on 6/2/77, Acc.#230303.)

Ninty Charles River mice weighing 23-29 g. were divided into 9 groups of 10 animals each (5 males, 5 females) and were fed either 0, 10, 30, 100, 300, 1000, 3000, 10000, or 30000 ppm Atrazine Technical in the diet for 28 consecutive days. Males were housed individually, whereas females were housed 5 per cage. Body weight was determined initially and at weekly intervals for the duration of the study. Food consumption data was collected, individually for males and on a group basis for females, during the 4 week study. Observations for abnormal reactions and mortality were made daily. Necropsies were performed on all animals.

Results

MTD = 1000 ppm

One male died at 300 ppm, 2 males died at 3000 ppm, 2 males and 5 females died at 10000 ppm and all animals died when fed 10000 ppm.

Toxic Signs: tremors and generalized weakness among animals fed 30000 ppm after 3 days of feeding - the response was more pronounced in females. The same reactions were seen among mice fed 10000 ppm after 7 days of feeding.

No adverse reactions were seen among animals feed 3000 ppm or less. Body weight gain and food consumption were normal in mice fed up to 3000 ppm.

Necropsy: unremarkable

Classification: Core-minimum data.

2. Acute Oral LD_{50} of Technical Atrazine in the Rat: (Ciba-Geigy, Project #Siss 4569, 3/10/75, submitted by Ciba-Geigy on 6/2/77), Acc # 230303.

Seventy Tif. RAI rats, ranging in body weight from 160-180 g., were divided into 7 groups of 10 animals each (5 male, 5 female) and administered 600, 1000, 1290, 1670, 3170, 4640 or 6000 mg/kg of the test material by gavage. Animals were housed in groups of 5 and observed for signs of toxicity and/or mortality for a period of 14 days. Necropsies were performed on all animals.

Results

LD_{50} = 1869 (1405-2487) mg/kg
Toxic Signs: sedation, dyspnea, exophthalmos, curved position and ruffled fur.

Necropsy: unremarkable

Classification: Core-minimum data
1) body weight and food consumption were not determined daily.

TOX CATEGORY:III

3. Acute Oral LD_{50} of Technical Atrazine in the Mouse - (Ciba-Geigy, Project #Siss 4569, 9/7/77, submitted by Ciba-Geigy on 6/2/77), Acc # 230303.

Sixty Tif. MAG mice, ranging in body weight from 20-30 g., were divided into 6 groups of 10 animals each (5 male, 5 female) and administered 1670, 2780, 3590, 4640, 5200 or 6000 mg/kg of the test material by groups. Animals were housed in groups of 5 and observed for signs of toxicity and/or mortality for a period of 14 days. Necropsies were performed on all animals.

Results

LD_{50} = 3992 (3557-4479) mg/kg
Toxic Signs: sedation, dyspnea, curved or ventral position and ruffled fur.

Necropsy: unremarkable

Classification: Core-minimum Data
1) body weight and food consumption were not determined daily.

TOX CATEGORY:III

4. Acute Dermal LD_{50} of Technical Atrazine in the Rat - (Ciba-Geigy, Project # Siss 5663, 12/6/76, submitted by Ciba-Geigy on 6/2/77, Acc # 230303).

Twenty Fif: RAIF(SPF) rats, ranging in weight from 180-200 g., were divided into 2 groups of 10 animals each (5 male, 5 female) and dermally administered 2150 or 3170 mg/kg of the test material as a 50% aq. suspension to intact skin. The material was allowed to remain in contact with the skin for 24 hrs. under an impervious cuff. Following the 24 hr. exposure the material was washed away and the animals observed for 14 days post exposure. Necropsies were performed on animals at the end of the observation period.

Results

LD_{50} > 3100 mg/kg (highest dose possible) - No deaths occured.
Toxic Signs: none, no local irritation.

Necropsy: unremarkable

Classification: Core-minimum Data
1) since the results are clear at the highest dose level possible was administered, further testing would be pointless. The study adequately reflects dermal hazard.

TOX CATEGORY:III

5. Primary Eye Irritation of Technical Atrazine -
(Ciba-Geigy, Project # siss 5663, 11/24/76, submitted by Ciba-Geigy on 6/2/77, Acc#230303)

100 mg. was inserted into the conjunctival sac of the left eye of each of six Himalayan rabbits. The treated eye of 3 of the 6 rabbits was flushed with 10 ml of water 30 sec. after treatment. Ocular irritation was recorded 1, 2, 3, 4, and 7 days past treatment.

Results

Unwashed Eyes: 0.0/110 at 1, 2, 3, 4 and 7 days
Washed Eyes: 0.0/110 at 1, 2, 3, 4 and 7 days.

Classification: Core-Minimum data
1) although readings were made on 3 unwashed eyes, these readings together with the 3 readings on the washed eyes indicate that the technical material is not an eye irritant.

TOX CATEGORY: IV

6. Primary Skin Irritation of Technical Atrazine -
(Ciba-Geigy, Project #siss 5663, 11/24/76, submitted by Ciga-Geigy on 6/2/77, Acc#230303)

500 mg. of test material was applied to one abraded and one intact skin site on 6 Himalayan rabbits and held in contact with the skin under an impervious cuff for 24 hrs. Dermal irritation was scored at 24 and 72 hrs. by the method of Draize.

Results

P.I. = 0.2/8.0

Classification: Core minimum data
1) readings were not made on 2 intact and 2 abraded skin sites.

TOX CATEGORY: IV

7. Mutagenicity Screening of Pesticides in the Microbial System - (Shirash, Moriya, Kato, Furuhashi, Kada; Mutation Research 10 (1976) 19-30)

A survey on the mutation induction capacity was made in the microbial system on 166 pesticides including 57 fungicides, 63 herbicides and 46 insecticides. The screening methods consisted of the rec-assay procedure, a sensitivity test utilizing H17 Rec + and M45 Rec - strains of Bacillus subtilis, as well as the reversion assays on plates utilizing auxotrophic strains of Escherechia coli (WP2) and Salmonella typhimurium (Ames series).

Rec Assay

Test strains (B. subtilis H17 Rec+ and M45 Rec-) were grown overnight in broth B-2. Two cultures were streated on the B-2 agar plates and the "starting points" were covered with a 10 mm diameter paper disc containing 0.02 ml. of each sample. All plates were incubated for 24 hrs. at 37°C and the length of the inhibition zones measured.

Reversion Assay

0.1 ml. sample of each bacterial culture was spread on the surface of MB or 9BB agar and a 10 mm diameter paper disc containing 0.02 ml. of each sample was placed in the center of each plate. Each plate was incubated for 2 days at 27°C and the formation of revertant colonies around each disc observed. For samples showing positive effects the "soft agar" procedure was used. 0.1 ml of the bacterial culture and 0.1 ml of drug solution were added to 2nd soft agar at 45°C and poured into a petric dish containing 50 ml of 9BB agar. Colonies formed by incubation at 37° for 2 days were counted.

Media

Liquid broth B-2 (10g. meat extract, 10g. polypeptone and 5g. NACl in 1000 ml. water pH 7.0 solidified with 1.5% Difco agar was used for the rec-assay. For reversion-assays with E. coli WP2 strains, a modified Vogel-Banner salts mixture was supplemented with 1% Difco broth and solidified with agar (MB agar). For the reversion assay with Salmonella strains, M9 minimal medium was supplemented with 1% Difco broth and 1mg/ml biotin (9BB agar).

A list of the pesticides assayed follows:

10 ~~Do not type~~

~~Table 1~~

Common name	Use	Chemical name
ACN	H.	2-amino-3-chloro-1,4-naphthoquinone
Alachlor	H.	2-chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide
Alanap	H.	sodium N-1-naphthylphthalamate
Aldrin	I.	1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-*endo*-1,4-*exo*-5,8-dimethanonaphthalene
Ametryne	H.	2-ethylamino-4-isopropylamino-6-methyl-thio-1,3,5-triazine
Amitrole	H.	3-amino-1,2,4-triazole
Aprocarb	I.	*o*-isopropoxyphenyl methylcarbamate
Asozin	F.	methylarsine sulfide
Asulam	H.	N'-methoxycarbonylsulfanilamide
Atrazine	H.	2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine
Baykel	F.	nickel propylenebis(dithiocarbamate)
BEBP	F.	S-benzyl butyl S-ethylphosphorodithioate
Benefin	H.	N-butyl-N-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine
Bensulide	H.	S-2-(benzenesulfonamide)ethyl diisopropyl phosphorothiolothionate
Benthiocarb	H.	S-*p*-chlorobenzyl diethylthiocarbamate
Benzalkonii chloridum	I.	alkylbenzyldimethylammonium chloride
BHC (mixture of α, β and γ)	I.	1,2,3,4,5,6-hexachlorocyclohexane
Binapacryl	F.	2-sec-butyl-4,6-dinitrophenyl 3-methylcrotonate
Bis-Dithane	F.	zinc bis(dimethyldithiocarbamate) ethylenebis(dithiocarbamate)
Blasticidin S	F.	
BPMC	I.	*o*-sec-butylphenyl methylcarbamate
Bromacil	H.	5-bromo-3-sec-butyl-6-methyluracil
Butachlor	H.	2-chloro-2',6'-diethyl-N-(butoxymethyl) acetanilide
Captafol	F.	N-(1,1,2,2-tetrachloroethylthio)-4-cyclohexene-1,2-dicarboximide
Captan	F.	N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide
Carbanolate	I.	6-chloro-3,4-xylyl methylcarbamate
Carbaryl	I.	1-naphthyl methylcarbamate
CBA	F.	pentachlorobenzaldoxime
CBN	H.	4-chloro-2-butynyl *m*-chlorocarbanilate
CPCA	I.	N-(2-cyanoethyl)chloroacetamide
Cellocidin	F.	acetylenedicarboxamide
Chinomethionate	I. (F.)	S,S-6-methylquinoxaline-2,3-diyl dithiocarbonate
Chlorfenson	I.	*p*-chlorophenyl *p*-chlorobenzenesulfonate
Chlorfenvinphos	I.	2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate
Chloronitrophen	H.	sodium 2,4-dichloro-6-nitrophenoxide
Chlorophenamidine	I.	N'-(4-chloro-o-tolyl)-N,N-dimethylformamidine
Chloropropylate	I.	isopropyl *p,p'*-dichlorobenzilate
Chloroxuron	H.	3-*p*-(*p*-chlorophenoxy)phenyl-1,1-dimethylurea
Chlorthiamid	H.	2,6-dichlorothiobenzamide
Cidial	I.	S-[α-(ethoxycarbonyl)benzyl] dimethyl phosphorothiolothionate
CMPT	H.	5-chloro-4-methyl-2-propionamide-1,3-thiazole
CPA	F.	pentachlorophenyl acetate
CVMP	I.	2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate
2,4-D	H.	2,4-dichlorophenoxyacetic acid
DAD	F.	2,3-dichloro-1,4-naphthylene diacetate
DAPA (Dexon)	F.	sodium *p*-dimethylaminobenzenediazosulfonate
DCPA	H.	3',4'-dichloropropionanilide
DDPP	F.	2,6-dichloro-4,5-dihex[illegible]-1-phenylpyridine
DDT	I.	1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane
Desmetryne	H.	2-isopropylamino-4-methylamino-6-methylthio-1,3,5-triazine
Diazinon	I.	diethyl 2-isopropyl-4-methyl-6-pyrimidinyl phosphorothionate
Dicamba dimethylamine	H.	dimethylamine 3,6-dichloro-*o*-anisate
Dichlobenil	H.	2,6-dichlorobenzonitrile
Dichlofluanid	F.	N-(dichlorofluoromethylthio)-N-(dimethylsulfamoyl)aniline
Dichlone	F.	2,3-dichloro-1,4-naphthoquinone

11

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Common name	Use	Chemical name
Dichlorvos (DDVP)	I	2,2-dichlorovinyl dimethyl phosphate
Dichlozoline	F.	3-(3,5-dichlorophenyl)-5,5-dimethyloxazolidine-2,4-dione
Dicloran	I.	2,6-dichloro-4-nitroaniline
Dieldrin	I.	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-1,4-*exo*-5,8-dimethanonaphthalene
Dimethoate	I.	dimethyl S-(N-methylcarbamoylmethyl)phosphorothiolothionate
Dimite	I.	1,1-bis(*p*-chlorophenyl)ethanol
Dioxathion	I.	S,S'-1,4-dioxane-2,3-diyl bis(diethyl phosphorothiolothionate)
Diphenamid	H.	*N,N*-dimethyl-2,2-diphenylacetamide
Diquatdibromide	H.	6,7-dihydrodipyrido(1,2-*a*: 2',1'-*c*) pyrazinediium dibromide
Dithianon	I.	2,3-dicyano-1,4-dithiaanthraquinone
Diuron	H.	3-(3,4-dichlorophenyl)-1,1-dimethylurea
DMTP	I.	S-[5-methoxy-2-oxo-2,3-dihydro-1,3,4-thiadiazolyl-(3)-methyl] dimethyl phosphorothiolothionate
DTAS	F.	poly[methyl-bis(thiocyanato)arsine]
Dursban	I.	*O,O*-diethyl-*O*-3,5,6-trichloro-2-pyridyl phosphorothionate
EMP	F.	bis(ethylmercury) hydrogen phosphate
Eradex	I	quinoxaline-2,3-diyl trithiocarbonate
ESBP	F.	S-benzyl ethyl phenylphosphonothiolate
ESTP	F.	S-benzyl ethyl tolylphosphonothiolate
Ethion	I.	tetraethyl S,S'-methylene bis(phosphorothiolothionate)
ETM	I.	*N,N'*-ethylenebis(thiocarbamoyl)sulfide
Fenthion	I.	dimethyl 4-methylthio-m-tolyl phosphorothionate
Fentiazon	F.	3-benzylideneamino-4-phenylthiazoline-2-thione
Ferbam	F.	iron dimethyldithiocarbamate
Folpet	I.	*N*-(trichloromethylthio)phthalimide
HEH	H.	*N*-(2-hydroxyethyl)hydrazine
Heptachlor	I.	1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methano
Hinosan	F.	*O*-ethyl diphenyl phosphorodithiolate
Hopcide	I.	o-chlorophenyl methylcarbamate
Hydrol	I.	4-diallylamino-3,5-xylyl methylcarbamate
IBP	F.	S-benzyl diisopropyl phosphorothiolate
Imidan	I.	dimethyl S-(phthalimidomethyl) phosphorothiolothionate
Ioxynil octanoate	H.	4-cyano-2,6-diiodophenyl octanoate
IPC	H.	isopropyl m-chlorocarbanilate
Karathane	I.	isomeric reaction mixture of 2,4-dinitro-6-octylphenyl crotonate and 2,6-dinitro-4-octylphenyl crotonate
Kasugamycin	I.	
Kelthane	I.	2,2,2-trichloro-1,1-bis(*p*-chlorophenyl) ethanol
Lenacil	H.	3-cyclohexyl-5,6-trimethyleneuracil
Linuron	H.	3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea
MAC	F.	calcium methanearsonate
Macbal	I.	3,5-xylyl methylcarbamate
MAF	F.	iron methanearsonate
Malathion	I.	S-[1,2-bis(ethoxycarbonyl)ethyl] dimethyl phosphorothiolothionate
MAS	F.	sodium methanearsonate
MCPB-ethyl	H.	ethyl 4-[(4-chloro-o-tolyl)oxy]butyrate
MCPB sodium	H	sodium 4-[(4-chloro-o-tolyl)oxy]butyrate
MCPCA	H.	[(4-chloro-o-tolyl)oxy]aceto-o-chloroanilide
MCPE	H	2-[(4-chloro-o-tolyl)oxy]ethanol
MCPEA	H	[(4-chloro-o-tolyl)oxy]aceto-o-trifluoromethylanilide
MCPP	H.	potassium 2-[(4-chloro-o-tolyl)oxy]propionate
Mecarbam	I.	S-(N-ethoxycarbonyl-N-methylcarbamoylmethyl) diethyl phosphorothiolothionate
Meobal	I.	3,4-xylyl methylcarbamate
Metiram	F.	[ethylenebis(thiocarbamoyl)disulfide] [zinc ethylenebis(dithiocarbamate)]copolymer

Common name	Use	Chemical name
Mipcin	I	o-cumenyl methylcarbamate
MO	H.	p-nitrophenyl 2,4,6-trichlorophenyl ether
Molinate	H.	S-ethyl hexahydro-1H-azepine-1-carbothioate
Monuron	H.	1,1-dimethyl-3-(p-chlorophenyl) urea
NBT	F.	2,4-dinitrophenyl thiocyanate
NIP	H.	2,4-dichlorophenyl p-nitrophenyl ether
NNN	F.	5-nitro-1-naphthonitrile
Omite	I.	2-(p-tert-butylphenoxy)cyclohexyl propynyl sulfite
PCNB	F.	pentachloronitrobenzene
PCP	H.	sodium pentachlorophenoxide
Pebulate	H.	S-propyl N-butyl-N-ethyl (thiocarbamate)
Pentanochlor	H.	3'-chloro-2-methyl-p-valerotoluidide
Phenazine	F.	phenazine 5-oxide
Phenisobromolate	I.	isopropyl p,p'-dibromobenzilate
Phenkapton	I.	S-(2,5-dichlorophenylthiomethyl) diethyl phosphorothiolothionate
Phenmedipham	H.	m-(methoxycarbonylamino) phenyl m-methylcarbanilate
Phenopylate	H.	2,4-dichlorophenyl pyrrolidine carboxylate
Phenothiol	H	S-ethyl [(4-chloro-o-tolyl)oxy] (thioacetate)
Phosalone	I.	S-[(6-chloro-2-oxo-3-benzoxazolinyl)methyl] diethyl phosphorothiolothionate
Phosvel	I	4-bromo-2,5-dichlorophenyl methyl phenylphosphonothionate
PMA	F.	phenylmercury acetate
PMC	F.	phenylmercury chloride
PMF	F.	phenylmercury dinaphthylmethane disulfonate
Polyoxin B	F.	
Polyoxin D	I	
Prometryne	H.	2,4-bis(isopropylamino)-6-methylthio-1,3,5-triazine
Propazine	H.	2-chloro-4,6-bis(isopropylamino)-1,3,5-triazine
Rabcide	F.	4,5,6,7-tetrachlorophthalide
Ronstar	H.	5-tert-butyl-3-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazoline-2-one
Salithion	I.	2-methoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide
Sankel	F	nickel dimethyldithiocarbamate
Siduron	H.	1-(2-methylcyclohexyl)-3-phenylurea
Simazine	H	2-chloro-4,6-bis(ethylamino)-1,3,5-triazine
Simetryne	H.	2,4-bis(ethylamino)-6-methylthio-1,3,5-triazine
Smite	I	2-[2-(p-tert-butylphenoxy)-1-methylethoxy]-1-methylethyl 2-chloroethyl sulfite
Styrocide	I.	6-methyl-4-nitrophenyl thiocyanatostyrene
Sumithion	I.	dimethyl 4-nitro-m-tolyl phosphorothionate
Swep	H.	methyl 3,4-dichlorocarbanilate
2,4,5-T	H	2,4,5-trichlorophenoxyacetic acid
Tachigaren	F	3-hydroxy-5-methylisoxazole
TCA	H	sodium trichloroacetate
TCBA	H.	sodium 2,3,6-trichlorobenzoate
TCTP	H.	dimethyl tetrachloroterephthalate
Tetradifon	I	p-chlorophenyl 2,4,5-trichlorophenyl sulfone
Tetrapion	H.	sodium 2,2,3,3-tetrafluoropropionate
Thiophanate	F.	diethyl 4,4'-o-phenylene 3,3'-dithiodiallophanate
TMTD	F.	bis(dimethylthiocarbamoyl) disulfide
Tokunol	H.	O-ethyl O-(2-nitro-4-methylphenyl) N-isopropyl thiophosphoroamidate
TOPE	H.	p-nitrophenyl m-tolyl ether
Triazine	F.	2,4-dichloro-6-(o-chloroanilino)-1,3,5-triazine
Trichlorfon	I	dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate
Trietazine	H	2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine
Trifluralin	H.	α,α,α-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine
Tsumacide	I.	m-tolyl methylcarbamate
[illegible]	F	[illegible] dimethyldithiocarbamate
Vamidothion	I.	dimethyl S-[2-(1-methylcarbamoylethylthio) ethyl] phosphorothiolate
Vernolate	H.	S-propyl dipropylthiocarbamate
Ziram	F.	zinc dimethyldithiocarbamate
ZM	F.	zinc methyldithiocarbamate

Result

The pesticides showing positive effect in broth rec-assay and reversion-assay were:

Captofol	Dexon	Dichlovos
Captan	NBT	Folpet
2-Hydrazinoethanol (HEH)	Vamidothion	5-Nitro-1-naphthonitrile

Atrazine did not exhibit a mutation induction capacity.

Classification: Core Minimum Data.

William Greear