

Rubin, Y., A. Nyska, and T. Waner. 1987.

Pyrinex teratogenicity study in the rabbit Conducted at Life Science Research Israel Ltd., Laboratory Study # MAK/103/PYR.

Pregnant rabbits of strain HY/CR (a NZW variety), with at least 14 animals per group, were dosed by gavage with chlorpyrifos (Pyrinex Technical, purity 96.1%) in corn oil on days 7-19 *post coitum* at doses of 0, 1, 9, 81, or 140 mg/kg/day (4 dose levels in addition to control). (The doses were chosen in part based on a pilot study in which 100% maternal lethality at a dose of 270 mg/kg/day was noted.) A decrease in plasma cholinesterase 10 days after dosing was noted in a dose-dependent manner at all levels of chlorpyrifos administration (decrease to 43%, 31%, 30% and 28% at 1, 9, 81 and 140 mg/kg-day respectively), as shown in Table 1 below (n.b., all tables are copied verbatim from the study report). Based on body weight gain decrement during the treatment period (Table 2), the authors concluded that the maternal NOEL was 81 mg/kg/day. However, bodyweight effects are generally recognized to be less useful as indicators of maternal toxicity in rabbits than in other species, because during gestation they are more variable (U.S. EPA., 1991).

Statistically significant differences were noted for an increase in post implantation loss at doses of 9 mg/kg/day and above (Table 3). Skeletal observations in the fetuses revealed reduced or incomplete ossification of the hyoid bone of the skull at all dose levels; the differences were statistically significant from the control group, but not in a dose-dependent manner (Table 4). While some visceral or internal effects were seen at the 9 mg/kg/day group they were mostly noted in a single fetus. At the high dose (140 mg/kg/day), fetal effects included reduced crown/rump length, reduced fetal weight, ossification delays (indicated by non ossification of the fifth sternebra and/or xiphisternum) and increased post-implantation fetal death. The authors concluded that while the high dose demonstrated slightly adverse fetal response in the form of reduced fetal size, delays in ossification and possibly post-implantation fetal death, Pyrinex did not demonstrate teratogenic potential in the current test system, and adverse fetal response was not noted in the absence of maternal toxicity. The authors suggested that the developmental NOEL was 81 mg/kg/day.

### Reference

U.S. Environmental Protection Agency (U.S. EPA). 1991. Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/600/FR-91/001, 1991.

Table 1.

Plasma cholinesterase (IU/l) - group mean values and standard deviations

Group	:	1	2	3	4	5
Test material	:			PYRINEX		
Dosage (mg/kg/day)	:	0	1	9	81	140

:	Group	Before commencement	After 10 days dosing	:
:				:

1	Mean	615.4	451.5
	SD	383.1	274.7
	N	13	13
2	Mean	377.6	196.4 <sup>c</sup>
	SD	276.7	57.0
	N	13	13
3	Mean	657.1	142.2 <sup>c</sup>
	SD	498.8	30.1
	N	13	13
4	Mean	571.1	136.2 <sup>c</sup>
	SD	394.7	29.6
	N	15	10
5	Mean	654.5	125.3 <sup>c</sup>
	SD	424.3	26.6
	N	12	12

c: Significantly different from control,  $p < 0.001$ , Student's t-test

Table 2.

Body weight during gestation (g) -  
group mean values and standard deviations

Group	:	1	2	3	4	5
Test material	:	PYRINEX				
Dosage (mg /kg/day)	:	0	1	9	81	140

		Day post coitum				
Group		29 (1)	0-29 (2)	0-7 (2)	7-19 (2)	19-29 (2)
1	MEAN	3177	439	94	88	257
	SD	199	134	98	176	82
	N	13	13	13	13	13
2	MEAN	3277	525	122	155	242
	SD	249	145	77	76	91
	N	13	13	13	13	13
3	MEAN	3321	525	116	168	241
	SD	241	173	109	104	110
	N	13	13	13	13	13
4	MEAN	3306	453	93	107	253
	SD	210	185	59	167	81
	N	15	15	15	15	15
5	MEAN	3275	461	168a	-99b	401c
	SD	226	178	91	193	120
	N	11	11	12	12	11

(1) Nett of gravid uterus

(2) Body weight change

a: significantly different from control, p<0.05, Student's t-test

b: significantly different from control, p<0.01, Student's t-test

c: significantly different from control, p<0.001, Student's t-test



Table 4.

Skeletal observations - litter distribution of affected fetuses

Group	1	2	3	4	5
Test material	PYRINEX				
Dosage (mg /kg/day)	0	1	9	81	140

  

: Group	1	2	3	4	5
: Number of litters examined	13	13	13	15	11
	N (Mean%)				

  

	1	2	3	4	5
: SKULL					
: -----					
: Anterior fontanelle					
: enlarged	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.5)
: Reduced or incomplete					
: ossification of					
: interparietal bone	2 (3.1)	3 (3.5)	3 (2.4)	3 (3.1)	2 (1.7)
: Interparietal bone					
: unossified	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (3.2)
: Interparietal-supra-					
: occipital suture open	5 (6.9)	2 (1.7)	4 (4.9)	3 (3.5)	6 (10.3)
: Reduced or incomplete					
: ossification of supra-					
: occipital bone	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
: Extra suture in one					
: or more cranial bone	1 (1.9)	1 (1.0)	0 (0.0)	1 (1.1)	1 (0.8)
: Reduced or incomplete					
: ossification of hyoid					
: bone	1 (1.4)	7a (8.5)	8b(12.2)	7a(10.3)	5 (7.5)

a: Significantly different from control. p<0.05, Fisher exact test

b: Significantly different from control. p<0.01, Fisher exact test

Table 4 (continued)

Skeletal observations - number (percent) of affected fetuses

Group	1	2	3	4	5
Test material	PYRINEX				
Dosage (mg /kg/day)	0	1	9	81	140
: Group	1	2	3	4	5
: Number of fetuses examined	108	117	126	142	99
: SKULL					
: -----					
: Reduced or incomplete ossification of supra-occipital bone	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
: Extra suture in one or more cranial bone	2 (1.9)	1 (0.9)	0 (0.0)	2 (1.4)	1 (1.0)
: Reduced or incomplete ossification of hyoid bone	2 (1.9)	10 (8.5) <sup>a</sup>	17 (13.5) <sup>c</sup>	16 (11.3) <sup>b</sup>	8 (8.1) <sup>a</sup>
: Hyoid cornu angulated	3 (2.8)	6 (5.1)	2 (1.6)	4 (2.8)	1 (1.0)

a: Significantly different from control, p<0.05, Fischer exact test

b: Significantly different from control, p<0.01, Fischer exact test

c: Significantly different from control, p<0.001, Fischer exact test