TERATOGENIC EFFECT OF TRIVALENT AND HEXAVALENT CHROMIUM COMPOUNDS IN RABBITS

BY

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ABSTRACT

Chromium is considered to be an essential element in the human body required for proper carbohydrate, protein, and fat metabolism. Previous studies indicate that hexavalent chromium (Cr-VI) is more toxic than trivalent chromium (Cr-III) as it is actively transported across the plasma membranes and is reduced via unstable reactive intermediate to Cr-III. Also, The published data indicate that exposure to Cr-VI decrease the number of viable fetuses and increase the number of dead ones. In the current investigation pregnant rabbits were exposed to Cr-III (chromium chloride) or Cr-VI (potassium dichromate) in drinking water at a dose of 500 ppm each during organogenesis on days 6 through 18 of gestation. Maternal and fetal parameters were evaluated on day 29 of gestation. Fetuses were weighed and examined for external, visceral and skeletal malformations. Exposure to Cr-VI significantly increased the number of resorption sites and decreased the number of viable fetuses compared to Cr-III and control groups. Exposure to either chemical induced dwarfism, kinky and short tails, lung hypoplasia, heart hypertrophy, intrathoracic hemorrhage and dilated nares and brain lateral ventricles. Furthermore, reduced ossification in parietal and interparietal bones was significantly increased in the fetuses from the females exposed to Cr-VI. Chromium levels in maternal blood, placenta and fetuses were significantly increased in treated groups compared to control group. The results of the present investigation may indicate that both Cr-III and Cr-VI are teratogenic for the tested concentration. However, the severity of effects is higher with the exposure to Cr-VI.

Keywords: Chromium, Teratogenicity, Rabbits

INTRODUCTION

Chromium, is an essential element for biological systems. There is growing interest in toxicological studies on chromium compounds because of their potential use in modern industries and the consequences of human exposure to these compounds (**Nriagu and Nieboer, 1988 and Bonde and Christensen, 1991**).

The toxic effects of chromium and its compounds have been reviewed recently (**Baruthio, 1992**). Occupational exposure to hexavalent chromium is of concern because of its mutagenic and carcinogenic actions (**Stern, 1981 and Langard, 1982**).

Chromium compounds are being used in ceramics, catalysts, pigments, metal finishing, corrosion control, tanning industry, wood preservatives, fungicides, printing and dyeing textiles and manufacturing magnetic tapes (**Nriagu, 1988**). The general population is also exposed to chromium as it contaminates surface and ground water, agricultural land and aquatic life (**Perlmutter and Lieber, 1970 and Handa *et al.*, 1985**).

High levels of chromium are reported to impair gestational development as evidenced by epidemiological studies in female workers exposed to this metal (**Shmitova, 1978**). Moreover, exposure to chromium (VI) resulted in complications during pregnancy and childbirth in the form of toxicosis and puerperal hemorrhages in women employees at a dichromate manufacturing factory (**Shmitova, 1980**). Parental administration of chromium to hamsters induced gestational impairment (**Gale, 1974; Gale and Bunch, 1979 and Gale, 1982**). However in mice chromium (VI) exposure in drinking water during various gestational periods resulted in embryo and fetotoxic effects (**Trivedi *et al.*, 1989 and Junaid *et al.*, 1996 a**).

Previous studies revealed developmental changes after oral exposure to chromium (VI) pregestationally in mice (**Junaid *et al.*, 1996 b**) and in rats (**Kanojia *et al.*, 1996**). However no study to date has been carried out to determine the teratogenic effect of chromium in rabbits. It is well known that the biochemical actions of chromium are dependent on its chemical form (**Baruthio, 1992**). Therefore, the present investigation was carried out to determine the effects of chromium compounds either trivalent (III) or hexavalent (VI) on embryo-fetal development in rabbits exposed via drinking water during the organogensis period of pregnancy. The

distribution of chromium either trivalent or hexavalent in maternal and feto-placental unit was also investigated.

MATERIAL AND METHODS

Adult New Zealand white female rabbits (3.5 - 4.0 kg body weight; 26-28 weeks old) were supplied from Faculty of Veterinary Medicine, Cairo University. They were mated with normal healthy adult males and the day of copulation was designed as zero day of gestation (**Gleich and Frohberg, 1977**). All animals were kept under good ventilation and standard hygienic conditions supplied with food and water ad libitum.

The pregnant females were randomly grouped into three equal groups of ten rabbits each. The first group was given drinking tap water and served as control. The second and third groups were given trivalent and hexavalent chromium compounds respectively, from day 6 to day 18 of gestation. Trivalent chromium (chromium chloride: Janssen Chimica, B-2441 Geel, Belgium) and hexavalent chromium (potassium dichromate: Fluka AG, chemicals Fabrik CH-9470, Bucks) were dissolved in drinking tap water, each at a concentration of 500 ppm. The dose of chromium was selected on the basis of previous studies in mice (**Junaid *et al.*, 1995 and 1996 b**) and in rats (**Saxena *et al.*, 1990 and Kanojia *et al.*, 1996**).

Teratological Examination:

All animals were observed daily for gross appearances and behavior. The mothers were sacrificed by slaughtering on day 29 of gestation. Care was used to avoid any physical trauma to the fetuses. Maternal blood samples were taken and kept at -20 °C for chromium estimation. Immediately after killing, the abdominal wall of the mothers was opened and the number of implantation sites and number of resorptions were determined as well as the number of dead and live fetuses. The living and dead fetuses were distinguished immediately by the appearance of a moving reflex after touching the fetus in the unopened uterus of the mother with a pair of tweezers. The fetuses were numbered beginning with the upper end of the left uterine horn and ending at the upper end of the right one (**Cock, Fairweather, 1968**).

Individual fetal weight with their respective placentae was recorded, and a gross examination for external fetal malformation was made macroscopically. Post-implantation loss

was calculated as described by **Palmer *et al.*, (1978)**. One fetus/litter with its placenta was kept at -20 °C for chromium estimation. One- third of the remaining fetuses was fixed in Bouin's solution for examining the visceral abnormalities using the free -hand razor blade sectioning method (**Wilson, 1965 and Barrow and Taylor, 1969**). The remainder of the fetuses from each group were fixed in 95% ethanol, eviscerated then cleared by 2 % potassium hydroxide and stained by Alizarin red S- stain solution (**Staples and Schnell, 1964**) for examining the skeletal deformities (**Kelsey, 1974**).

Chromium estimation:

Maternal blood, placentae and fetuses were digested in Nitric acid: perchloric acid (6:1) mixture until a white residue remained at the bottom of the flask. This residue was dissolved in 0.1 N Nitric acid and the chromium was estimated on Atomic Absorption (Unican 929 Atomic Absorption Spectrometer). Blank and chromium-spiked samples were run and analyzed simultaneously (**Berman, 1980 and NIOSH, 1987**).

Statistical analysis:

Data is presented as mean ± standard error of the mean. The litter was regarded as the experimental unit of comparison for all analysis, except were otherwise noted. Treatment effects on fetal and placental weight and external morphological examination were determined by one way analysis of variance (ANOVA). The Chi-square test was used for the comparison of the different gross, visceral and skeletal anomalies between the groups. The significance values were at $P < 0.05$.

RESULTS

No notable changes in behavior or clinical signs were observed in control or in treated dams. No mortality was observed during the experimental period.

Table (1) summarizes the embryotoxic effects of trivalent and hexavalent chromium compounds administered during the organogenesis period. The number of implants and live fetuses per dam were significantly reduced in both chromium treated groups in compared to the control group. The resorption sites (Fig. 1) and dead fetuses number per dam were found significantly increased in hexavalent treated group compared with trivalent and control groups.

Post-implantation loss was also significantly increased in trivalent and hexavalent chromium treated groups. However, the fetal and placental weights were significantly reduced in both treated groups compared to the control group.

Gross examination of the fetuses from trivalent and hexavalent groups revealed significant increases in stunted growth (Fig. 2), subdermal hemorrhagic patches and short and kinky tails (Table 2).

The incidence of visceral anomalies in fetuses of control and treated groups was demonstrated in Table (3). Trivalent and hexavalent chromium treatment significantly increased the total foetal visceral anomalies compared to the control. There visceral anomalies in treated groups were in the form of dilated brain lateral ventricles (hydrocephaly) (Fig. 3), dilated nares (Fig.4), olfactory pulp hypoplasia, thymas gland congestion, heart hypertrophy, lung hypoplasia, intrathoracic hemorrhage (Fig. 5), dilated renal pelvis, dilated ureter and adrenal gland congestion. The incidence of these anomalies was much higher in hexavalent than trivalent treated group.

There were significant skeletal anomalies observed in hexavalent treated group in the form of incomplete ossification of frontal, parietal, interparietal bones and sternbrae. In addition to a wide separation of parietal bones (Fig. 6), deformed ribs and absence of carpal and /or metacarpal bones. On the other hand, in both chromium treated groups there was significant increase in the incidence of reduced sternbrae number (Fig.7), absence of tarsal and /or metatarsal bones and incomplete ossification of caudal bones (Table 4).

Chromium levels were recorded significantly increased in the trivalent and hexavalent treated rabbits as evidenced by significantly higher chromium levels in maternal blood, placenta and fetuses (Table 5).

DISCUSSION

Chromium, an essential trace element, is found in nature in either trivalent or hexavalent forms. It has been documented to produce teratogenic effect on golden hamsters (**Gale, 1982**), rats (**Kanojia *et al.*, 1996**) and mice (**Junaid *et al.*, 1995**). However, studies on teratogenicity of this metal on rabbits are surprisingly limited. Therefore, a comprehensive

studies on the teratogenic effect of trivalent and hexavalent chromium compounds in rabbits was designed.

In the present study, rabbits exposed to chromium chloride or potassium dichromate at dose level of 500 ppm each through drinking water during the organogenesis period (6-18 day of gestation). Generally there were no mortality or clinical signs of toxicity in rabbits exposed to trivalent or hexavalent chromium compounds at the concentration used. Exposure of rabbits to either chromium compounds resulted in reduced number of implantations, retarded fetal development and embryo and fetotoxic effects as evidenced by decreased fetal weight, reduced number of live fetuses per dam and higher incidence of post-implantation loss. The number of resorptions and dead fetuses was increased in rabbits exposed to hexavalent compound.

Junaid *et al.*, (1996 b) reported a complete absence of implantation sites in 750 ppm potassium dichromate pregestationally treated mice. However, at a concentration 500 ppm increased number of resorptions and post-implantation loss were noted. As well as, in rats pregestationally treated with 500 ppm potassium dichromate revealed significant reduction in the number of implantations and number of fetuses and increase in the number of resorptions and pre and post-implantation loss rats (**Kanojia *et al.*, 1996**).

In light of these results, embryonic resorptions noticed in female rabbits exposed to chromium compounds most probably resulted from modification of uterine lining function before the arrival of the embryo. The litter size in hexavalent chromium dosed group was significantly reduced. This may be due to the effect of chromium (VI) on pre-implantation embryo as evidenced by the study of **Jacquet and Draye (1982)**.

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

The maternal chromium is reported to pass freely through the placental barrier to the growing fetuses (**Tipton, 1960 and Pribluda, 1963**). The presence of chromium (VI) in fetuses and infants has been reported in women working or living near the dichromate industry

(**Shmitova, 1980**). The levels of chromium used in the present study are not usually found in the environment but may be encountered at the work place or in effluents from the industrial establishments (40-50 000 ppm) (**Kumar, 1987**). In the present study, chromium accumulation in the fetuses especially of hexavalent treated group might be attributed to the excessive transfer from maternal blood through placenta to fetus as evidenced by the placental/fetal chromium ratio. Therefore, the impaired fetal parameters in hexavalent treated group resulting in embryo-and fetotoxic effects might be due to chromium accumulation as also seen with other heavy metals (mercury and cadmium) and other xenobiotics (**Miller *et al.*, 1983**). Hexavalent chromium is more readily transferred to the embryo and fetus (**Tipton, 1960 and Danielsson *et al.*, 1982**) and is reported to produce teratogenic effects probably due to higher embryonic concentration (**Danielsson *et al.*, 1982**).

Chromium (VI) is absorbed to a greater extent than chromium (III) through gastro-intestinal tract (**Mackenzie *et al.*, 1958). Coogan *et al.* (1991)** reported higher tissue levels of chromium (VI) compared to chromium (III) which reflects the greater tendency of chromium (VI) to cross the plasma membrane and bind to the intracellular protein in various tissues, and this may explain the greater degree of teratogenic effects associated with chromium (VI) compared to trivalent compound. Embryonic and fetal levels of chromium (VI) after chromate exposure to pregnant mice is reported to be 10 times greater than that found after exposure to corresponding doses of chromium (III) (**Danielsson *et al.*, 1982**). In general, hexavalent chromium compounds produce toxic effects in various tissues of humans and experimental animals more than trivalent form (**Baetjer *et al.*, 1974**).

The marked embryotoxic and teratogenic effect of hexavalent chromium compound than that of trivalent one may be attributed to what mentioned by Venitt and Levy (1974). They investigated the mutagenicity of chromates in bacteria, they found that hexavalent (but not trivalent) chromium compounds were mutagenic in certain strain of Esherichia Coli. The mutagencicity of chromate was not modified by the genetic absence of pathways for repair of DNA. They concluded that chromates are among mutagens which exert their effects by directly modifying DNA bases so that base-pair errors arise at subsequent cell divisions.

Therefore, the present study indicates that sufficiently high chromium compounds (III or VI) intake through drinking water during organogenesis period of development affect the

embryonic and fetal development in rabbits. Chromium (VI) compound exposure caused severe deleterious teratogenic effects compared to chromium (III). Also the hexavalent chromium when given in drinking water has greater affinity to pass the feto-placental unit of rabbits and reach to the growing fetus than trivalent compound.

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Table (1): Chromium-induced embryo- and fetotoxicity in rabbits treated during organogenesis period.

Parameter	Control	Chromium in drinking water (500 ppm)	
		Trivalent	Hexavalent
Number of pregnant dams	10	10	10
Total No. of implantations	120	90	85
No. of implants/dam	12.0 ± 0.60 [a]	9.0 ± 0.42 [b]	8.5 ± 0.25 [b]
No. of resorptions/dam	Nil	1.3 ± 0.42	2.4 ± 0.45 [b]
No. of dead fetuses/dam	0.10 ± 0.09	0.8 ± 0.23	1.7 ± 0.31 [b]
No. of live fetuses/dam	11.8 ± 0.44	5.8 ± 0.27 [b]	1.8 ± 0.44 [b]
Post-implantations loss (%)	0.10 ± 0.09	1.1 ± 0.26 [b]	2.3 ± 0.28 [b]
Fetal body weight (g)	40.0 ± 1.31	32.1 ± 1.65 [b]	21.5 ± 1.09 [b]
Placental weight (g)	1.42 ± 0.08	0.88 ± 0.05 [b]	0.62 ± 0.04 [b]

(a) Values represent mean ± S.E. of 10 rabbits in each group.

(b) Significantly different from control by one-way ANOVA, p <0.05

Table (2): Incidences of gross abnormalities in the fetuses of chromium treated rabbits during organogenesis period.

Parameter	Control	Chromium in drinking water (500 ppm)	
		Trivalent	Hexavalent
Total fetuses examined			
Stunted growth			
Subdermal hemorrhagic patches			
Short tail			
Kinky tail			

(a) Values represent percentage of gross deformed fetuses in relation to total number of fetuses examined.

(b) Significantly different from control based on Chi-square test, p <0.05

Table (3): Incidences of visceral abnormalities in the fetuses of chromium treated rabbits during organogenesis period.

Parameters (500 ppm)	Control	Chromium in drinking water	
		Trivalent	Hexavalent
Total fetuses examined	40	22	12
Total fetuses with visceral anomalies	1	8	9
Total fetuses with head & neck anomalies	0	5	7
Hydrocephaly	0 [a]	13 [b]	50 [b]
Dilated nares	0	18 [b]	58 [b]
Olfactory pulp hypoplasia	0	9 [b]	33 [b]
Thymus gland congestion	0	13 [b]	41 [b]
Total fetuses with thorax anomalies	0	7	9
Heart hypertrophy	0	27 [b]	66 [b]
Lung hypoplasia	0	31 [b]	75 [b]
Intrathoracic hemorrhage	0	22 [b]	58 [b]
Total fetuses with pelvic anomalies	1	6	8
Dilated renal pelvis	2	27 [b]	66 [b]
Dilated ureter	0	23 [b]	58 [b]
Adrenal gland congestion	2	9 [b]	41 [b]

(a) Values represent percentage of visceral deformed fetuses in relation to total number of fetuses examined .

(b) Significantly different from control based on Chi-square test, $p < 0.05$

Table (4): Incidences of skeletal abnormalities in the fetuses of chromium treated rabbits during organogenesis period.

Parameters	Control	Chromium in drinking water (500 ppm)	
		Trivalent	Hexavalent
Total fetuses examined			
Total fetuses with skeletal anomalies			
Total fetuses with skull anomalies			
Incomplete ossification of frontal bone			
Incomplete ossification of parietal bones			
Incomplete ossification of interparietal bone			
Wide separation of parietal bones			
Total fetuses with sternebrae anomalies			
Incomplete ossification of stenebrae			
Reduced Sternebrae number			
Deformed ribs			
Total fetuses with limb anomalies			
Absence of carpal and/or metacarpal bones			
Absence of tarsal and/or metatarsal bones			
Incomplete ossification of caudal bones			

(a) Values represent percentage of skeletal deformed fetuses in relation to total number of fetuses examined.

(b) Significantly different from control based on Chi-square test, $p < 0.05$.

Table (5): Chromium levels in different tissues of rabbits treated during organogensis period.

Parameters	Control	Chromium in drinking water (500 ppm)	
		Trivalent	Hexavalent
Blood (μg/ml)	0.034 ± 0.001^{a}	0.061 ± 0.001^{b}	0.192 ± 0.003^{b}
Placenta (μg/g; fw)	0.086 ± 0.003	0.172 ± 0.002^{b}	0.239 ± 0.003^{b}
Fetuses (μg/g; fw)	0.051 ± 0.002	0.087 ± 0.006^{b}	0.228 ± 0.008^{b}

(a) Values represent mean ± S.E. of 10 rabbits in each group, fw : fresh weight.

(b) Significantly different from control by one-way ANOVA, $p < 0.05$.

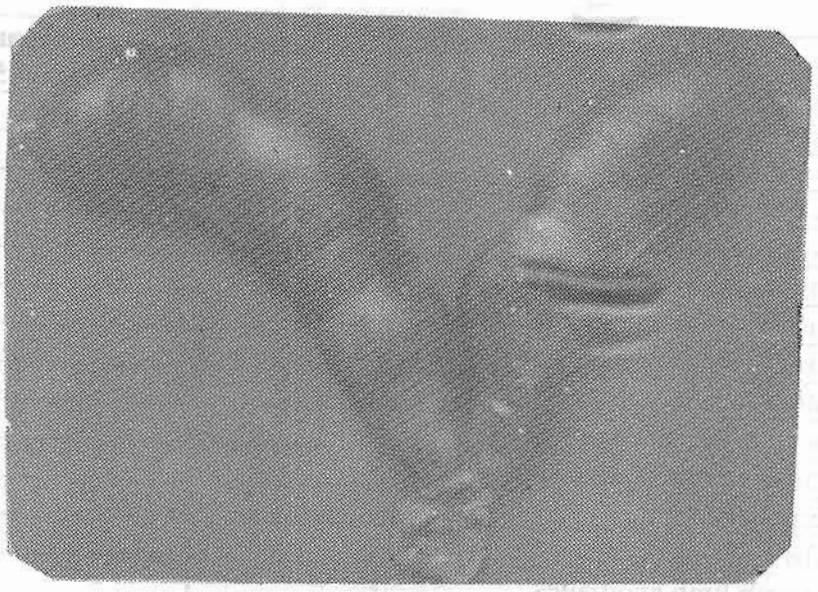

Fig. (1): Uterus of pregnant rabbit treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing a resorption site in the right horn.

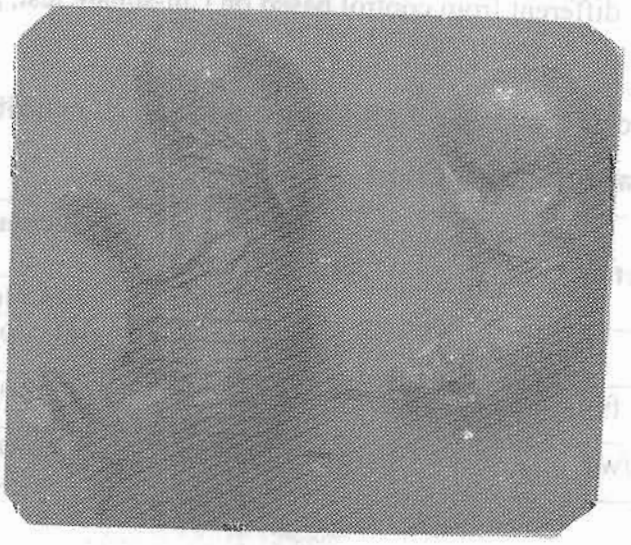

Fig. (2): Two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing stunted growth and kinky tail.

Fig. (3): A transverse section in the head of two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing hydrocephaly.

Fig. (4): A transverse section in the head of two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing dilated nares.

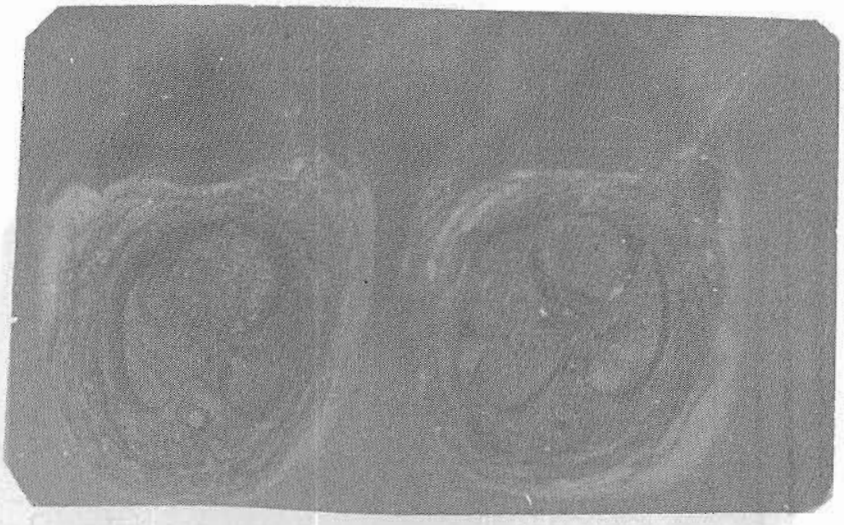

Fig. (5): A transverse section in the chest of two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing heart hypertrophy, lung hypoplasia and intrathoracic hemorrhage.

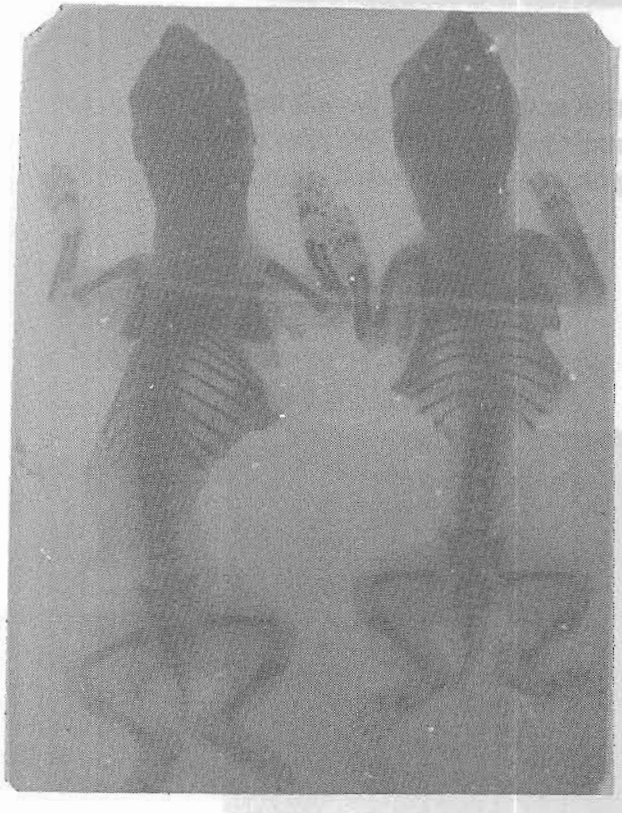

Fig. (6): Two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing wide separation of parietal bones.

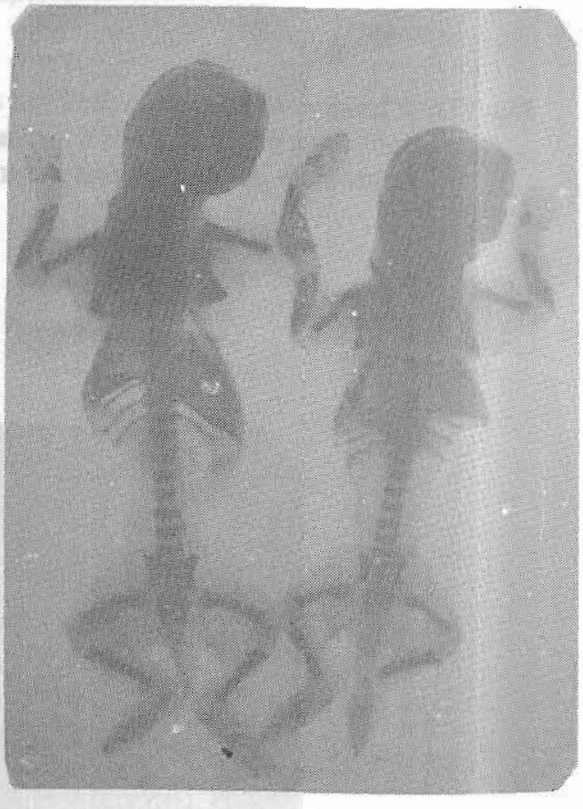

Fig. (7): Two rabbit fetuses, the left one is control, the right fetus obtained from a mother treated orally with 500 ppm potassium dichromate in drinking water during organogenesis period showing reduced sternbrae number.

الملخص العربي

أثر مركبات الكروميوم الثلاثية والسداسية المشوه للأجنة في الأرانب

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يعتبر الكروميوم من العناصر الضرورية اللازمة للأيض الصحيح للكربوهيدرات والبروتين والدهون في جسم الإنسان. أكدت الدراسات السابقة أن الكروميوم السداسي أكثر سمية من الكروميوم الثلاثي حيث أنه ينتقل خلال الأغشية البلازمية ويختزل خلال مركب وسطي غير ثابت إلى الكروميوم الثلاثي. وأكدت المعلومات المنشورة أيضا أن التعرض للكروميوم السداسي يؤدي إلى نقص عدد الأجنة الحية ويزيد من عدد الأجنة الميتة.

في هذه الدراسة تم تعريض الأرانب الحوامل للكروميوم الثلاثي (كلوريد الكروميوم) أو السداسي (ثاني كرومات البوتاسيوم) في الماء عند جرعة ٥٠٠ جزء في المليون لكل واحد خلال فترة تكوين الأعضاء من اليوم ٦ إلى ١٨ من الحمل. تم تقييم مقاييس الأم والأجنة عند اليوم التاسع والعشرين من الحمل.فقد تم وزن الأجنة وفحصها لوجود أي تشوهات خارجية أو تشوهات في الأعضاء الداخلية والهيكل العظمي. وقد تبين أن التعرض للكروميوم السداسي قد أدي إلى حدوث زيادة معنوية في عدد الأجنة الممتصة والي نقص في عدد الأجنة الحية مقارنة بمجموعة الكروميوم الثلاثي والمجموعة الضابطة.

تبين أن التعرض لكلا الكيميائيين قد أدي إلى حدوث تقزم الأجنة وأجنة ذات ذيل مثني وقصير وضمور في الرئة وزيادة في حجم القلب وأنزفة داخل الصدر واتساع فتحتي الأنف وبطينات المخ. وأكثر من ذلك حدوث تمعظم غير كامل في عظام الجمجمة بزيادة معنوية في أجنة الأمهات المعرضة لكروميوم السداسي. كان مستوي الكروميوم في دم الأم والمشيمة والأجنة أعلي معنويا في المجموعات المعالجة مقارنة بالمجموعة الضابطة. بينت نتائج هذه الدراسة أن كلا الكروميوم الثلاثي والسداسي له أثر مشوه للأجنة عند التركيزات المستخدمة وكانت شدة الآثار أكثر مع التعرض للكروميوم السداسي.