



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

007659

JAN 4 1990

JAN 4 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Azinphos-Methyl

Project No.: 9-2283

TOX Chem No.: 374

FROM: Ray Landolt *12/13/89*
Review Section I
Toxicology Branch II - Herbicide, Fungicide and
Antimicrobial Support
Health Effects Division (H7509C)

TO: Vivian Prunier, PM 74
Insecticide-Rodenticide Branch
Registration Division (H7508C)

THRU: Mike Ioannou, Section Head *J.M. Ioannou 12/19/89*
Review Section I
Toxicology Branch II - Herbicide, Fungicide and
Antimicrobial Support
Health Effects Division (H7509C)

and

Marcia van Gemert, Branch Chief *M van Gemert 12/21/89*
Toxicology Branch II - Herbicide, Fungicide and
Antimicrobial Support
Health Effects Division (H7509C)

Registrant: Mobay Corporation, letter of September 13, 1989

Action Requested

In response to the deficiencies cited in the review by D. Ritter, May 8, 1989 of A Teratology Study in the Rabbit with Azinphos-methyl (MRID 407139-01), Mobay Corporation has submitted the requested historical control data (412400-00) on the incidence of pre-sacral vertebrae.

1/2/90

Conclusion

Azinphos-methyl (87.7%) was administered orally to four groups of 20 pregnant rabbits per group at 0, 1.0, 2.5, 6.0 mg/kg/day for 13 consecutive doses during days 6 through 18 of gestation.

This study may be upgraded from Supplementary to Guideline.

Maternal NOEL = 1.0 mg/kg/day

Maternal LEL = 2.5 mg/kg/day with a significant (p < 0.05) decrease in plasma cholinesterase activity (13%) during day 19 of the study.

Developmental NOEL = 6.0 mg/kg/day

A/D ratio - 0.4

Background Information

In the review by D. Ritter (Dynamic) the following conclusions were drawn from their evaluation of the rabbit teratology study (MRID 407139-01).

Classification: Core Supplementary data

Maternal NOEL = 1.0 mg/kg/day

Maternal LEL = 2.5 mg/kg/day with inhibition of plasma cholinesterase activity.

A dose-related increase was observed in the incidence of fetuses and litters affected with lumbar and sacral vertebrae abnormalities (missing or extra arch; missing or extra centra) in the low- and mid-dose groups but not in the high-dose group. Additional historical control data are required before the developmental toxicity of azinphos-methyl can be assessed.

Discussion

With their letter of September 13, 1989, Mobay Corporation has addressed the concerns cited in the May 8, 1989 review of the rabbit teratology. In the following table, the range of historical control incidence (from 20 studies), of pre-sacral vertebrae can be compared to the incidence of extra lumbar/missing sacral vertebrae reported in this rabbit teratology study.

1
1

	<u>Control</u>	<u>Dose Level mg/kg/day</u>			<u>Historical Control Range*</u>
		<u>1.0</u>	<u>2.5</u>	<u>6.0</u>	
No. of Litters (Fetuses) Examined	17(124)	18(112)	17(118)	18(97)	318(1938)
Extra Lumbar/Missing Sacral					
No. Fetuses (%)	2(1.6)	4(3.6)	7(5.9)	2(2.1)	2(1.9) - 10(9.2)
No. Litters (%)	2(11.8)	4(22.2)	7(41.1)	2(11.1)	1(5.3) - 6(35.3)
Sacral Shift					
No. Fetuses (%)	2(1.6)	3(2.7)	4(3.4)	1(1.0)	0(0) - 3(4.5)
No. Litters (%)	2(11.8)	3(16.7)	3(17.6)	1(5.5)	0(0) - 4(25.0)

The incidence of extra lumbar/missing sacral in this rabbit teratology study are within the historical control range except for the incidence at the mid dose level (2.5 mg/kg).

At the mid dose level the fetal incidence of 5.9% is within the historical control range of 1.9 to 9.2%, however, the litter incidence of 41.1% is outside of the historical control range of 5.3 to 35.3%. This appears to be a spurious event and not related to the test material administered.

* From the attached table of Historical Control Pre-Sacral Vertebrae submitted by Mobay Corporation.

Table I

Historical Control Pre-Sacral Vertebrae

Study Number	Number of Litters	Litter Incidence		Number of Fetuses	Fetal Incidence		Combined Pre-Sacral Vertebrae and Shift	
		Lumbar Extra/Missing Sacral	Shift		Lumbar Extra/Missing Sacral	Shift	Litter (%)	Fetal (%)
1	14	2 (14.3)	--	77	2 (2.6)	--	2 (14.3)	2 (2.6)
2	15	5 (33.3)	1 (6.7)	95	6 (7.1)	1 (1.2)	5 (33.3)	7 (8.2)
3	16	4 (25.0)	--	103	4 (3.9)	--	4 (25.0)	4 (3.9)
4	12	2 (16.7)	--	48	3 (6.2)	--	2 (16.7)	3 (6.3)
5	16	5 (31.2)	1 (6.2)	87	6 (6.9)	1 (1.1)	5 (31.2)	7 (8.0)
6	17	1 (5.9)	2 (11.8)	82	1 (1.2)	2 (2.4)	2 (11.8)	3 (3.7)
7	16	3 (18.8)	2 (12.5)	102	8 (7.8)	3 (2.9)	4 (25.0)	11 (10.8)
8	16	2 (12.5)	4 (25.0)	115	5 (4.3)	4 (3.5)	6 (37.5)	9 (7.8)
9	15	4 (26.7)	3 (20.0)	94	6 (6.4)	3 (3.2)	5 (33.2)	9 (9.6)
10	13	3 (23.1)	2 (15.4)	66	6 (9.1)	3 (4.5)	4 (30.8)	9 (13.6)
11	16	5 (31.2)	--	95	8 (8.4)	--	5 (31.3)	8 (8.4)
12	15	2 (13.3)	--	111	3 (2.7)	--	2 (13.3)	3 (2.7)
13	16	2 (12.5)	2 (12.5)	116	4 (3.4)	2 (1.7)	3 (18.8)	6 (5.2)
a 14	17	2 (11.8)	2 (11.8)	124	2 (1.6)	2 (1.6)	4 (23.5)	4 (3.2)

^aGuthion (azinphos-methyl) study

Table I (cont'd)

Study Number	Number of Litters	Litter Incidence			Number of Fetuses	Fetal Incidence			Combined Pre-Sacral Vertebrae and Shift Litter (%)	
		Lumbar Extra/Missing Sacral	Shift			Lumbar Extra/Missing Sacral	Shift		Litter (%)	Fetal (%)
15	17	6 (35.3)	2 (11.8)		109	10 (9.2)	3 (2.8)		7 (41.2)	13 (11.9)
16	17	1 (5.9)	1 (5.9)		104	2 (1.9)	1 (1.0)		1 (5.9)	3 (2.9)
17	18	4 (22.2)	2 (11.1)		111	7 (6.3)	2 (1.8)		4 (22.2)	9 (8.1)
18	19	1 (5.3)	--		104	2 (1.9)	--		1 (5.3)	2 (1.9)
19	18	5 (27.8)	1 (5.6)		120	5 (4.2)	1 (0.8)		6 (33.3)	6 (5.0)
20	15	4 (26.7)	1 (6.7)		85	7 (8.2)	2 (2.4)		4 (26.7)	9 (10.6)