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TERATOGENIC EFFECT OF ORALLY ADMINISTERED TECHNICAL DIMETHOATE IN RATS

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ABSTRACT

Dimethoate (O, O- dimethyl-S- (N- methylcarbamoyl- methyl) phosphorodithioate), an organophosphate insecticide, was examined for its potential to produce developmental toxicity in rats after oral administration. Pregnant Fischer 344 rats were given sublethal doses of 0 (corn oil), 7, 15, and 30 mg/kg/day dimethoate by gavage on Gestation Days 6 through 15. Maternal effects in the 30 mg/kg/day dose group included cholinergic signs, decreased body weight, and decreased feed consumption. No maternal effects were apparent in the 7 and 15 mg/kg/d dose groups. Maternal exposure to dimethoate during organogenesis significantly affected the number of live fetuses, early resorption, mean fetal weight, and the incidence of skeletal malformations in the 30 mg/kg/d dose group. On the basis of the present results dimethoate showed maternal and developmental toxicity at 30 mg/kg/day.

Keywords: developmental toxicity, dimethoate, rats, malformations, teratogenic effects

INTRODUCTION

Dimethoate (O, O- dimethyl-S- (N- methylcarbamoyl- methyl phosphorodithioate) is not only a commonly used agricultural insecticide and acaricide, but also it is one of the most widely- used insecticides in the world. Dimethoate is used in the control of houseflies, as well as a wide range of insects and mites on a variety of fruit, vegetable, field and forestry crops (Hays and Lows, 1990; Meister, 1992). It releases to the environment and does not absorb onto the soil and is subject to considerable leaching. It is lost from the soil through evaporation and biodegradation (Hazardous substances database, 1988). Although dimethoate is moderately toxic by ingestion, inhalation, and dermal absorption (the reported acute oral LD50 value for the rats is 310 mg/kg/d, and for humans is anticipated to be about 30 mg/kg) (WHO/ IPCS, 2001; FAO/ WHO, 1980), it is listed as one of the contaminants and hazardous waste sites that pose the most significant potential threat to the human health (United States Department of Health and Human Services,1997). The toxicity of dimethoate, however, is attributed to its biotransformation to another more toxic pesticide, omethoate; which plays a dominant role in the toxicity of this compound in insects and mammals (FAO/ WHO, 1985). In fact, the investigators have shown that repeated exposure to dimethoate as neurotoxicant considerably altered the functioning of the central nervous system at the dose level of 28 mg/kg/d (Nagymgtenyi *et al.*,1998). Dimethoate has a carcinogenic potential (Gibel *et al.*, 1973; Stieglitz *et al.*, 1974; Hayes, 1982; Hallenback and Cunningham-Burns, 1985; Desi *et al*, 2000), and has been shown to produce malignant tumors in the rats treated with 5, 15, and 30 mg/kg/d for long terms (Hayes and Laws,1990). In addition, dimethoate induced increasing in malignant neoplasm's, and granulocytic leukemia in male and female rats and mice (Reuber, 1984). However, recent histological examination and reevaluation of the US National Cancer Institute (NCI) concluded that dimethoate is oncogenic in two strains of rats and probably in mice (Reuber, 1984). Benign and malignant neoplasm of the liver, endocrine organs and lymphatic system were observed as well as other toxic effects (atrophy of the testes, chronic renal disease and hyperplasia) (Reuber, 1984). Owing to inadequacies of the available studies, the International Agency for Research on Cancer (IARC) was unable to classify dimethoate with regard to its potential carcinogenicity (IARC, 1983). Dimethoate has mutagenic effects in a number of in vivo and in vitro short term tests (FAO/ WHO, 1985; Hayes, 1982; Hallenbeck and Cunningham-Burns, 1985). Studies using the bone marrow cells chromosomes demonstrated the mutagenic effects of dimethoate in rats at dose levels of 1/100, 1/75, and 1/50 of the LD50 (Hayes and Laws, 1990; Nehez *et al.*,1994). On the other hand, dimethoate has a direct effect on the ovary in the mice treated with 28 mg/kg/d (Mahadevaswami and kaliwal, 2002). Dimethoate decreased serum testosterone levels, testicular weight, and sperm motality, and increased the percentage of dead and abnormal sperm in rats and rabbits (Salem *et al.*, 1988; Afifi *et al.*,1991). Moreover, it accumulated in the testes where it persisted for weeks even after oral administration was stopped (Afifi *et al.*, 1991). However, dimethoate inhibited steroidogenesis primarily by blocking transcription of the steroidogenic acute regulatory (STAR) gene (walsh *et al.*, 2000). In mice drinking water containing 60 ppm (9.5 to 10.5 mg/kg/d) dimethoate caused adverse reproductive effects on mating success, survival of pups and growth of surviving pups; however, no teratogenic effects were observed (Budrea and Singh, 1973). The absence of abnormalities in fetal gross, visceral morphology and skeleton suggested that dimethoate was not teratogenic in rats up to dose level 15 mg/kg/d (Srivastava and Raizada, 1996). Indeed, at dose levels up to 20 mg/kg/d, dimethoate did not produce fetotoxicity, fetal lethality or

malformations in the mice fetuses (Courtney *et al.,* 1985). On the other hand, a dermal absorption of dimethoate (349 mg/kg) in rats resulted in an increase of the rate of absorption, retardation and deformation (Weber, 1990). Furthermore, effects on foetal development were observed in cats and rats exposed to 12 mg/kg bw/ d but not at 3 or 6 mg/kg bw/d in either species (Khera, 1979; Khera *et al.,* 1979). Intraperitoneal administration of 40 mg/kg, given to rats as a single dose on the day of mating, caused a high incidence of embryonic loss (Scheufler, 1975). Although dimethoate still remains one of the most widely used insecticides in the world, there is limited recent information regarding the developmental toxicity of this compound. The present study provides information on the incidence and types of malformations induced in the fetuses of rats exposed orally to dimethoate on Days 6-15 of gestation at dose levels considerably higher than those reported to cause no teratogenic effects (Srivastava and Raizada, 1996).

MATERIALS AND METHODS

Chemical

Dimethoate was obtained from the US Environment Protection Agency (Research Triangle Park, NC, USA). The purity of the test material was 98% (Lot # 106-52 A).

Animals and conditions

Male and female Fischer 344 rats, approximately 10 weeks old, were obtained from the High Institute of Public Health, Alexandria University, Alexandria, Egypt. All rats were examined for health status and acclimated to the laboratory environment for 2 weeks prior to use. Temperature was maintained at 23 ± 2 °C, and relative humidity at approximately 50%, with a 12 h: 12 h light: dark photoperiod. Animals were housed in stainless – steel cages and given standard diet and water *ad libitum* throughout the study. Adult virgin female rats were mated with adult males (one male/two females). Sperm – positive females were considered to be in Day 0 of pregnancy. Pregnant rats (24 – 28 per group) were treated by oral gavage starting at Day 6 through Day 15 of gestation with 0, 7, 15, 30 mg/kg/d dimethoate. Corn oil served as the vehicle control. The administered volume of each dose was 4 ml/kg body weight per day, adjusted for recorded body weight changes during the study.

Maternal endpoints

Females were examined daily throughout the experimental period for signs of toxicity. Maternal body weight was recorded daily throughout the treatment period. Feed consumption was recorded on days 6, 9, 12, 15, and 20 of gestation. Weights of maternal liver, kidneys, and brain were recorded at the time of Cesarean section on day 21 of gestation.

Fetal endpoints

Pregnant females were anaesthetized using diethyl ether on day 21 of gestation. The uterine horns were examined for the number and location of fetuses and resorption sites. Fetuses were removed, weighed, sexed, and evaluated for external abnormalities. The uteri of apparently on pregnant rats were stained with 10 % sodium sulfide (Salewski, 1964) and examined for evidence of implantation sites. One – third of the fetuses were fixed in Boiun's solution for razer blade sectioning (Wilson and Wurkany, 1965). The remaining fetuses were fixed in alcohol, double stained with alizarin red S for ossified bone and alcian blue for cartilage, and cleared in 2 % KOH and glycerin (Peters, 1965).

Statistical evaluation

An estimation of maternal toxicity was made from maternal body weights, feed consumption, and absolute and relative organ weights and the dose groups were compared utilizing the one- way analysis of variance procedure (ANOVA) followed by Tukey's multiple comparisons. The maternal body weight on Day 6 of gestation was used as a covariant (ANCOVA) for comparing weights of the treatment groups with those of the control. The proportions of maternal deaths and resorbed litters were compared using the Z test for differences of proportions (Walpole and Meyers, 1978) with a modified Bonferroni correction (Simes, 1986). Fetal weights were analyzed with a nested ANOVA followed by Tukey's multiple comparisons (Winer, 1971). Percentage of resorptions and fetuses with abnormalities were evaluated with pairwise Mann- Whitney tests with a modified Bonferroni correction to compare each treatment to the control (Lehmann, 1975). Sex ratio and litter size data were compared with the Kruskal – Wallis test (Lehmann, 1975; Norusis, 1994). The statistical tests were conducted using a nominal $\alpha = 0.05$.

RESULTS

Maternal Parameters

Clinical signs of toxicity

There were no deaths or abortions during the course of the present study. Signs of cholinergic toxicity including tremors, diarrhea, weakness, and vomiting were noted in dams at 30 mg/kg/d dimethoate compared to the control and the other treated groups. These signs appeared on day 12 of gestation (day 7 of treatment) and progressed throughout the period of the treatment. These signs were shown in 60 % of dams.

Table 1. Maternal parameters in rats after exposure to dimethoate on Days 6 through 15 of gestation.

		Dimethoate (mg/kg/d)			
	Days	0	7	15	30
Number of dams		26	24	28	26
Change in body weight[a]	6-9	3.6 ± 2	3.5 ± 1	3.01 ± 2	3.1 ± 4
	9- 12	3.4 ± 3	3.7 ± 7	3.6 ± 1	1.2 ± 3*
	12- 15	8.8 ± 6	7.7 ± 3	7.8 ± 2	2.2 ± 3**
	15- 18	9.7 ± 5	10.2 ± 3	10.2 ± 5	4.0 ± 2**
	18- 20	9.8 ± 3	10.5 ± 2	9.8 ± 2	4.7 ± 3**
Body weight for all dams (g)	6	157.87 ± 1.1	158.19 ± 1.8	158.68 ± 1.5	162.51 ± 1.7
	20	223.23 ± 1.7	222.52 ± 1.9	225.35 ± 1.2	188.79± 1.6*
% weight gain for all dams[b]	6- 20	41.5 ± 5	40.8 ± 6	39.3 ± 9	16.0 ± 7**
Adjusted % weight gain[c]		20.6 ± 8	22.2 ± 6	19.5 ± 4	10.01 ± 9**
Absolute organ weight[d]					
Liver		7.95 ± 0.11	7.25 ± 0.21	7.97 ± 0.32	7.01 ± 0.11
Brain		1.30 ± 0.11	1.27 ± 0.25	1.32 ± 0.28	1.31 ± 0.11
Kidneys		0.42 ± 0.13	0.45 ± 0.70	0.40 ± 0.55	0.28 ± 0.13*
Relative organ weight[e]					
Liver		0.04 ± 0.01	0.04 ± 0.1	0.04 ± 0.3	0.04 ± 0.01
Brain		0.01 ± 0.1	0.01 ± 0.3	0.01 ± 0.2	0.01 ± 0.1
Kidneys		0.002 ± 0.1	0.002 ± 0.1	0.002 ± 0.1	0.002 ± 0.1

[a]Average percentage of maternal weight change ± SD
[b]Average percentage of maternal weight change from gestation day 6-20.
[c]Weight gain adjusted for fetal weight and omitting females with totally resorbed litters
[d]Organ weights in gram
[e]Organ weight/body weight
*Significant different from control at P< 0.05; **Significantly different from control at P < 0.01

Table 2. Feed consumption (g/kg/d) in rats after exposure to dimethoate on Days 6 through 15 of gestation.

	Days of gestation				
Dimethoate (mg/kg/d)	6	9	12	15	20
0	316.72 ±32	330.33 ± 39	354.86 ± 16	380.52 ± 21	449. 97 ± 46
7	316.07 ± 42	336.25 ± 30	340.60 ± 25	360.58 ± 11	422.43 ± 28
15	327.70 ± 55	332.72 ± 19	342.94 ± 52	363.05 ± 17	421.57 ± 45
30	307.67 ± 37	322.29 ± 55	235.90 ± 19*	288.53 ± 27*	264.84 ± 18**

Data are presented as mean ± SD
*Significant different from control at P< 0.05; **Significantly different from control at P < 0.01

Maternal body and organ weights

Maternal body change and organ weights are presented in table 1. Early in the treatment period from day 9 through 12 of gestation, the percentage of the change in weights of dams in the 30 mg/kg/d group was reduced compared to the control and the other treated groups. This reduction was continuous throughout the gestation days at the same dose group. Analysis of the average percentage maternal change from days 6-20 revealed a reduction in the weight gain which, when compared to the control was statistically significant in the 30 mg/kg/d treated group. Data from adjustment for the litter weight component (Day 20 body weight – total fetal weight) revealed that the percentage of weight gain reduced in the highest treated group 30 mg/kg/d. Dimethaote treatment resulted in

decrease in the absolute kidneys weight in the treated group of 30 mg/kg/d compared to the control group and other treated groups. No significant differences in the relative kidneys weight in any of the treated groups compared to the control. There were no significant differences in the absolute and relative weights of the liver and brain in any of the treated groups compared to the control group.

Feed Consumption

Feed consumption is given in table 2. Feed consumption was statistically significantly decreased in the treatment group of 30 mg/kg/d dimethoate compared to the control and the other treated groups. These decreases were started at the day 12 through 20 of gestation.

Table 3. Developmental toxicity in rats fetuses after exposure to dimethoate on Days 6 through 15 of gestation.

	Dimethoate (mg/kg/d)			
	0	7	15	30
Number of females	30	30	30	30
Number of pregnant (%)[a]	26 (87)	24 (80)	28 (93)	26 (87)
Number of litters	26	24	28	26
Number of implantation/litter	10.4 ± 1	9.5 ± 3	10.8 ± 1	9.9 ± 1
% postimplantation loss[b]	4.8 ± 9	5.3 ± 8	7.4 ± 10	49.5 ± 13**
Live fetuses/litter (%)[c]	9.9 ± 0.9 (95)	9.0 ± 0.3 (95)	10.0 ± 0.1 (93)	5.0 ± 2.0** (51)
Dead fetuses/litter (%)[c]	0.0 ± 0	0.0± 0	0.0± 0	1.8 ± 3** (18)
Early resorptions/litter (%)[c]	0.5 ± 4 (5)	0.5 ± 1 (5)	0.8 ± 2 (7)	3.1 ± 5** (31)
Litters with resorption	6 (23)	7 (29)	8 (29)	20 (77)**
Litters totally resorbed	0	0	0	5 (19)*
Sex ratio (M/F)/litter	1.2 ± 1.0	1.2 ± 0.8	1.1 ± 1.0	1.4 ± 0.9
Fetal body weight (g)/litter	4.28 ± 0.15	4.11 ± 0.20	4.75 ± 0.55	3.00 ± 0.22**

Data are presented as ± mean SD

[a]Number of females detected as being pregnant by visual inspection of the uterus/total number of females with vaginal plugs x 100. Sodium sulfide staining was performed on all uteri without gross evidence of pregnancy but did not disclose resorption sites in any of the evaluated dams

[b][(No of implants – No live fetuses)/No of implants]x 100

[c] % of implantations

*Significant different from control at P< 0.05; **Significantly different from control at P < 0.01

Table 4. Incidence of fetal abnormalities in rats after exposure to dimethoate on days 6 through 15 of gestation.

	Dimethoate (mg/kg/d)			
	0	7	15	30
Number of fetuses/number of litters examined	30	30	30	30
External examinations	257/26	216/24	280/28	130/26
Visceral examinations	86/26	72/24	93/28	43/26
Skeletal examinations	171/26	144/24	187/28	87/26
External examinations/littera	9.9 ± 0.90	9.0 ± 0.30	10.0 ± 0	10 5.0 ± 2.0
Visceral examinations/littera	3.3 ± 0.55	3.0 ± 0.35	3.3 ± 0.85	1.7 ± 0.46
Skeletal examinationsa	6.6 ± 0.23	6.0 ± 0.21	6.7 ± 0.14	3.3 ± 0.38
External abnormalities/litter (%)	0.18 ± 9 (2)	0.20 ± 7 (2)	0.21 ± 10 (2)	0.10 ± 9 (2)
Visceral abnormalities/litter (%)	0.12 ± 10 (4)	0.10 ± 8 (3)	0.11 ± 8 (3)	0.06 ± 11 (4)
Skeletal abnormalities/litter (%)	0.04 ± 10 (1)	0.04 ±10 (1)	0.36 ±12 (5)	2.9 ± 13 (88)**

Data are presented as mean ± SD

[a]Only live fetuses were examined

**Significantly different from control at P < 0.01

Fetal observations

Developmental parameters and fetal weights are summarized in table 3. The number of the implants per litter was not significantly altered in the dimethoate treated groups. Dimethoate produced a significant increase in embryolethality in the 30 mg/kg/d treated group with approximately 50% of the implants resorbed compared to the

control and the other treated groups. Total resorption of litters was significantly increased in the treated group of 30 mg/kg/d compared to the control group. A significant decrease was observed in the number of live fetuses in the 30 mg/kg/d group compared to the control and the dimethoate treated groups. While no significant difference was observed in the number of the late resorptions or sex ratio of the fetuses in any of the treatment groups, a statistically significant increase in the number of dead fetuses and early resorptions was shown in the group treated with 30 mg/kg/d dimethoate. Fetal weights for rat fetuses were significantly lower than those in the control group at the 30 mg/kg/d treated group.

Table 4 depicts the frequency of abnormalities in the surviving fetuses from dams exposed to dimethoate. No significant external and visceral abnormalities were observed in any of the treated groups compared to the control group. Skeletal abnormalities were statistically significant at the highest treated group 30 mg/kg/d compared to the control and the other treated groups. 88 % incidences of skeletal abnormalities shown in the treated group of 30 mg/kg/d compared to the control and the other treated groups.

The types of skeletal abnormalities found and the number of affected fetuses are listed in table 5. Skeletal abnormalities were principally in the form of malformed sternal centers (hypoplastic; off center; and missing), Fused ribs, malformed long bones of fetal hind limbs (missing fibula and hypoplastic ulna), and absence of phalanges.

Table 5. Number of fetuses affected after exposure to dimethoate on gestation days 6 through 15 gestation.

	Dimethoate (mg/kg/d)			
	0	7	15	30
abnormalities (%)	5/257 (2)	5/216 (2)	6/280 (2.1)	3/130 (2.3)
yly	1 (1) [a]	2 (1)	2 (1)	2 (2)
yly	3 (2)	1 (1)	0 (0)	0 (0)
il	0 (0)	1 (1)	3 (2)	1 (1)
almia	1 (1)	1 (1)	1 (1)	0 (0)
abnormalities (%)	3/86 (4)	2/72 (3)	3/93 (3.2)	2/43 (4.7)
lation of lateral ventricles	2 (2)	2 (1)	2 (2)	1 (1)
hrosis (bilateral)b	1 (1)	0 (0)	1 (1)	0 (0)
ilated ureter	0 (0)	0 (0)	0 (0)	1 (1)
abnormalities (%)	1/171 (1)	1/144 (1)	10/187 (5)	76/87 (87)**
ed sternal centers	0 (0)	0 (0)	2 (1)	15 (13)
s	0 (0)	0 (0)	3 (2)	10 (6)
fibula	0 (0)	0 (0)	2 (2)	30 (25)
stic ulna	0 (0)	0 (0)	1 (1)	9 (5)
of phalanges	1 (1)	1 (1)	2 (2)	12 (6)

[a] Number of litter affected in parentheses
[b] Grade 0 kidney; renal papillae not developed
*Significant different from control at P< 0.05; **Significantly different from control at P < 0.01

DISCUSSION

In the present developmental toxicity study, treatment of the pregnant rats from day 6 through 15 of gestation with dimethoate did not produce maternal or embryotoxicity in both the treated groups 7, and 15 mg/kg/d compared to the control group. These results are consistent with the published data from the studies which concluded that dimethoate has no teratogenic effects at the previous dose levels (Srivastava and Raizada, 1996; Courtney *et al,* 1985; IPCS/ WHO, 1992). These results also are consistent with the studies suggested that dosages of the anticholinesterases that are not maternally toxic do not produce embryotoxicity or teratogenicity (Farag *et al.,* 2000; Farag *et al.,* 2003; Clemens *et al.,*1990). In our study, dimethoate at 30 mg/kg/d produced systemic toxicity in the pregnant rats evidenced by the appearance of signs of toxicity, reduction of the maternal weight gains, and decreases of feed consumption. Adjustment for the litter weight component (Day 20 body weight – total fetal weight) indicated that this difference was the result of maternal systemic toxicity and reduced in the amount of feed consumption rather than reduced litter weight or embryolethality. Furthermore, at the highest dose group, pregnant females lost their weights in the period immediately following the initiation of dosing, a factor that could have contributed to the early resorption of entire litters. Total resorption of litters in which only implant sites were visible suggested that a substantial portion of this embryonic death occurred early in the gestation. No significant change was observed in the relative organ weights in any of the treated groups. The incidences of embryolethality and

skeletal malformations were significantly increased in the 30 mg/kg/d. These results are in agreement with the published data which indicated that dimethoate has teratogenic effects in the experimental animals (Khera, 1979; Khera *et al.*,1979; Scheufler, 1975). At the highest dose group, the increase in dead fetuses and early resorptions can likely account for the decrease in the number of live fetuses/litter. On the other hand, the maternal toxicity may have been the trigger for the decreased fetal weights. The published results of the study of the developmental toxicity of dimethoate in the rats indicated that dose of 30 mg/kg/d produced high mortality rate in dams and was not considered for developmental evaluation (Srivastava and Raizada, 1996). These results differ from the current study, one possibility that might explain the difference in results is that the strain of rat used in the previous study may be more susceptible to dimethoate toxicity than the strain used in the present study. Dimethoate is moderately toxic, and is rapidly and extensively absorbed from the gastrointestinal tract and rapidly excreted.

There was no accumulation in fat tissue. In rats and humans, up to 90% of the radiolabel dimethoate was found in the urine within 24 h (Ballantyne and Marrs, 1992). Four metabolites with anticholinesterase activity have been identified in rats and humans. One seems to result from thiono oxidation, leading to the formation of the oxygen analogue of dimethoate which is omethoate; this step was followed by hydrolysis to a thiocarboxyl product, said to be the main metabolite in rats and humans (IPCS/ WHO, 1992). The presence of the oxygen analogue dimethoxon (omethoate) has been demonstrated in insects, plants, and mammals; it appears to be the metabolites responsible for the toxic action of dimethoate (FAO/WHO, 1980; FAO/ WHO, 1997). In vitro and in vivo studies showed that dimethoate is biotransformed to p=o analogue via the liver cytochrom p-450 system (Kaloyanova *et al.,* 1984). Dimethoate toxicity to be markedly increased by Phenobarbital pre- treatment, as a result of induction of hepatic microsomal enzymes including the mixed function oxidases responsible for the conversion of p=s to p=o (Menzer and Best, 1968). However, the toxicity of omethoate is about 10 times more toxic and is a more potent inhibitor of cholinesterase activity than dimethoate (FAO/WHO, 1980; FAO/ WHO, 1997). In conclusion, the present study data demonstrate that dimethoate can produce developmental toxicity in rats at 30 mg/kg/d, which was a maternally toxic dose. No evidence of maternal and developmental toxicity was observed at 7, and 15 mg/kg/day. An ADI of 0-0.002 mg/kg bw was established for dimethoate on the basis of the apparent NOAEL of 1.2 mg/kg bw per day for reproductive performance in the study of the reproductive toxicity in rats, applying a safety factor of 500 (IPCS/WHO,1992). The 15 mg/kg/d dose is about 7500 times the acceptable daily intake for human (ADI = 0.002 mg/kg/d). Although 30 mg/kg/d is about 15,000 times the ADI, we are concerned that such an exposure might occur occupationally, particularly if appropriate industrial hygiene measures are not followed. Thus, there may be a need to re- evaluate the toxicity of dimethoate especially regarding the potential developmental toxicity.

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