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PIPERONYL BUTOXIDE INDUCED REPRODUCTIVE TOXICITY IN MALE MICE.

By

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ABSTRACT

The effect of piperonyl butoxide (PBO) on reproductive performance of male mice was investigated. Male CD-1 mice (20 mice/group) were administered piperonyl butoxide in the diet at levels of 0 (control), 0.1, 0.3, and 0.6% for 4 weeks (20 days). Reduction of sperm measurements was induced in all the treated groups in a dose-dependent manner. PBO caused obvious adverse effects in pregnancy outcomes including decreased the number of implantations and live fetuses, increased number of early resorptions and dead fetuses in all the treated groups. The testicular toxicity was observed in all the treated groups. Testes and epididymis weights were reduced and severe histological changes in testes appeared in all the treated groups, especially at the higher dose level group (0.6%). On the basis of the present results and under the condition of this investigation and at the tested levels, PBO showed potential reproductive toxicity.

INTRODUCTION

Piperonyl butoxide (α-[2-(2-butoxyethoxy) ethoxy]-4,5-methylenedioxy-2-propyl-toluene) is a pesticide synergist used to enhance the effect of

pyrethrins, rotenone, tetramethrin, and other insecticides in oil solutions, aerosols, dusts, wettable powders and slurries, and is registered for use on a variety of fruit, forage, and grain crops, as well as on livestock and agricultural premises (Cardy *et al.*, 1979, Kennedy *et al.*, 1977).

Piperonyl butoxide is used as a food additive in Japan, and its maximum allowable used level is 0.024 g/ kg (24 ppm) in raw cereals while the acceptable daily intake (ADI) is 0.03 mg/kg body weight (Joint FAO/WHO Meeting, 1973). The toxicity of piperonyl butoxide is attributed to its an unmetabolized form, together with its slow rate of elimination from the body, its ability to inhibit microsomal enzymes and thereby enhance toxicity of other chemicals (Fishbein *et al.*, 1969, Epstein *et al.*, 1967, Khera *et al.*, 1979). Therefore, the presence of piperonyl butoxide (PBO) in the environment could be hazardous to humans and other organisum. Potentially, it may be hazardous to man since PBO constitutes 5-10 % of the ingredients in pyrethroid formulations of domestic aerosols used to control insects (Khera *et al.*, 1979). Takahashi *et al.*, 1994 reported that PBO was a carcinogen in rats at higher dose levels (1.20 % in the diets). Besides, piperonyl butoxide has been shown to produce adverse effects on developmental toxicity parameters (Tanaka *et al.*, 1994). Studies which have examined the ability of PBO to induce nodules in mouse liver revealed a formation of eosinophilic nodules in mouse liver and induced microsomal cytochrome P_{450} content and mixed function oxidase activities in the mouse and rat (Phillips *et al.*, 1997). Furthermore, piperonyl butoxide showed adverse effects on reproductive and neurobehavioural parameters in mice (Tanaka 1992).

Although toxicity data on acute and subacute exposure to PBO, and scanty and controversial data on the genotoxic, carcinogenic, teratogenic activities of piperonyl butoxide are available, there is little studies of PBO in the reproductive toxicity of male animals. Such deficiency in information stressed the need for evaluation of the reproductive toxicity of piperonyl butoxide in males. The present study provides an evaluation of fertility and reproductive toxicity of piperonyl

butoxide in male mice. The selected dietary levels of PBO were less than dietary levels administered in the studies of Takahashi *et al.*, 1994 and Phillips *et al.*, 1997 and the highest level (0.6%) is equal to 1/5 LD_{50} of PBO for mice (LD_{50} = 8.000 mg/kg/day, Wayland *et al.*, 19). Besides, the present tested levels of PBO are representing the actual of human exposure to aerosols containing PBO.

MATERIAL AND METHODS

Test Maternal:

Piperonyl butoxide (α-[2-(2-butoxyethoxy)ethoxy]-4,5-methylenedioxy-2-propyl-toluene) was obtained from the EPA (Environmental Protection Agency, R.T.P., N.C. USA). The purity of the chemical was 98.00 % (Lot: 121-112A).

Test Species and Husbandry:

Male and female ICR (CD-1) mice, approximately 10 weeks old, were obtained from the High Institute of Public Health, Alexandria University, Alexandria, Egypt. All mice were examined for health status and acclimated to the laboratory environment for 2 weeks prior to use. The animal room was designed to maintain temperature at 25°C, relative humidity at approximately 50 % and a 12 hr light: 12 hr dark photoperiod. All animals were housed in stainless- steel cages and given standard diet and water *ad Libitum* throughout the study.

Experimental design:

Piperonyl butoxide was administered in the diet to 60 male mice (20/ group) at dietary levels of 0.1, 0.3, and 0.6 % for 4 weeks (5 days/week). The 20 mice in the control were given the basal diet (sterilizable diet, the High Institute of Public Health, Alexandria, Egypt). Feed consumption was recorded daily for each mice every week.

Reproductive performance study:

In a study of fertility and general reproductive performance, groups of piperonyl butoxide treated male mice (twenty males per concentration) were mated with untreated female mice from the same strain (1:1) for 4 days (time for completion of one estrous cycle in mice). Vaginal plugs were daily observed, the day the vaginal plugs were observed was considered Day 0 of gestation. Mated females were anaesthetized and necropsied on day 12 of gestation to determine the pregnancy status and the number of implantations.

Evaluation of sperm motility and morphology:

After mating, male mice were anaesthesized, and the weights of the body were recorded. Immediately liver, kidneys, brain, epididymis, and testes weights were recorded. The left epididymis was excised and placed in a prewarmed petri dish containing 0.2 ml of calcium and magnesium free Hank's solution at 37°C. The tissue was minced with scalpels for approximately 1 min and placed in 37°C incubator for 15 min., prior to examination of the movement of sperms. Afterward, the suspension was stirred, one drop was placed on a warmed microscope slide, and a 22 X 22 mm coverslip was added. Each of at least 10 microscopic fields per sample was observed at 400 – fold magnification under standard optical microscope, and the percentage of motile cells was calculated (Blazak *et al.*, 1985, Linder *et al.*, 1995, Llobet *et al.*, 1995).

After the previous observations, the coverslip was removed and the spermatozoa suspension was allowed to dry in air. It was stained with, Eosin Y 1%- Nigrosin 5% and examined (400x) for morphological abnormalities. Three hundred or more spematozoa per sample from different fields were examined (Linder *et al.*, 1995).

Assessment of sperm production:

The right epididymis and speciemens of testis were frozen immediately after weighing until examination. After thawing at room temperature, the whole epididymis and speciemens of testis were homogenized in 0.5 ml of a solution of 0.9% NaCl containing 0.01 of

Triton X-100. Ten strokes of a manual homogenizer were used for each sample. The homogenates were diluted with 1.5 ml of the same solution and observed under the microscope (400x) in a Neubauer hemocytometer to count spermatid and spermatozoa. The counts per sample were averaged, (Llobet *et al.*, 1995).

Histological examination:

Histological examination of testes was done. The left testis and speciemens of the right testis were fixed in Bouin's solution and processed to get six microns thick paraffin sections. The speciemens were stained with hematoxylin & eosin and examined by light microscope.

Statistical Analyses:

Statistical analyses were performed with the Statistical Analysis system SPSS (Noursis, 1994). Litter means and frequencies per litter were used as the experimental units for analyzing fetal examination data. Organ weights were subjected to analysis of covariance using the final body weight as the covariant. Sperm measures were analyzed by one-way ANOVA. Average food intake was assessed with Bonferroni multiple comparison test after Kruskal-Wallis test. A P value of less than or equal to 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

In the present reproductive toxicity study, administration of PBO to male mice, in diet, resulted in significant adverse reproductive effects.

Food and chemical intake:

While average food intake was increased in the 0.1, and 0.3% treated groups, it was normal in the 0.6% treated group compared to the control. Therefore, piperonyl butoxide was taken in propartion to dietary levels in the treatment weeks (Table 1).

Clinical signs of toxicity:

Clinical signs of toxicity was observed in the treated groups. Abnormal behaviour and mortality were observed in the treated males during the course of the experiment. Mortality was observed in two males in the 0.3% treated group and four males in the 0.6% treated group. The activity of males was increased in all the treated groups especially in the 0.6% treated group compared to the control. Males moved long distances rapidly.

Body and organ weights:

Body and organ weights at termination are given in table 2. No significant effect in male body weights in any of piperonyl butoxide treated groups, were noted. Therefore, there was no significant differences was found between relative and absolute organ weights. Kidneys and liver weights were increased in all the treated groups. Epididymis and testes weights were decreased in all the treated groups. No effects in the brain weights in any of the treated groups, were noted. Liver and kidneys weights were increased in all the treated groups. A possible explaination for these findings is that PBO caused hepatocellular adenoma and carenoma in male CD-1 mice (Takahashi *et al.*, 1994). Besides the kidneys of treated rats (0.6% PBO) showed atrophy of epithelium in the proximal convoluted tubules which might cause increase of kidneys weight (Butler *et al.*, 1998). The results provided from the organ weight measurements alone showed evidence of an apparent adverse effects of PBO treatments on the male reproductive accessory organs, including the epididymis.

Reproductive performance:

The reproductive performance of male mice treated with piperonyl butoxide appears in Table 3. While mating index was decreased in the 0.6% treated group, fertility index was decreased in all the treated groups compared to the control. Number of implantation sites and live fetuses were significantly reduced in all the treated groups. Number of early resorptions and dead fetuses was increased in all the treated groups. However, the maximum increases occurred in the 0.1, and

Table (1):Average Food and Chemical Intake of Male Mice Treated with Piperonyl Butoxide

Dose Levels (%)				
	0	0.1	0.3	0.6
Food intake (g/kg/day)				
Weeks of treatment [a]				
1	264.61 ± 1.19	284.98 ± 4.15*	279.82 ± 5.16*	261.94 ± 3.11
2	255.87 ± 2.10	285.55 ± 2.70*	280.10 ± 3.01*	253.26 ± 4.22
3	255.60 ± 3.17	285.55 ± 1.77*	270.99 ± 2.7*	256.51 ± 5.00
4	265.70 ± 2.81	285.55 ± 3.70*	284.66 ± 4.90*	271.44 ± 2.99
Chemical intake (mg/kg/day)				
Weeks of treatment [a]				
1	-	284.98 ± 5.70	839.46 ± 2.70	1571.64±1.70
2	-	285.98 ± 2.70	840.30 ± 5.11	1519.56±2.77
3	-	285.55 ± 3.15	812.97 ± 2.17	1539.06±5.11
4	-	285.55 ± 1.70	853.98 ± 1.80	1628.64±3.00

[a] Data are presented as mean ± S.D.

* Significant different from control at $P \leq 0.05$.

Table (2):Body and Organ Weights in Male Mice Treated with Piperonyl Butoxide[a]

	Dose levels (%)			
	0	0.1	0.3	0.6
Body weight (g)	36.62 ± 0.15	35.02 ± 0.15	35.13 ± 0.70	36.84 ± 0.20
Absolute weight [b]				
Liver	1.50 ± 0.14	2.45 ± 0.22*	2.35 ± 0.14*	2.99 ± 0.13*
Kidneys	0.45 ± 0.04	0.54 ± 0.05*	0.55 ± 0.08*	0.59 ± 0.06*
Brain	0.33 ± 0.04	0.33 ± 0.06	0.33 ± 0.04	0.36 ± 0.06
Epididymis	0.06 ± 0.08	0.04 ± 0.01*	0.04 ± 0.00*	0.04 ± 0.00*
Testes	0.27 ± 0.02	0.15 ± 0.21**	0.14 ± 0.79**	0.15 ± 0.0**
Relative weight [c]				
Liver	4.10 ± 0.54	7.00 ± 0.90*	10.93 ± 0.54*	9.58 ± 0.44*
Kidneys	1.23 ± 0.15	1.54 ± 0.22*	1.53 ± 0.34*	1.60 ± 0.20*
Brain	0.90 ± 0.15	0.94 ± 0.20	0.94 ± 0.16	0.98 ± 0.27
Epididymis	0.16 ± 0.02	0.11 ± 0.02*	0.11 ± 0.12*	0.11 ± 0.01*
Testes	0.74 ± 0.05	0.43 ± 0.10**	0.40 ± 0.18**	0.41 ±0.03**

[a] Twenty mice per group were examined. Data are presented as mean ± SD.

[b] Organ weights (g)/ body weight.

[c] Organ weights/ 100g body weight. *Significant different from control value at $P \leq 0$

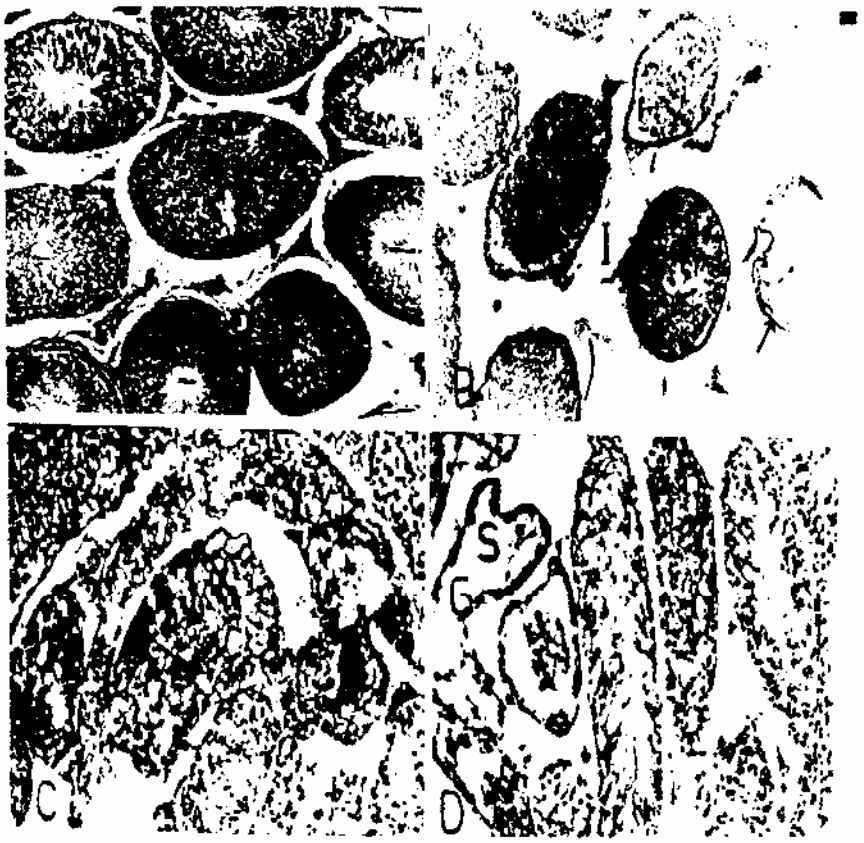

Fig. 1. Photomicrographs of testes from (A) control mouse, (B) seminiferous tubules from mouse treated with 0.1% showing exfalation and slaughing of the cells (arrow) and widening of interstitial spaces (I), (C) testes from mouse treated with 0.3% showing deposition of eosinophilic material in seminiferous tubules (E) with lose cellular differentiation, and (D) some seminiferous tubules showed complete destruction and lysis of the cells (S) in the testes from mouse treated with 0.6% PBO. Notice preservation of spermatogenic cells (G).

0.3% treated groups for percentage of dead fetuses and in the 0.6% for percentage of early resorptions. Number of late resorptions was unaffected. The results of this study showed adverse effects on pregnancy outcomes in all the treated groups. PBO caused increases in the number of dead and early resorptions fetuses in all the treated groups. The severe effects in the number of dead and early resorptions were noted in the 0.1, and 0.6% treated groups, respectively. Thus, there was a relationship between an increasing of PBO dose levels and kill fetuses in early stages.

Based on data reported by Takahashi *et al.*, 1997, piperonyl butoxide may be looked upon as a nongenotoxic and nonmutagenic and can cause hepatocarcinogens and hepatomegaly (Fujitani *et al.*, 1992). In the present study PBO caused adverse reproductive toxicity in unexposed females mated with exposed males. Thus, the mechanism of these effects can not be attributed to the mutagenic effects of PBO.

Sperm parameters:

Sperm parameters showed in Table 4. Percentage of motile cells, spermatid and spermatozoa counts were highly statistically significant decrease in all the treated groups compared to the control group. Percentage of morphological normal spermatid was unaffected in any of the treated groups. The effects of PBO on sperm motion, sperm production in all the treated groups suggested that these qualitative spermatogenic changes alone could have affected the males fertility, this was confirmed by the reduction in the fertility rates in all the treated groups. Thus, the spermatogenic alterations might reflect the infertility in males exposed to PBO in all the treated groups.

Histological examination:

Significant histopathological changes were detected in the testes of males treated with piperonyl butoxide. The testes on mice receiving 0.1% piperonyl butoxide showed sloughing and disorganization of spermatogenesis. This dose also caused exfoliation of tubules in lumen (Fig. 1B). The middle dose group of PBO (0.3%) showed deposition of eosinophilic acidophilic material in the seminiferous tubules. No cellular

Table (3):Fertility and Reproductive Parameters in Male Mice Treated With Piperonyl Butoxide

	Dose levels (%)			
	0	0.1	0.3	0.6
Number of females	20	20	18	16
Mating index [a]	90 (18/20)	90 (18/20)	83 (15/18)	69 (11/16)*
Fertility index [b]	100 (18/18)	72 (13/18)*	73 (11/15)*	55 (6/11)**
Implantation sites/ litter [c]	9.40 ± 1.35	5.00 ± 1.94**	4.80 ± 0.79**	3.90 ± 1.29**
Live fetuses/Litter [d]	9.00 ± 1.33	3.00 ± 1.23**	2.90 ± 0.74**	1.90 ± 0.70**
%	96.00	60.00	61.00	48.80
Dead fetuses/Litter [d]	0.00 ± 0.00	1.20±1.00**	1.00±0.95**	0.55±0.88*
%	0.00	24.00	20.83	14.10
Early resorptions/Litter [d]	0.40 ± 0.70	0.80 ± 0.15*	0.90 ± 0.28*	1.45 ± 0.75*
%	4.10	16.00	18.75	37.18
Late resorptions/Litter [d]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
%	0.00	0.00	0.00	0.00

[a] No. of males which mated resulting in vaginal plug or pregnant female/ No. of males cohoused with females X 100 [b] No. of males which sired a litter/ No. of males resulting in vaginal plug or pregnant female X 100. [c] Data are presented as mean ± SD. [d] Data are presented as mean ± SD and as percentage in basis of implant number. *Significantly different from control value at $P \leq 0.05$. **Significantly different from control value at $P \leq 0.01$.

Table (4):Sperm Parameters in Male Mice Treated With Piperonyl Butoxide[a]

	Dose Levels (%)			
	0	0.1	0.3	0.6
Number of males	20	20	18	16
Spermatozoa counts				
No.X 10^6/ epidiymis	4.74 ± 0.18	1.69 ± 0.14**	1.30 ± 0.13**	0.26 ± 0.13**
Spermatid counts				
No. X 10^6/ testis	22.74 ± 0.71	9.08 ± 0.16**	7.32 ± 0.29**	4.33 ± 0.56**
% of motile cells	38.89 ± 14	19.40 ± 16**	11.41 ± 11**	3.91 ± 5**
% of abnormal morphologic forms	1.88 ± 5	1.70 ± 14	2.01 ± 15	1.99 ± 9

[a] Data are presented as mean ± SD.

** Significant different from control value at $P \leq 0.01$.

PBO caused preservation of the spermatogonia and complete distruction of the rest of spermatogenic cells. Some seminiferous tubules showed diffrentiation between spermatogensis and loss of stratification. They were scattered in the lumen of the tubules. The spermatogenic cells had small size with dark stained nuclei (Fig. 1C). The high dose (0.6%) of complete lysis of the germenative cells. Complete loss of architecture of seminiferous tubules was noted in the treated group of 0.6% PBO (Fig. 1D). Sperm isolated from epididymis of treated males showed reduction in percentages of motile sperm, and spermatozoa counts compared to the control group. In addition, the spermatide count were also highly statistical significant reduced in all the treated groups. It seemed usual that epididymal sperm counts were reduced with the concurrent reduction in testicular spermatid. However, examination of the testes from the histological preparations revealed that PBO may be considered as an exfoliative antispermatogenic agent that it caused premature sloughing of spermatids and alter seminiferous tubular function as evidenced by histological alterations and reduced testes weight.

Although PBO treatments caused severe effects on the sperm measurements and histological testicular alteration, 13\18, 11\15, and 6\11 males in 0.1, 0.3, and 0.6% treated groups, respectively remined fertile and sired litters. It seemed unusual that PBO appeared to be highly potentially testicular toxicant and some of exposed males remained fertile. However, examination of the seminiferous tubules from the histological preparations revealed the evidence of impaired spermiation and possible phagocytosis of late- step spermatids allows the possibility that late- step spermatids were retained and sequently lost without being transferred to the epididymis. The most striking histological changes were the proportional spermatogenic hypoplasia and the spermatogenic cells showed variable degree if degenerative changes varied from cloudy swelling to complete destruction of the cells. Spermatogetes and spermatids were the most severely affected cells. Most of them were detached appearing in the lumina of the seminiferous tubules. The sloughed cells revealed pyknotic nuclei. Spermatogonia were the least cells to be affected or evenly seem to be resistant, and they preserved

their normal structure. These findings were in agreement with Dunnick *et al.*, 1984 who found that the most affected cells were the mature spermatids and spermatozoa, while the stem spermatogonia seemed to be resistant.

Adverse reproductive effects on male mice was induced at 0.1, 0.3, and 0.6%. Therefore, a maximum no-effect level in the present study is lower than 0.1% of PBO.

Piperonyl butoxide is used not only as a food additive for rice, wheat, and other grain crops but also as a synergist of pyrethrins post harvest and in domestic insecticides. Even if the use level of piperonyl butoxide remains unchanged, we need to reevaluate the approved levels of all usages on the basis that PBO has adverse effects on male reproductive system at the dietary exposures reported in this study.

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الملخص العربى

مركب البيبرونيل بيوتكسيد أحدث تأثيرات عكسيه فى الجهاز التناسلى لذكور فئران التجارب

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تم دراسة تأثير البيبرونيل بيوتكسيد على الجهاز التناسلى لذكور فئران التجارب. تم استخدام فئران التجارب CD-1 (٢٠ فأر/مجموعه) وإعطائها جرعات من مركب البيبرونيل بيوتكسيد (٠,١ ، ٠,٣ ، ٠,٦%) لمدة ٤ أسابيع (٢٠ يوم). حدث انخفاض واضح فيخصائص الحيوانات المنويه فى كل المجاميع المعامله in a dose-dependent manner.

أوضحت النتائج أيضا أن مركب البيبرونيل بيوتكسيد قد أحدث تأثيرات عكسيه على خصوبة الإناث الغير معامله التى تم تزاوجها مع ذكور معامله. زادت نسبة الإمصاص المبكر وموت الأجنه ونقص عدد الأجنه الحيه ومواضع الأجنه. أيضا حدث نقص فى وزن الخصى ومخزن الحيوانات المنويه. ظهرت تغييرات فسيولوجيه كبيره فى الخصى فى كل المجاميع المعامله خاصة علىأعلى تركيز ٠,٦%.

بناء على هذه النتائج وتحت ظروف هذه الدراسه ، مركب البيبرونيل بيوتكسيد يحدث تأثيرات عكسية على الجهاز التناسلى لذكور فئران التجارب.