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Toxic and Teratogenic Effects of Azadirachtin of Neemix-4.5 on Fetuses and Pups of SWR/J Mice

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Abstract

Inbred normal adult SWR/J mice were used to evaluate the toxic and teratogenic short- and long term effects of various dose levels (0.9, 1.8, 3.0, 9.0, 45.0, which represent 1/100, 1/50, 1/30, 1/10, 1/2 LD_{50}, respectively) of azadirachtin of neemix-4.5 (insecticide product)on fetuses and pups of pregnant females.

The oral administration of the different dose levels of azadirachtin on days 7-12 of gestation or on a 80-day period has not produced any morphological or skeletal changes in fetuses and pups of SWR/J mice. As the pharmacokinetics of azadirachtin and its bioavailability to the fetus are unknown, the essentially negative results obtained in the present study may be due either to the lack of toxic potential or to lack of fetal exposure.

Key Word : Neemix-4.5, Azadirachtin, Teratogenicity, Fetotoxicity SWR/J mice.

Introduction

Control of insect pests generally has been achieved with broad-spectrum synthetic insecticides. However, there are many potential problems associated with continued long-term use of such insecticides including pest resistance and negative impacts on nontarget organisms (Magaro and Edelson, 1990 ; Leskovar and Boales, 1996). Moreover, increasing documentation of negative environmental and health impact of synthetic toxic insecticides and increasing stringent government regulation of pesticides have resulted in renewed interests in the development and use of botanical pest management products (Ascher, 1993; Liang *et al.*, 2003).

Neem-based insecticides were containing azadirachtin that was derived from extracts of neem tree, *Azadirachta indica* A. Juss, have played a important role in crop protection (Liang *et al.*, 2003). Azadirachtin, a very complex tetranortriter-penoids, has been effectively used against more than 400 species of insects, including many key crop pests, and has proved to be one of the most promising plant ingredients for integrated pest management at the present time (Jacobson, 1989 ; Rembold, 1989 ; Schmutterer, 1990 ; Isam, 1999 ; Walter, 1999 ; Liang *et al.*, 2003). It displays an array of effects on insects, acting inter alia, as a phago-and oviposition deterrent, repellent, antifeedant, growth retardant, molting inhibitor, sterilant and preventing insect larvae from developing into adults (Schmutterer, 1990 ; Mordue and Blackwell, 1993 ; Schmutterer, 1995).

Although azadirachtin has low acute toxicity in mammalian species, with LD_{50} greater than 5000 mg/kg in the rat (Raizada *et al.*, 2001), the possibility of future hazards should not be ignored (Anon, 1992). As potential use of crude neem oil as an antifertility agent has been claimed (Lal *et al.*, 1986), a toxicological safety assessment is required for azadirachtin in order to establish its potential human use. In acute and chronic studies, several workers have shown aderse effects of neem

oil in rats (Quadari *et al*, 1984 ; Jacobson, 1986 ; Narayanan *et al.*, 1993). Furthermore, the subacute effects of neem oil (25 and 50 mg/kg), administered daily for 8 days to adult male rats, caused significant decrease in sperm counts, epididymal weight, and biochemical and marked structural changes in the testes (Manoranjitham *et al.*, 1993 ; Sampathraj *et al.*, 1993).

Because of the wide scale of use of neem-based insecticide, Neemix-4.5, in agriculture, vulnerable groups such as pregnant women may be exposed continuously to it. Hence, the present study has been conducted to assess the embryo/ fetotoxic and teratogenic potential of this commercial neem-based insecticide.

Materials and Methods

Inbred normal SWR/J male and female mice, 8-10 weeks old and weighing 29.7-37.3 g, were used throughout this study. Animals were kept and bred in an environmentally controlled room with a temperature of 22±1 °C, a relative humidity of 45±5 % and a light/dark cycle of 10/14 h. Mouse food (Commercially available in Saudi Arabia) and water were offered *ad libitum*.

In each box, 4-5 females were caged together with a single male. The females were examined each morning for the presence of a vaginal plug; the day the plug was detected was considered as day0 of gestation and the pregnant females were placed in separate cages. A total of 189 pregnant females were used, and were divided into 26 groups as follow:

a-Effect of azadirachtin (of neemix-4.5) on embryos and fetuses of the first pregnancy:

On days 7-12 of pregnancy, females of groups 1-5, (10 females in each group), were treated orally once daily with 0.9, 1.8, 3.0, 9.0 or 45.0 mg/kg (1/100 LD_{50}, 1/50 LD_{50}, 1/30 LD_{50}, 1/10 LD_{50}, or 1/2 LD_{50}, respectively) of azadirachtin of neemix-4.5 (Thermo Trilogy Corp., USA) dissolved in sterile dist. water. Control mice (group 6) were similarly treated with the corresponding volumes of the vehicle alone, and the dams were kept under daily observations. On day 17 of gestation, the pregnant females were killed by cervical dislocation and the numbers of alive, dead fetuses and resorption sites were recorded. Each fetus was then examined macroscopically for gross developmental abnormalities. Five to ten fetuses from each group were then cleared and stained according to a modification of the method of McLeod (1980) for skeletal examination.

b-Effect of azadirachtin on the pups of the first pregnancy:

On days 7-12 of gestation, females of groups 7-11, (10 females in each group), were treated orally once daily with the same dose levels mentioned of azadirachtin. Control mice (group 12) were similarly treated as mentioned before and the dams were kept under daily observations. Dams of these groups (7-12) were allowed to give birth. At parturition, the numbers of alive and dead pups were recorded, weighed and then examined macroscopically for gross abnormalities. Numbers and weight of these pups were also recorded every week for the first ten weeks of their postnatal lives.

c-Effect of azadirachtin on the pups of the second pregnancy:

On days 7-12 of the first gestation, females of groups 13-17, 5 females in each group, were treated orally once daily with the same dose levels mentioned of azadirachtin. Control mice (group 18) were similarly treated and the dams of there groups (13-18) were kept under daily observations and were allowed to give birth. Two weeks after their parturition, the dams recaged with fertile males, examined for vaginal plug and pregnant ones kept in separate cages and kept under daily observations until they gave birth. At parturition, the numbers of alive and dead pups were recorded, weighed and examined macroscopically for gross abnormalities. Numbers and weight of these pups were

also recorded every week for the first five weeks of their postanatal lives.

d-Effect of azadirachtin on the pups of the second generation (F_2):

On days 7-12 of the pregnancy, females of groups 19-23, 5 females in each group, were similarly treated as groups 7-18. Control mice (group 24) were also similarly treated. The pregnant females were kept under daily observation until they gave birth. Their offspring (F_1) were kept until they reached the age of 8 weeks and then caged with their brothers, 4-5 females with a single male, examined for vaginal plug, and pregnant females were placed in separate cages and kept under daily observation. At parturition, the numbers of alive and dead pups were recorded, weighed and then examined as mentioned. Number and weight of these pups were also recorded every week for the first five weeks of their postnatal lives.

e-Long-term effect of azadirachtin on the pups of a 80-day treated male and female mice:

Four females and three males (of group 25) were treated orally once daily with 9 mg/kg (1/10 LD_{50}) of azadirachtin of neemix-4.5 for 80 days. Then, those treated females were recaged with the treated males (2 females with a single male) and examined for the vaginal plug. The pregnant females were kept under daily observation until they gave birth. The control animals (group 25) were similarly treated with vehicle alone and pregnant females were kept under daily observation. At parturition, the numbers of alive and dead pups were recorded, weighed and then examined as mentioned. Number and weight of these pups were also recorded every week for the first five weeks of their postnatal lives.

The data obtained were statistically analysed using a student's t-test and a 2x2 contingency table (X^2) for the actual numbers obtained (Sokal and Rohlf, 1981).

Results

None of the dams treated with azadirachtin (of neemix-4.5) at any of the dose levels used in the present study died during the experimental period and all treated dams failed to reveal overt signs of maternal toxicity.

Data in Table 1 show that there is no significant ($p>0.05$) effect on the mean number of fetuses, mean number of alive fetuses, proportions of resorption, mean alive fetal body weight or on the mean placental weight at any of the dose levels used of azadirachtin. Moreover, azadirachtin at the dose levels used did not induce any malformations in any of those fetuses.

No significant ($p>0.05$) effect was observed on the number of alive pups, mean number of alive pups, percent of total mortality or on the mean body weight of pups obtained from the first or second pregnancy (F_1), of treated dams, at birth and at the first ten weeks of their lives postnatally at any of the dose levels used of azadirachtin. Furthermore, no malformations of any type were observed in any of those pups (Tables 2-5).

Data in Tables 6-7 also show that there is no significant ($p>0.05$) effect on the number of alive pups, mean number of alive pups, percent of total mortality or on the mean body weight of pups obtained from the second generation (F_2), of treated dams, at birth and at the first five weeks of their lives postnatally. Moreover, no malformations were observed in any of those pups at any of the dose levels used of azadirachtin.

No significant ($p>0.05$) long-term effect was observed on the number of alive pups, percent of total mortality or on the mean body weight of pups obtained from the first pregnancy (F_1), of 80-day treated dams and sires, at birth and at the first five weeks of their lives postnatally at the dose level (9 mg/kg) of azadirachtin. However, the mean number of these alive pups was significantly ($p<0.05$) decreased at birth only, but no malformations were observed in such pups (table 8, 9).

Table 1 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the fetuses of the first pregnancy.

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of implantation sites	No. of fetuses/dam (Mean ±SE)	No. of alive fetuses/dam (Mean±SE)	Total no. of resorptions (%)	Alive fetal body wt. in g. (Mean±SE)	Placental wt. in g. (Mean±SE)	Abnormalities Observed
Control	10	122	12.20 ± 0.74	11.70 ± 0.72	5 (4.10)	0.88 ± 0.03	0.124 ± 0.003	None
0.9	10	111	11.10 ± 0.43	10.60 ± 0.45	5 (4.51)	0.93 ± 0.02	0.124 ± 0.003	None
1.8	10	115	11.50 ± 0.40	11.10 ±0.42	4 (3.48)	0.88 ± 0.02	0.126 ± 0.004	None
3.0	10	133	11.30 ± 0.85	10.80 ± 0.51	5 (4.42)	0.86 ± 0.06	0.122 ± 0.004	None
9.0	10	113	11.30 ± 0.61	11.10 ± 0.54	3 (2.65)	0.85 ±0.03	0.121 ± 0.002	None
45.0	10	114	11.40 ± 0.70	10.70 ± 0.87	7 (6.14)	0.83 ± 0.04	0.130 ± 0.006	None

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 2 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the mortality rate of offsprings (first gestation/F_1).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive pups at (% mortality)						Overall % mortaliry at 10 weeks
		birth	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	
Control	10	103 (3.74)	93 (9.71)	88 (5.38)	86 (2.27)	86 (0.00)	86 (0.00)	16.51
0.9	10	97 (3.00)	89 (8.25)	85 (8.25)	85 (0.00)	85 (0.00)	85 (0.00)	12.37
1.8	10	99 (3.88)	87 (12.12)	85 (2.30)	85 (0.00)	84 (1.18)	84 (0.00)	15.15
3.0	10	98 (4.85)	93 (5.10)	89 (4.30)	89 (0.00)	88 (1.12)	88 (0.00)	10.20
9.0	10	100 (6.54)	87 (13.00)	85 (2.30)	83 (2.41)	83 (0.00)	83 (0.00)	17.00
45.0	10	102 (8.93)	95 (6.86)	93 (3.11)	92 (1.08)	90 (2.17)	90 (0.00)	11.76

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 3 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the body weight and congenital malformations of offsprings (first gestation/F_1).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive newborn pups	No. of newborn pups/litter (Mean ±SE)	Alive pup's body weight in g (Mean ± SE)						Abnormalities Observed
				Birth	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	
Control	10	103	10.30 ± 0.34	1.50±0.02	7.13±0.33	16.80±0.58	26.39±0.39	30.69±0.53	34.81±0.35	None
0.9	10	97	9.70 ± 0.56	1.48±0.03	7.20±0.34	17.32±0.32	28.36±0.36	30.75±0.35	34.61±0.30	None
1.8	10	99	9.90 ± 0.57	1.53±0.03	6.85±0.30	17.74±0.48	27.33±0.42	30.85±0.29	34.65±0.36	None
3.0	10	98	9.80 ± 0.70	1.54±0.04	6.97±0.15	16.95±0.38	26.87±0.64	30.88±0.54	35.39±0.47	None
9.0	10	100	10.00 ± 0.25	1.46±0.08	6.93±0.44	16.15±0.89	26.19±0.77	29.83±0.51	35.11±0.32	None
45.0	10	102	10.20 ± 0.81	1.49±0.03	6.97±0.43	16.18±0.47	25.89±0.58	31.03±0.52	35.23±0.36	None

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 4 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the mortality rate of offsprings (second pregnancy/F_1).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive pups at (% mortality)						Overall % mortality at 5 weeks
		Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	60 (3.23)	59 (1.67)	57 (3.39)	57 (0.00)	57 (0.00)	57 (0.00)	5.00
0.9	5	60 (3.23)	58 (3.33)	58 (0.00)	58 (0.00)	58 (0.00)	56 (3.45)	6.67
1.8	5	56 (3.57)	55 (1.79)	55 (0.00)	54 (1.82)	53 (1.85)	53 (0.00)	5.36
3.0	5	60 (1.64)	59 (1.67)	57 (3.39)	57 (0.00)	55 (3.51)	55 (0.00)	8.33
9.0	5	56 (5.09)	56 (0.00)	54 (3.57)	54 (0.00)	54 (0.00)	54 (0.00)	3.57
45.0	5	54 (10.00)	52 (3.70)	52 (0.00)	52 (0.00)	51 (1.92)	50 (1.96)	7.41

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 5 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the body weight and congenital malformations of offsprings (second pregnancy/F_1).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive newborn pups	No. of newborn pups/litter (Mean ±SE)	Alive pups' body weight in g (Mean ± SE)						Abnormalities Observed
				Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	60	12.00±0.32	1.61±0.03	3.97±0.11	7.54±0.36	11.64±0.31	18.78±0.35	25.90±0.52	None
0.9	5	60	12.00±0.55	1.63±0.04	3.98±0.08	7.18±0.21	11.81±0.12	17.96±0.14	25.23±0.23	None
1.8	5	56	11.20±0.58	1.59±0.04	3.93±0.12	7.37±0.39	11.65±0.60	18.25±0.30	24.78±0.22	None
3.0	5	60	12.00±0.71	1.57±0.03	4.10±0.06	7.01±0.31	11.03±0.28	19.06±0.12	25.32±0.32	None
9.0	5	56	11.20±0.37	1.55±0.03	3.90±0.08	7.18±0.30	11.62±0.24	17.35±0.49	24.89±0.16	None
45.0	5	54	10.80±0.58	1.62±0.04	4.03±0.07	7.09±0.32	11.34±0.55	18.51±0.46	24.79±0.29	None

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 6 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the mortality rate of offsprings (second generation/F_2).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive pups at (% mortality)						Overall % mortality at 5 weeks
		Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	61 (1.62)	60 (1.64)	59 (1.67)	59 (0.00)	59 (0.00)	59 (0.00)	3.28
0.9	5	57 (3.39)	56 (1.75)	56 (0.00)	56 (0.00)	56 (0.00)	56 (0.00)	1.75
1.8	5	57 (0.00)	55 (3.51)	55 (0.00)	55 (0.00)	55 (0.00)	55 (0.00)	3.51
3.0	5	59 (0.00)	58 (1.69)	57 (1.72)	57 (0.00)	56 (1.76)	55 (1.79)	6.78
9.0	5	59 (1.67)	57 (3.39)	57 (0.00)	57 (0.00)	57 (0.00)	57 (0.00)	3.39
45.0	5	58 (3.33)	56 (3.45)	56 (0.00)	55 (1.79)	55 (0.00)	54 (1.82)	6.90

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 7 : Effect of various dose levels of azadirachtin (of neemix-4.5) applied into pregnant SWR/J mice on days 7-12 of gestation on the body weight and congenital malformations of offsprings (second generation /F_2).

Azadirachtin dose used* (mg/kg)	No. of dams used	No. of alive newborn pups	No. of newborn pups/litter (Mean ±SE)	Alive pups' body weight in g (Mean ± SE)						Abnormalities Observed
				Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	61	12.20±0.20	1.53±0.04	3.96±0.06	8.62±0.25	12.71±0.42	19.59±0.26	25.50±0.21	None
0.9	5	57	11.40±0.40	1.54±0.02	3.91±0.08	7.93±0.15	11.86±0.13	18.78±0.22	25.62±0.21	None
1.8	5	57	11.40±0.25	1.52±0.02	4.22±0.11	7.84±0.15	11.89±0.22	18.51±0.51	25.19±0.22	None
3.0	5	59	11.80±0.20	1.53±0.03	4.05±0.15	7.93±0.26	11.94±0.27	18.58±0.49	24.97±0.08	None
9.0	5	59	11.80±0.37	1.55±0.02	4.02±0.07	8.14±0.24	11.81±0.13	18.41±0.39	25.18±0.09	None
45.0	5	58	11.60±0.25	1.51±0.03	3.94±0.13	7.92±0.28	11.76±0.26	18.60±0.46	25.24±0.31	None

* 0.9 mg/kg = 1/100 LD_{50} , 1.8 mg/kg = 1/50 LD_{50} , 3.0 mg/kg = 1/30 LD_{50} , 9.0 mg/kg = 1/10 LD_{50} , 45.0 mg/kg = 1/2 LD_{50} .

Table 8 : Effect of the dose level 9 mg/kg of azadirachtin (of neemix-4.5) applied into male and female SWR/J mice for 80 days on the mortality rate of offsprings.

Group	No. of dams used	No. of alive pups at (% mortality)						Overall % mortality at 5 weeks
		Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	59 (3.28)	58 (1.69)	58 (0.00)	58 (0.00)	57 (1.72)	57 (0.00)	3.39
Treated	4	41 (12.77)	38 (7.32)	38 (0.00)	38 (0.00)	38 (0.00)	38 (0.00)	7.32

Table 9 : Effect of the dose level 9 mg/kg of azadirachtin (of neemix-4.5) applied into male and female SWR/J mice for 80 days on the body weight and congenital malformation of offsprings.

Group	No. of dams used	No. of alive newborn pups	No. of alive newborn pups/litter (Mean ±SE)	Alive pups' body weight in g (Mean ± SE)						Abnormalities Observed
				Birth	One week	2 weeks	3 weeks	4 weeks	5 weeks	
Control	5	59	11.80 ± 0.37	1.59±0.02	3.95±0.07	7.39±0.23	11.65±0.20	18.40±0.31	25.59±0.71	None
Treated	4	41	10.25 ± 0.43*	1.58 ± 0.03	3.89±0.09	7.42±0.20	11.59±0.14	18.37±0.23	25.08±0.22	None

* Differences are statistically significant from the control group at $p<0.05$.

Discussion

Evaluation of a fetotoxicity/teratogenicity hazards is an initial determination of approximate safety factor and assessment of a no-observed-teratogenic-effect dose level (Wang, 1988 ; Srivastava and Raizada, 2001). Hence, the present study was conducted to evaluate the toxic and tertogenic short-and long-term effects of different dose levels (0.90, 1.80, 3.0, 9.0 and 45.0 mg/kg, which represent the 1/100, 1/50, 1/30, 1/10 and 1/2 LD_{50}, respectively) of azadirachtin of neemix-4.5 on fetuses and pups of pregnant SWR/Jmice.

The oral administration of various dose levels mentioned of azadirachtin of neemix-4.5 on days 7-12 or an 80-day period has not produced any morphological and skeletal changes in fetuses and pups of SWR/J mice. Similar results have been obtained using azadirachtin technical 12 % (at 500, 1000 and 1500 mg/kg/day azadirachtin on gestation days 6-15) throughout major organogenesis in rats (Srivastava and Raizada, 2001). Moreover, the toxicological evaluation of debitterized neem oil by multigeneration breeding studies did not produce any adverse effects on reproductive performance or histopathological analysis (Chinnasamy *et al.*, 1993). Furthermore, a 90-day subchronic toxicity study of azadirachtin in rats also failed to show any adverse effects, as evidenced by organs to body weight ratio, clinical enzyme assay, histopathological and hematological parameters (Raizada *et al.*, 2001). In addition, Stewart (1998) reported that administration of NeemAzal at dose levels 50, 225 and 1000 mg/kg during days 6-19 of pregnancy in rats have no obvious adverse effect on embryo-fetal survival or development.

Fetotoxic/ teratogenic effects are manifested by the presence of increased resorption, skeletal malformations and loss in fetal body weight (Srivastava and Raziada, 2001). In the present study, azadirachtin of neemix-4.5 at the tested dose levels did not induce fetal or pup death or malformation as compared with those of the control groups.

Transfer and compartmentalization of the chemical from the mother to fetus through the placenta is an important factor for determining fetal resorption (Nau and Scott, 1985). The placental transfer is significantly moderated by free drug characteristics (e.g. lipid solubility, degree of ionization and molecular weight) and placental properties (such as maternal and fetal blood flow, drug metabolism and placental age) (Srivastava and Raizada, 2001). It is evident that chemicals with a molecular weight less than 600 may readily transfer through the placenta (Mirkin, 1973). Azadirachtin has a molecular weight of 720.7 which may reduce placental transfer to some extent. Moreover, the cumulative chemical exposure of the fetus is more important than the rate of chemical transfer across the placent (Eriksson *et al.*, 1973). As the pharmacokinetics of azadirachtin and its bioavailability to the fetus are unknown, the essentially negative results in the present study may be due either to lack of toxic potential or the lack of fetal exposure (Srivastava and Raizada, 2001). Further studies are needed to investigate the histopathological and biochemical changes in foetal and maternal mammals treated with AZ to examine the safety of the insecticide.

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التأثيرات السمية والتشويهية لأزاديراكتين النيمكس - 4.5 على أجنة وولائد فئران السلالة SWR/J

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استخدمت في هذه الدراسة فئران مختبرية صادقة التوالد ناضجة جنسياً من سلالة SWR/J لتقييم التأثيرات السمية والتشويهية قصيرة وطويلة المدى لجرعات مختلفة من مادة أزاديراكتين النيمكس - 4.5 المستخرجة من شجر النيم والتى تستخدم كمبيد حشرى (0.9 ، 1.8 ، 3.0 ، 9.0 أو45.0 مجم/كجم والتي تمثل 100/1 ، 50/1 ، 30/1 ، 10/1 ، 2/1 من الـ LD_{50} ، على الترتيب) على أجنة وولائد الإناث الحوامل .

لم تؤدِ المعاملة عن طريق الفم وبالجرعات المستخدمة من الأزاديراكتين خلال أيام الحمل 7-12 أو خلال فترة 80 يوماً إلى إنتاج أية تغيرات شكلية أو هيكلية في أجنة أو ولائد إناث السلالة SWR/J من الفئران المختبرية . وحيث إن تأثير الأزاديراكتين وتوفره الحيوي حول الأجنة خلال الحمل غير معروفة ، فإن النتيجة السلبية المتحصل عليها في هذه الدراسة قد تعود إما إلى فقدان الأزاديراكتين للقدرة السمية والتشويهية أو إلى عدم تعرض الأجنة لهذا المركب خلال الحمل لعدم قدرة الأزاديراكتين على عبور المشيمة وتوفره الحيوي والمؤثر.

مما سبق يتضح عدم تأثير هذه المادة على الأجنة عند تناول أمهاتها للجرعات السابقة مما يؤشر الى امكانية استخدام هذه المادة كمبيد حشرى أكثر أماناً ولذا يوصى بإستكمال بعض الدراسات الخاصة بالديناميكية الدوائية لهذا المركب داخل الخلية حتى يمكن الجزم باستخدامة بأمان كمبيد حشرى.