

## TERATOGENIC EFFECTS OF CARBOSULFAN IN FEMALE ALBINO RATS

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### ABSTRACT

Teratogenic effects of carbosulfan in albino female rats (*Rattus rattus*) during organogenesis period (from the 6<sup>th</sup> to 15<sup>th</sup> day of gestation) was investigated. Three doses 18.5, 9.25 and 4.63 mg/kg b.wt. corresponding to 1/10, 1/20, 1/40 of the LD<sub>50</sub>, respectively, were used. The morphological changes revealed that, the alive foetus per dam was decreased with selected doses, while the percent post-implantation death, percent of implantation loss and the number of dead fetuses per dam were increased at the tested doses. Also, the mean foetal weights, the mean foetal crown-rump length and the mean weight of placenta were reduced markedly. However, visceral examination of viable fetuses showed dilated renal pelvis, distended urinary bladder with urine, cleft palate, dilation of lateral ventricles and cerebral hemispheres (a symmetric). The most common skeletal malformations were wavy and shorting ribs, reduce or absence of sternbrae and absence of digits of fore- and hind-limbs and some coccygeal vertebrae. Also, cranial bone absent (skull incomplete ossification) was observed.

### INTRODUCTION

The spread use of pesticides is usually connected with serious problems of pollution and health hazards. Male and female reproductive toxicity, fetotoxicity and teratogenicity are of special concern. Owing to pesticides methods of application as sprays, accidental and/or prolonged exposure to these agrochemical cause great public health concern and economic losses. Unfortunately, very little is known about the possible adverse long-term effects of chronic exposure to these chemicals on male fertility and their teratogenic effect in animals and human.

The present investigation was initiated to study the teratogenic effects of carbosulfan as carbamate insecticide. Experiments were carried out on adult female pregnant rats as highly selected experimental animal model to perform such studies.

### MATERIALS AND METHODS

#### 1- Insecticides used :

Carbosulfan (Marshal) 25 % WP [2, 3-dihydro-2,2-dimethyl benzofuran-7-yl (dibutyl amino)thio] methyl carbamate]. This compound introduced by FMC, Rhone-Pollence (U.S.A.).

#### 2- Experimental animals :

Sexually mature female albino rats were obtained from the Organization of Biological and Vaccine (Helwan farm). The mature animals

having an average  $170 \pm 10$  gm body weight (2.5-3 months old) were periodically examined. The females were kept in hygienic conditions and introduced into the metallic cages for one month before being used and the food (23 % protein) and mated *ad libitum*.

### 3- Experimental procedure :

The acute oral toxicity [median lethal dose, ( $LD_{50}$ )] of tested compound to female albino rats was calculated according to Weil (1952). The remained females were paired with untreated males (1 male : 2 female) of proven fertility in a separate cage, usually in the early afternoon. In the next morning, a vaginal smear was stained with methylene blue (1 %) to verify first day of pregnancy. The female was considered mated when sperms plus cornified cells and leucocytes were found in the vaginal smears or vaginal plugs was detected, and that day is designed (zero-time) of pregnancy (Manson and Kang, 1989). In addition, the body weight was recorded daily for pregnant females which were proved to be in continuous oestrus and showed increased body weight:

At the 5<sup>th</sup> day of pregnancy, females were divided into four equal experimental groups of 10 females each and treated as follows :

Group A : was orally administered 0.5 ml distilled water without any insecticidal treatment as control (untreated control).

Groups B, C, D : were given carbosulfan at the dosage levels of 18.5, 9.25 and 4.63 mg/kg b.wt. (1/10, 1/20, 1/40  $LD_{50}$ ), respectively.

The tested materials were daily given by gavage from the 6<sup>th</sup> to 15<sup>th</sup> day of gestation period. This period (6<sup>th</sup> - 15<sup>th</sup>) was considered the time of maximum organogenesis. Both control (group A) and dosed pregnant females were kept under observation until the 20<sup>th</sup> day of gestation at which they were weighed, sacrificed, and dissected to investigate the effect of tested substance on the foetal development (morphological, visceral, and skeletal examination). The uterus was examined morphologically to estimate the resorption sites (Kople and Salewski, 1964). Foetuses were collected from each dam.

The method of Manson and Kang (1989) was used for morphological examinations. The evaluation of skeletal abnormalities was performed after clearing by using 95 % ethyl alcohol with potassium hydroxide and staining the skeleton by Mallsch's solution with alizarin red S stain (Staples and Schnell, 1964). For the visceral examination, the foetuses were preserved in Bouin's fixative and sectioned by free hand razor using the technique described by Wilson (1965).

Skeletal and visceral malformation of each fetuses were recorded as explained by Cook and Fairweather (1968) and Manson and Kang (1989).

### 4- Statistical analysis :

Statistical significance between experimental and control values were calculated according to Dixon and Massay (1957). A difference was considered statistically significant at  $P < 0.05$ .

## RESULTS AND DISCUSSION

The teratogenic effects of carbamate insecticide (carbosulfan) was investigated in pregnant rats as a mammalian system and hence, to other domestic animals exposed accidentally to this compound. The teratogenic effect was assessed by morphological, visceral and skeletal malformations of the obtained fetuses after oral administration of the pregnant dams at dose levels of 18.5, 9.25 and 4.64 mg/kg b.wt. of carbosulfan from the 6<sup>th</sup> to 15<sup>th</sup> day of gestation.

### 1- Acute oral toxicity (LD<sub>50</sub>) of tested compound :

The median lethal dose (LD<sub>50</sub>) of experimental substance to female albino rats was 185 mg/kg b.wt. (Weil, 1952).

### 2- Morphological changes of the uterus and foetuses :

The external examination of the uterus and foetuses of female rats treated with carbosulfan are obtained in Table (1). Results of the present investigation revealed that, oral administration of carbosulfan during organogenesis period (from 6<sup>th</sup> to 15<sup>th</sup> day of gestation), resulted in no significant differences in all parameters; while, an increase in the number of corpora lutea per dam, number of implantation sites per dam, number of dead fetuses/dam, number of resorption sites (early or late), percent pre-implantation loss/dam and percent post-implantation death/dam was observed. Contrast of these findings, the number of implantation sites/litter, number of corpora lutea/litter, number of alive fetuses/dam or litter, the mean fetal weight and the mean fetal crown-rump length (Plate, 1) were decreased. Moreover, the mean weight of placenta was increased at the lowest dose of carbosulfan.

Also, external examination revealed that, fetuses had oedematous foot and large subcutaneous haematous in several offspring of carbosulfan treated rats.

Such findings are incoincidence with the results of Soni and Bhatnager (1989), Hemeida *et al.* (1989) and Hasan *et al.* (1990).

Soni and Bhatnager (1989) reported that, the higher dose of phosphamidon (35 ppm) reduced the number of implantations and fetal weight. Also, Hemeida *et al.* (1989) mentioned that, oral administration of trichlorfon to pregnant female rats resulted in foetal resorption, growth retardation and death. Hasan *et al.* (1990) observed that treatment with methomyl from the 6<sup>th</sup> to 15<sup>th</sup> day of gestation caused early resorption of foetuses and decreased their weights.

Table (1) : Effect of treatment with different concentrations of carbosulfan (Marshal) on external morphological of uterus and fetuses in pregnant rats.

Parameters	Treatments (mg/kg b.wt.)			
	Control	18.5	9.25	4.63
No. of corpora lutea per dam	7.5000±0.6368	8.3000±0.4230	8.4000±0.5207	8.4000±0.6532
No. of implantation sites per dam	7.4000±0.6360	8.1000±0.4333	8.2000±0.4899	3.2000±0.6289
No. of corpora lutea per litter	1.4685±0.3938	1.3460±0.1215	1.0680±0.0435	1.1450±0.0603
No. of implantation sites per litter	1.4685±0.3938	1.3100±0.1157	1.0390±0.0200	1.1160±0.0514
No. of dead fetuses per dam	0.1000±0.0999	0.6000±0.3999	1.3000±0.7157	2.1000±0.9244
No. of alive fetuses per dam	6.5000±0.8724	5.9000±0.7250	6.5000±1.1571	5.4000±0.7180
No. of alive fetuses per litter	0.9000±0.0999	0.9000±0.0667	0.7760±0.1303	0.7580±0.2397
No. of resorption sites-early	0.1000±0.0999	0.7000±0.4230	0.0000±0.0000	0.2000±0.2000
No. of resorption sites-late	0.4000±0.1633	0.9000±0.1795	0.5000±0.2236	0.5000±0.2680
% pre implantation loss per dam	1.0000±0.0000	1.5150±0.3436	1.3580±0.3580	1.3580±0.3580
% post implantation death per dam	3.0350±0.9116	5.1150±0.7274	4.1100±1.0593	4.8240±0.9740
Sex ratio	0.9830±0.2257	1.4330±0.4218	0.8130 ±0.2164	1.5830±0.6117
Mean foetal weight (gm)	3.8900±0.2310	3.6320±0.2594	3.2820±0.1487	3.4170±0.08134
Mean foetal crown rump length (cm)	3.4000±0.0650	3.3600±0.0897	3.1700±0.0517	3.3100±0.0433
Mean weight of placenta (gm)	0.4660±0.0191	0.4570±0.0330	0.4274±0.0135	0.4750±0.0221

Sherif (1991) mentioned that, an increase of the mean neonatal death and percentage of resorbed fetuses in Tamaron-treated rats (methimidaphos) was observed. While, the foetal weight and length were decreased. Mathur and Bhatnager (1991) noticed that, carbaryl tend to reduce litter size, increase the percentage of resorbed fetuses and to reduce fetal weight in female mice treated with the tested compound on day 8 or day 12 of pregnancy, or daily (as daily doses) from 6th-15th day of gestation.

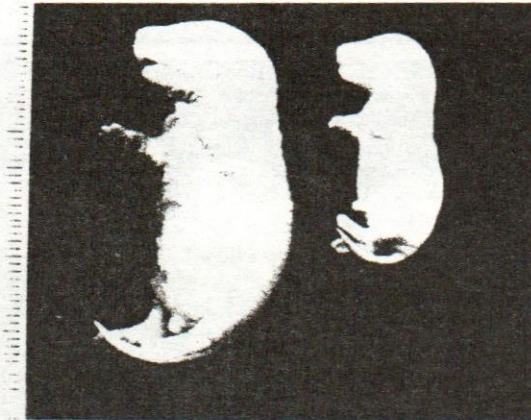
Similar results were also reported by Abd El-Khalik *et al* (1993), Junaid *et al* (1995) and Farid (1997).

Abd El-Khalik *et al.* (1993) who showed that, early embryonic death, retardation of growth and increase the incidence of placenta weight were occurred in deltamethrin-treated female rats from 6th-15th day of gestation. Junaid *et al.* (1995) stated that, a decrease in fetal weight and crown-rump length was observed on chromium-treated female (through drinking water), on days 14-19 of pregnancy. Also, a significantly higher incidence of post-implantation loss was observed. Farid (1997) recorded that, buprofezin and diafenthuron caused decrease in the number of alive fetuses per dam, a

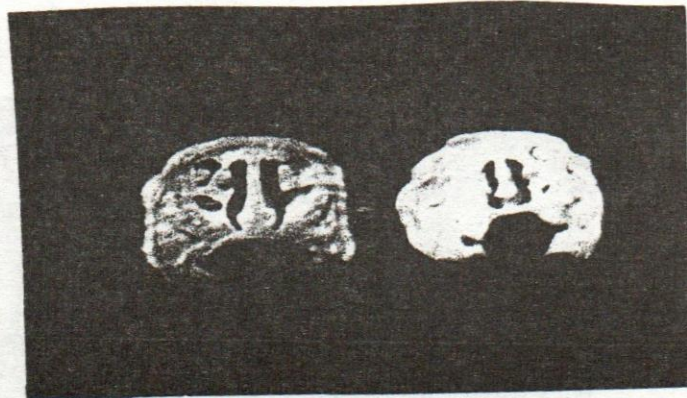
marked reduction in the mean of foetal weight and the mean of fetal crown-rump length and the mean weight of placenta during the organogenesis period, in pregnant rats.

**3- Visceral examination :**

Regarding visceral abnormalities induced by the oral administration of 18.5, 9.25 and 4.63 mg/kg b.wt. of carbosulfan, cross section in the head of foetuses obtained from treated dams showed cleft palate (Plate, 2), microcephalic, dilation of lateral ventricles and asymmetric cerebral hemispheres (Plate, 3).



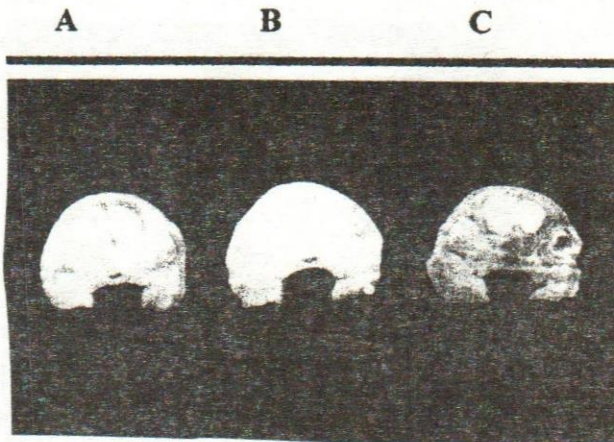
**Plate (1) : Showing retardation in growth of rat foetuses obtained from dams given orally carbosulfan (control on the left).**



**Plate (2) : Cross section in the head of rat foetuses showing cleft palate in head of rat foetuses obtained from dams treated with carbosulfan (control on the left)**

Table (2) show the visceral examination of living foetuses obtained from female rats given carbosulfan at doses 18.5, 9.25 and 4.63 mg/kg b.wt., the most prominent anomalies were dilated renal pelvis with 10.2, 9.6 and 4.8 % at the investigated doses, respectively. The urinary bladder was abnormality, distended with urine (8.2, 3.8 and 2.4 %) at tested doses respectively, (Plate, 4). Also, dilated ureter (hydroureter) was observed (10.2, 5.8 and 4.8 %) at the experimental doses (Plate, 4).

Also, oral administration of carbosulfan to pregnant rats from 6th-15th day of gestation showed hypoplasia of heart and lung, liver and kidney, split of thymus and hydronephrosis.



**Plate (3) : Cross section in the head of rat foetus showing hypoplasia of brain, cerebral hemispheres were unequal size (asymmetric) after oral administration of carbosulfan to the dams from 6th to 15th day of gestation.**

**A- Control, B & C = Treated.**



**Plate (4) : Showing distention of the urinary bladder with urine and dilated ureter (Hydroureter) after oral administration of carbosulfan to dams (control on the left).**

Table ( 2 ) : Visceral examination of rat fetuses from dam given orally carbosulfan from the 6th to 15th day of gestation as compared to the control group .

Dose ( mg/kg b.wt. )	Malformation of																										
	Head												Thorax						Abdomen								
	Cleft palate		Microcephalic		Dilation of lateral ventricles		Cerebral hemispheres (asymmetric)		Hyoplasia of heart		Split of thymus		Hypoplasia of lung		Hypoplasia of liver		Hypoplasia of kidney		Hydronephrosis		Dilated renal pelvis		Hydro-ureter		Distend urinary bladder		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
18.50	49	14	28.6	3	6.1	15	30.6	20	40.8	7	14.3	3	6.1	12	24.5	13	26.5	11	22.1	2	4.1	5	10.2	5	10.2	4	8.2
9.25	52	8	15.4	2	3.8	9	17.3	12	23.1	6	11.5	3	5.8	10	19.2	10	19.2	8	15.4	2	3.8	5	9.6	3	5.8	2	3.8
4.63	42	3	7.1	1	2.4	5	11.9	7	16.7	4	9.5	0	0.0	3	7.1	3	7.1	2	4.2	0	0.0	2	4.8	2	4.8	1	2.4
0.00	44	1	2.3	0	0.0	0	0.0	2	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	4.5	2	4.5	1	2.3

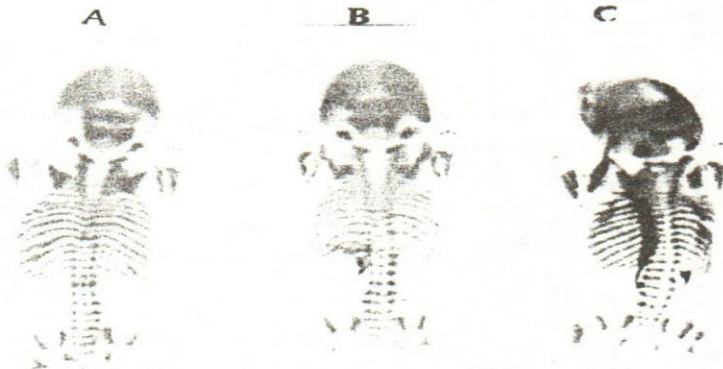
**4- Skeletal examination :**

The skeletal examination of the remaining third of rat fetuses obtained from dams given orally carbosulfan (18.5, 9.25 and 4.63 mg/kg b.wt.) are presented in Table (2). The most common abnormalities were incomplete ossification of the skull (cranial bone absent), 20.8, 23.1 and 19.2 %, at the three doses, respectively (Plate, 5).

Treatment of carbosulfan in pregnant rats induced wavy and shorting in ribs (Plate, 6). Reduced or absence of sternbrae were noticed (20.8, 19.2 and 11.5 %), at 18.5, 9.25 and 4.63 mg/kg b.wt., respectively (Plate, 7). Moreover, absence of xiphoides was observed in fetuses of treated pregnant rats. This carbamate insecticide induced malformations in the fore and hind limbs (e.g. absence of digits).



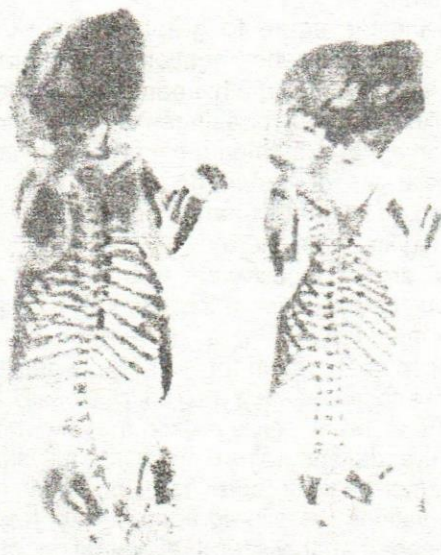
**Plate (5) : Showing incomplete ossification (cranial bone absent) descended from dams treated with carbosulfan (control in the left).**



**Plate (6) : Showing wavy and shorting ribs in rat fetuses obtained from dams given orally carbosulfan).**

**A = Control                      B & C = Treated**





**Plate (7) : Showing absence of sternbrae in rat fetuses obtained from dams treated orally with carbosulfan (control in the left).**

Regarding to the malformations in vertebrae (absent of some coccygeal vertebrae) were 37.5, 26.9 and 23.1 % at the tested doses respectively. Also, hypoplastic, split off center and missing of sternal centers were noticed. Extra ossification center between the 13<sup>th</sup> thoracic arches and the 1<sup>st</sup> lumber vertebrae was observed.

Several insecticides were shown to be highly teratogenic agents such as, trichlorfon on rats (Hemeida *et al.*, 1989), methomyl on rats (Hasan *et al.*, 1990), and Tamaron on rats (Sherif, 1991).

Hemeida *et al.* (1989) stated that, oral administration of trichlorfon to pregnant rats caused foetal abnormalities. The most common visceral abnormalities were represented by cleft palate, microcephaly, cardiac hyperplasia and hypoplasia. The skeletal abnormalities include shorting of some ribs, absence of sternbrae and absence of phalanges of fore- and hind limbs.

Hasan *et al.* (1990) found that the smallest dose of methomyl in pregnant rats resulted in hyperplasia of heart and liver, corrugation of some ribs and absence of sessamoid bones of fore- and hind limbs. Sherif (1991) observed great abnormalities in skull, ribs, limbs and vertebral column in treated rats with Tamaron.

The present findings agree to great extent with data obtained by Koemeil and Abd-Allah (1991) who mentioned that oral administration of pregnant albino mice with carbaryl, methyl-parathion and fenvalerate, resulted in extra-rib, unossified proximal phalanges of foot and middle phalanges of hand which observed at 250 mg/kg of carbaryl. In addition, cervical-rib, unossified distal phalanges of hand and middle phalanges of foot were observed at 24 mg/kg of methyl-parathion. Otherwise, cervical-rib was observed only at 200 mg/kg of fenvalerate.

Such results are in coincidence with the results of Mathur and Bhatnagar (1991) on carbaryl in mice, Abd El-Khalik *et al.* (1993) on deltamethrin in rats, and Eckhoff *et al.* (1994) on 13-cis-retinoic acid in rabbits. They mentioned that treatment with these pesticides increased the incidence of anomalous fetuses such as, reduced ossification, hypoplasia of the lungs and dilation of renal pelvis. Also, the most frequently observed malformations were eye defects (open eyes, micro- and exophthalmia), cardio megalia and haemorrhagic cerebral hemispheres in treated animals.

These observations were in agreement with description reported by Farid (1997) who reported that visceral examination of fetuses showed dilated renal pelvis and ureter and distended urinary bladder with urine. The most common skeletal malformations were wavy and shorting ribs, reduce or absence of sterna and absence digits of fore- and hind limbs.

Contrary to our results, are these previously reported by Abd El-Khalik (1993) who mentioned that no skeletal changes in fetuses recovered from deltamethrin-treated female rats were observed. Also, Srivastava and Riazada (1995) found that, there were no fetotoxicity/teratogenic effects of isoproturon (phenyl-urea, herbicide) at the tested dosage level. The tested material did not cause external, visceral and skeletal fetal observations.

The present study revealed that carbosulfan produced fetotoxicity among litters of treated rats which evidenced by decreased mean foetal weight, mean foetal crown-rump length and mean weight of placenta.

A number of large molecular potent teratogenic agents are thought to affect the fetuses by acting on placenta, thus interfering with embryo nutrition without being able to reach of fetuses because of their large molecules (Williams, 1982).

Sternberg (1979) mentioned that, the fetuses may react poorly to toxic substances absorbed in the maternal blood, in part, due to that foetal liver is poorly developed in terms of its detoxifying ability.

The placenta plays an important role for developing fetuses as it provides nutrition and hormonal regulation and transfers metabolic waste products. Accumulation of toxic compounds may alter placental function and impair embryonic and foetal development. The placenta may be directly involved in many instances of early spontaneous abortions, foetal death and intrauterine growth retardation (Faulk, 1981 and McIntyre & Faulk, 1983).

Harbison (1975) mentioned that embryo and fetuses are highly susceptible to cytotoxic agents, because they constantly have groups of cells in the growth phase. Acute toxic doses may cause cellular death and result in foetal death. Survivors may show symptoms damage to systems that contain cells in cycle and with a short cycle time.

The decrease in placenta weight associated with the decrease in fetal weight in carbosulfan-treated females rats was observed. This findings strongly suggest that the teratogenic effects of carbosulfan may be attributed, at least in part, to the effect of the compound on placenta. There is a risk to the development of foetus if the mother is exposed to high concentrations of the toxic agents during pregnancy, because this agent could penetrate the placental barrier and accumulate in the fetal tissue (Junaid *et al.*, 1995).

Finally, these findings may emphasize to the fact that sublethal doses of a given toxic agent might inflict toxic hazards and serious disorders on man and his domestic animals.

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التأثيرات التشوهية لمركب الكاربوسلفان على أجنة الفئران البيضاء  
رفعت مصطفى شريف<sup>١</sup> ، كمال عبد الرازق جوهر<sup>١</sup> ، محمد محمود فريد<sup>٢</sup> و  
احمد عبد الله غريب<sup>٢</sup>

١ - كلية الزراعة - جامعة الزقازيق - قسم وقاية النبات

٢ - المعمل المركزي للمبيدات - مركز البحوث الزراعية - الدقى الجيزة

تم دراسة تأثير مركب الكاربوسلفان على أجنة الفئران البيضاء - حيث أخذت عدد ٤٠  
من إناث الفئران البيضاء الحوامل و قسمت إلى أربعة مجموعات متساوية (كل مجموعة عشرة  
فئران)

- ١- المجموعة الأولى : اعتبرت كمجموعة ضابطة
  - ٢- المجموعة الثانية : عوملت بمركب الكاربوسلفان بالتركيز ٤,٦ مجم / كجم من وزن الجسم (و هي تعادل ٤٠/١ من LD50) و ذلك من اليوم السادس إلى اليوم الخامس عشر من الحمل (فترة تكوين الأعضاء) و ذلك عن طريق اللي المعدي .
  - ٣- المجموعة الثالثة : عوملت بالتركيز ٩,٣ مجم / كجم من وزن الجسم من المركب (و هي تعادل ٢٠/١ من LD50) و ذلك بنفس الطريقة.
  - ٤- المجموعة الرابعة : حيث عوملت بالتركيز ١٨,٥ مجم / كجم من وزن الجسم من نفس المركب (و هي تعادل ١٠/١ من LD50) وذلك بنفس الطريقة السابقة .
- في اليوم العشرين من الحمل تم استخراج الأجنة من أرحام إناث الفئران البيضاء الحوامل و كذلك تم فحص المبيض و الرحم حيث تم عد الأجسام الصفراء و الأجنة المدمصة ثم بعد ذلك أجريت الفحوصات المورفولوجية للأجنة من حيث التشوهات الخارجية  
ثم قسمت بعد ذلك الأجنة إلى قسمين (٣/٢ ، ٣/١) حيث أجرى فحص الأحشاء الداخلية ل  
٣/٢ أجنة الفئران أما ال ٣/١ الباقي فاجرى له فحص الهيكل العظمى .  
وقد أدت معاملة إناث الفئران البيضاء الحوامل بمركب الكاربوسلفان بكل من ٤٠/١ ، ٢٠/١ ،  
١٠/١ من الجرعة النصفية المميتة ( LD50 ) إلى

- ١- نقص عدد الأجنة الحية ، زيادة عدد الأجنة الميتة بعد الغرس و زيادة عدد الأجنة الميتة
- ٢- لوحظ نقص واضح في وزن و طول الأجنة بالإضافة إلى نقص وزن المشيمة
- ٣- عند فحص الأحشاء الداخلية للأجنة لوحظ اتساع كل من الحوض الكلوي و الحالب و عدم تماثل فصي المخ و حدث شق في سقف الحلق و امتلاء المثانة البولية بالماء
- ٤- و عند الفحص الهيكل العظمى لوحظ غياب بعض عظام الفحص ووجود تعاريج في الضلوع وحدث قصر في طول الضلوع