Effects of Imidacloprid and Gestational Age on Biodistribution and Maternal Toxicity in Pregnant Mice Compared to Non- Pregnant

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ABSTRACT

Imidacloprid (IMI) is a systemic insecticide belonging to a class of chemicals called the neonicotinoids which act on the central nervous system of insects. It was the most widely used insecticide in the world. However, currently there are limited information regarding the impact of pregnancy on their biodistribution and toxicity. In this study, the biodistribution and potential toxic effects of IMI in pregnant and non–pregnant mice at different critical gestational ages (Gds 8,10,12, and 14) administrated one day treatment of 10, 15, and 20 mg/kg/d IMI by gavage were determined. Also, the effects of IMI on the biodistribution were recorded on pregnant mice administrated repeated doses of 10, 15, and 20 mg/kg/d IMI on different critical gestational days (6- 15, 8- 15, 10- 15, 12- 15, and 14- 15) compared to non- pregnant at the corresponding age. No significant biodistribution changes were observed between non-pregnant and pregnant mice treated on 8, 10, 12, and 14 Gds on all the treated groups of 10, 15, and 20 mg/kg. Apparent toxic effects (e.g., signs of toxicity, reduction in body weights and weight gains at all difference gestational days) were observed by repeated dose of 20mg/kg comparable to controls and non-pregnant. Also, there was a positive relationship between the accumulation of IMI at different gestational ages and maternal toxic effects. These results indicated that the maternal biodistribution patterns of IMI in pregnant mice dependent on dose, exposure length, and gestational ages.

Keywords: Teratogenicity, developmental toxicity, Imidacloprid

INTRODUCTION

Imidacloprid (IMI) is the first chloronicotinyl systemic insecticide belonging to neonicotinoids. It was firstly commercialized in the market in the year 1991 for crop protection and veterinary use. it has become one of the largest selling insecticides worldwide accounting for 41.5% of the whole neonicotinoid market (Jeschke *et al.*, 2010). It is proposed mainly as a seed treatment for wide-ranging crops like rice, cotton, wheat and other crops (potatoes, vegetables, sugar beets, fruits, cotton, hops and turf) (El-Zahi and Farag, 2017).Besides its agricultural use for seed treatment, it is also used to control houseflies on poultry farms, and as foliar spray applications in fruit crops and orchards. Tremendous use of IMI in agriculture may have added to its soil persistence and soil storage (Sarkar, *et al.*, 2001) and ground water contamination (Gervais, *et al.*, 2010). Additionally, it may enter water bodies from spray drift or accidental spills, leading to local point-source contamination. In water sediment system, IMI is degraded by microbes into guanidine compound.

Despite original belief that imidacloprid has low mammalian toxicity, there is increasing evidence that it may cause heart, kidney, and other organ damages along with gastrointestinal irritation, neurological symptoms and even death when ingested along with alcohol (Yeh, *et al.*, 2010). It has been reported that, 90 days oral administration of IMI at 20 mg/kg/day produces pathomorphological changes and hormonal imbalance in female rats (Kapoor, *et al.*, 2011). Previous study with IMI have shown genotoxic effects in rats (Karabay and Oguz, 2005) and cultured human lymphocytes (Demsia, *et al.*, 2007). In albino rats, IMI induced immunological effects (at single dose tested, i.e., 0.21 mg/kg/day for 28 days) were successfully ameliorated with daily supplementation of thymoquinone, an anti-oxidant (Mohany, *et al*., 2012).

Effects of imidacloprid on human health depend on the dose, duration, and frequency of exposure. However, to optimize the beneficial effects of IMI applications, it is essential to understand the fundamental interaction of IMI with biological systems. On the other hand, IMI may be harmful to human health, especially during the formation of the embryo. Therefore, comprehensive knowledge about the distribution or biological fate and toxicity of IMI is needed.

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Distribution of the IMI through the fatal organs adds another important factor to toxicity, especially during pregnancy. A single oral dose of radio-labeled imidacloprid at 20 mg/kg was administered to rats. One hour after dosing, imidacloprid was detected throughout the bodies with the exception of fatty tissues and the central nervous system (Klein, 1987). Embryos are most sensitive to the harmful factors in the critical periods of embryogenesis when mortality or different congenital anomalies are highly possible. The classical critical periods of fetus formation in mice are as follows: implantation and early organogenesis (6- 9 Gds), placenta formation and active organogenesis (10-13 Gds), and the time before birth, when placental activity decreases (18 Gd) (Zalgeviciene *et al.*, 2006).

To date, there is a paucity of data available regarding impacts of IMI potential risks particularly at critical periods of pregnancy. Therefore, the current study was considering the first on literature for determining the effects of Imidacloprid distribution on some maternal parameters on different critical periods of pregnancy. Hence, this study was conducted to prove or negate our theory assumed that "Does accumulation of IMP in the fatal organs and blood at the critical periods of pregnancy give different toxic effects of IMI? To prove or disprove this theory, pregnant mice were treated at the critical pregnancy's periods using three dose levels: one that induces some toxicity on pregnant females (20 mg/kg/d), one unable to induce toxicity (10 mg/kg/d) and intermediate one (15 mg/kg/d) compared to control and non-pregnant mice. These doses were approximately equal 1/15, 1/10, 1/8 of acute oral LD_{50} imidacloprid in mice which equal to 150 mg/kg/d *(Gupta, et al., 2019)*.

MATERIALS AND METHODS

1. Tested insecticide and reagents:

Imidacloprid technical 95% pure was obtained from Changlong Chemical Industrial Group (Changzhou, Jiangsu, China). Methyl sulfoxide (DMSO), methanol and acetonitrile (HPLC-grade) were purchased from Acros-Organics (USA).

2. Tested animals:

Four hundred forty pregnant, 440 non-pregnant, and 220 male mice (CD- 1 Wistar strain) were obtained from the Faculty of Science, Alexandria University, Alexandria, Egypt. All animals were maintained under standard management conditions (23 ± 2 °C, 50–60% relative humidity, and 12 h light-dark cycles). The animals were given standard pellet diet (Feed Animal Private Company, Alexandria, Egypt) and tap water for drinking *ad-libitum*. Animals were acclimatized in the laboratory conditions for a period of two weeks prior to the start of experiment. An approval from Alexandria Animal Ethics Committee (AUAEC), Alexandria University, Alexandria, Egypt was obtained.

2. Experimental design and treatment:

2.1. Pregnant mice:

440 females mated with 220 males (2 females / one male) and the presence of vaginal plug was confirmed 12 hr later and considering as day 0 of gestation. Bred females were randomly assigned to treatment groups according to the body weights.

The pregnant mice were divided into nine groups as follows:

Four groups of pregnant mice according to the gestational ages (critical gestational periods) were: gestation days (Gds) 8, 10, 12, and 14 (40 mice / each). Each group was devided into four subtreatment groups (n = 10 pregnant) as follows:

Subgroup 1: Control, receiving corn oil as vehicle by gastric gavage in the same amount as that used for disolving imedacloprid in the other groups.

Subgroup 2: Received imedaclprid at a dose of 10 mg/kg/ day.

Subgroup 3: Received imedaclprid at a dose of 15 mg/kg/day.

Subgroup 4: Received imedaclprid at a dose of 20 mg/kg BW/day.

The administered volume of each dose was 0. 4 ml/kg body weight per day and adjusted for recorded body weight changes during the study.

Other four groups of pregnant mice (fourty/ each) for studying the effects of distribution of the IMI on maternal parameters toxicity through different gestational periods as follow: 8- 15, 10- 15, 12-15, and 14- 15 Gds. Each group was divided into four group subtreatment groups (10 mice / each) as descriped prevouisly.

The last group of pregnant mice was treated by gavage on gestation days 6- 15 to confirm the results of distribution of IMI and its effects on maternal parameters compared to the controls. Also it was devided to four subtreatment groups as prevouisly decribed (n= 30 mice).

2.2. Non pregnant mice:

Fourty hundred and fourty of non pregnant mice were randomaly assigned to the same nine groups as pregnant mice at the same crossponding ages. Each group was divided into four subtreatment groups of 0, 10, 15, and 20 mg/kg/day. The administered volume of each dose

was 0. 4 ml/kg body weight per day and adjusted for recorded body weight changes during the study. Treated non pregnant mice were used to compare the results of the distribution of IMI for pregnant mice.

2.3. Maternal Observations:

3.1. Clinical Signs of Toxicity:

Pregnant and non- pregnant females for each group were examined daily (between 9:00 and 10:00 am) for signs of toxicity in the form of salivation, vomiting, diarrhea and muscle weakness according to Hovda *et al.*, 2005.

3.2. Maternal weights and weight gains:

Maternal body weights were recorded on gestational days (Gds.) according to the critical gestational periods. Maternal weights were recorded on Gds. of 6, 8, 10, 12, and 14 (one treatment day) after 24 hr. of the treatment. For the repeated doses group, maternal weights were recorded on day 0, first day of the treatment, and the day of caesarian sections for all the treated groups. Body weights for non-pregnant mice were also recorded at the same manner of pregnant mice and at the same crossponding ages.

3.2. Maternal Organ Weights:

Weights of maternal liver, kidneys, and brain were recorded at the Cesarean section time on day 18 of gestation (8- 15, 10- 15, 12- 15, 14- 15, and 6- 15 Gds.). Also, organs weight were recorded for one treatment day groups (Gds. 8, 10, 12, and 14).

3. Determination of Imidacloprid accumulation in the organ tissues and blood by HPLC:

3.1. Extraction of Imidacloprid from organ tissues and blood:

Extraction of the IMI was carried out on all the treated groups of pregnant and non- pregnant mice. While Pregnant treated by one day treatment ((Gds. 8, 10, 12, 14) were killed after 24 hrs. of treatment, pregnant mice treated on Gds. 6- 15, 8- 15, 10- 15, 12- 15, and 14- 15 were killed on day 18 of gestation. Non pregnant groups in the same crossponding ages and treated groups were killed at the same time. Three tissues (brain, liver, and kidneys) and blood samples from each group were collected. Imidacloprid was extracted from brain, liver, kidneys, and blood, of pregnant and non- pregnant mice by using the methods of Yang *et al.*, 2014 and Devan *et al*., 2015 with slight modifications.

Brain, liver, kidneys tissues and 0.5 ml of blood samples/ each were excised, weighed, and minced finely and then homogenized for 2 mins with 5 ml of acetonitrile, 5 ml of methanol and 1g sodium sulfate anhydrous. The homogenates were clarified through a filter paper (No.1). The combined acetonitrile extracts were frozen for 2h at -4 C° to remove the remaining fatty acids. The extracts were clarified once more and De-ionized water and HPLC grade solvent were degassed in an ultrasonic bath just before used. Evaporated to dryness using rotary vacuum evaporator and reconstituted with 1ml of methanol.

3.2. Determination of Imidacloprid content:

Estimation of imidacloprid were done on Agilent 1260 infinity II chromatographic system encompassed with a quaternary pump, a micro vacuum degasser, a thermo stated column compartment equipped with a diode array UV detector at 270 nm. 5 ul of samples were injected by autosampler into Agilent Zorbax SB-C_{18} (250 × 4.6 mm, 5 µm) column. Mobile phase was water: methanol HPLC grade (50:50, v/v) and the flow rate 1 ml/min. Filtration of the mobile phase was carried out before injection using 0.45 µm Millipore membrane filter. Agilent OpenLAB CDS ChemStation software, version C.01.07 was utilized to collect and process data. The utilized mobile phase consisted of water: methanol (50:50, v/v). Filtration of the mobile phase was carried out before injection using 0.45 µm Millipore membrane filter. The HPLC calibration standards of imidacloprid with 95% purity were prepared from a 100 µg mL^{-1} stock solution in HPLC grade methanol was used for the preparation of working standard solution up to 0.0625 µg/ml. For standard calibration curve according to the method described by (Yang *et al.*, 2014 and Devan *et al*., 2015). The total run time was about 3.2 min.

Recovery studies: Untreated organ were spiked with 3 incremental concentrations of the technical grade of imidacloprid (0.75, 1.50 and 3.00 µg) prior to extraction and clean-up. Three replicates of each concentration were passed through the entire process of extraction, clean-up and analysis. The recovery values were calculated, and the obtained results were corrected according to the recovery rate.

2.4. Statistical Evaluation:

Maternal toxicity was estimated from maternal body weight, weight gain, and absolute and relative organ weights. Analysis of obtained data was carried out using one-way analysis of variance (ANOVA) test using SPSS 19.0 software (IBM Corporation, Armonk, NY, USA)., followed by multiple comparisons test to determine the least significance of differences among groups. Data are presented as mean ± SE. The criterion of statistical significance was fixed at probability level $P < 0.05$, with the litter as the treatment unit was used to compare toxicity rates between the treated groups. The maternal body weight on GD6 was used as a covariant

(ANOVA) for comparing weights of the treated groups with those of the control.

Statistical significance between different groups for them was evaluated by LSD t-test or Tukey's method after analysis of variance (ANOVA). Statistical analyses were performed by comparing the treatment groups with the control group. (Lehmann and D'Abrera 1975, Norušis 1994).

RESULTS

Maternal tissue and blood accumulation of imidacloprid:

1. In Organ tissues:

Distribution levels of imidacloprid in the pregnant and non-pregnant brain, liver, and kidneys mice tissues as well as the blood serum after oral administration of Imidacloprid (IMI) by gavage shown in Tables 1- 4.

There were no significant detectable levels of IMI were recorded in any of organ tissues for tested gestational ages (8, 10, 12, and 14 (one- treatment day) on all treated groups of 10, 15, and 20 mg/kg/d compared to the controls (Data not shown).

Results obtained in the present work revealed a dose-related accumulation of IMI residues in all examined tissues of different dosed. The residues of imidacloprid showed a rising tendency with increasing the exposure length period for pregnant and non-pregnant mice. The imidacloprid contents in all the organs were significantly increased with increasing maternal exposure length compared to non-pregnant (8-15 Gds. (0.282, 0.422 µg/g brain; 0.140, 0.148 µg/g kidneys; 0.306, 0.588 µg/g liver, on 15 and 20 mg/kg, respectively); (10 - 15 Gds. (0.249 µg/g brain; 0.093 µg/g kidneys on 20 mg/kg; 0.230, 0.312 µg/g liver on 15 and 20 mg/kg, respectively); (12- 15 Gds. (0.220 µg/g brain; 0.031 µg/g kidneys; 0.288 µg/g liver on 20 mg/kg/d); (14- 15 Gds. (0.190 µg/g brain on 20 mg/kg; 0.011 µg/g kidneys; 0.170 µg/g liver on 20 mg/kg). For non- pregnant, the same trend for the IMI contents in the different organs was shown as follows: (8- 15 Gds. (8 continuously treatment days) (0.91, 0.127 µg/g brain; 0.083, 0.112 µg/g liver on 15 and 20 mg/kg, respectively; 0.003 µg/g kidneys on 20 mg/kg/day); (10-15 Gds. (6 treatment days) (0.093 µg/g liver on 20 mg/kg). For 4 and 2 continuously treatment days for non- pregnant groups, there were no detectable levels of IMI found on all the organs compared to the controls.

Pregnant mice treated on 6-15 Gds. (10 continuously doses) had dose dependent effects of IMI organ contents as follows: 0.328, 0.636, 0.800 µg/g brain; 0.131, 0.154, 0.577 µg/g kidneys; 0.182, 0.428, 0.622 µg/g liver for 10, 15, and 20 mg/kg/day compared to the control. For non-pregnant, IMI contents were found on all the organ tissues in the same manner of pregnant mice. IMI contents were as follows: 0.039, 0.144, and 0.254 µg/g brain; 0.094, 0.097, 0.217 µg/g liver on 10, 15 and 20 mg/kg/day, respectively; 0.06, 0.09 µg/g kidneys on 15 and 20 mg/kg/day, respectively compared to the controls.

2. In blood serum:

Data are shown in Tables 3 and 4 While the deposition of imidacloprid in the blood serum of dams treated on Gds. 8 and 10 (one day treatment) was detected on 15 mg/kg/ day (0.144, 0.264 µg/ml on 8 and 10 Gds., respectively) and 20 mg/kg/day (0.261, 0.570 µg/ml on 8 and 10 Gds., respectively), a dose dependent manner was appeared on Gds. 12 and 14 for serum level of IMI content. IMI serum levels were as follows: 0.392, 1.295, 2.692 µg/ml for 12 Gd; 0.570, 1.954, 4.514 µg/ml on 14 Gd compared to the controls. In the same trend, accumulation of IMI in serum blood was detected for non- pregnant mice on the treated groups of 15 and 20 mg/kg/day at the same age and one day treatment compared to the controls. IMI serum contents for non-pregnant were: 0.123, 0.218 µg/ml for corresponding age of 8 Gd; 0.128, 0.220 µg/ml for corresponding age of 10 Gd; 0.130, 0.227 µg/ml for corresponding age of 12 Gd, and 0.135, 0.227 µg/ml for corresponding age of 14 Gd on 15 and 20 mg/kg/day, respectively compared to the control group.

In a dose dependent manner, levels of IMI were increased significantly by increasing the dose and exposure length except treated group on 14-15 Gds. as follows: 8- 15 Gds. (2.137, 4.162, 5.836 µg/ml); 10 - 15 Gds. (1.192, 1.793, 3.255 µg/ml); 12- 15 Gds. (0.632, 1.232, 1.354 µg/ml); 14- 15 Gds. (0.263 µg/ml on 20 mg/kg/d) compared to the controls. In the same trend and in a dose dependent manner, IMI serum contents of non- pregnant mice were measured. IMI serum contents for non-pregnant were: 0.972, 1.894, 2.655 µg/ml for corresponding age of 8-15 Gds.; 0.235, 0.629 µg/l on 15 and 20 mg/kg/day, respectively for corresponding age of 12-15 Gds. compared to the control group.

Table 1. Relative IMI (µg/g) accumulation in pregnant mice organs after repeated doses at different critical gestational periods:

Dose	Brain				Kidneys				Liver			
(mg/Kg/d)	0	10	15	20	0	10	15	20	0	10	15	20
Gds												
6- 15	N	0.328 ± .1**	0.634 ± .02**	0.800 ± .1**	N	0.131±.06**	0.154±.08**	0.577±.07**	N	0.182±.01**	0.428±.04**	0.622±.05**
8- 15	N	N	0.282 ± .01**	0.422 ± .07**	N	N	0.140 ± .08**	0.148 ± .01**	N	N	0.306 ± .02**	0.588 ± .07**
10 - 15	N	N	N	0.249 ± .09**	N	N	N	0.093 ± .04*	N	N	0.230 ± .01**	0.312 ± .03**
12- 15	N	N	N	0.220 ± .03**	N	N	N	0.031 ± .01**	N	N	N	0.288 ± 11**
14 - 15	N	N	N	0.190 ± .04**	N	N	N	0.011 ± .08*	N	N	N	0.170 ± .05**

N= Nondeductible

*Significantly different from control at P ≤0.05

**Significantly different from control at P ≤ 0.01 by ANOVA with Tukey's test post –hoc

Table 2. Relative IMI (µg/g) accumulation in non-pregnant mice organs after repeated doses at the crossponding ages:

Dose	Brain				Kidneys				Liver			
(mg/Kg/d)	0	10	15	20	0	10	15	20	0	10	15	20
Gds.												
6- 15	N	0.390 ± .05**	0.144 ± .02**	0.0.254 ± .01**	N	N	0.06 ± .04*	0.09 ± .05*	N	0.094 ± .09*	0.097 ± .08	0.217 ± .04**
8- 15	N	N	0.091 ± .01*	0.127 ± .07**	N	N	N	0.03 ± .03*	N	N	0.083 ± .02*	0.112 ±.0**
10 - 15	N	N	N	0.249 ± .09**	N	N	N	0.093 ± .04*	N	N	0.230 ± .01**	0.093 ± .03*
12- 15	N	N	N	N	N	N	N	N	N	N	N	N
14 - 15	N	N	N	N	N	N	N	N	N	N	N	N

N= Nondeductible

*Significantly different from control at P ≤0.05

**Significantly different from control at P ≤ 0.01 by ANOVA with Tukey's test post –hoc

Table 3. Relative IMI (µg/g) accumulation in pregnant mice blood serum after administration of single dose at different gestational periods compared to the accumulation on non- pregnant blood serum at the crossponding ages

Gds	P[1] Dose (mg/kg/d)				NP[2] Dose (mg/kg/d)			
	0	10	15	20	0	10	15	20
8	N	N	0.144 ±12 **	0.261± 14**	N	N	0.123 ± 16**	0.218 ±28**
10	N	N	0.264 ± 18**	0.570 ± 27**	N	N	0.128 ± 12**	0.220 ± 22**
12	N	0.392 ± 10**	1.295 ± 55**	2.692 ± 54**	N	N	0.130 ± 15**	0.227 ± 23**
14	N	0.570 ± 28**	1.954 ±46**	4.514 ± 60**	N	N	0.135 ± 18**	0.227 ± 23**

[1]Pregnant mice

[2]Non-pregnat

**Significantly different from control at P ≤ 0.01 by ANOVA with Tukey's test post –hoc.

Table 4. Relative IMI (µg/g) accumulation in pregnant mice blood serum after administration of repeated doses at different gestational periods compared to non- pregnant at the crossponding ages

Gds	P[1] Dose (mg/kg/d)				NP[2] Dose (mg/kg/d)			
	0	10	15	20	0	10	15	20
6 – 15	N	3.045 ± 55**	5.932 ±87**	6.617 ± 88**	N	1.488 ± 45**	2.900 ± 88**	4.665 ± 67**
8 – 15	N	2.137 ± 62**	4.162 ± 57**	5.836 ± 68**	N	0.972 ± 67**	1.894 ± 55**	2.655 ± 45**
10 – 15	N	1.192 ± 45**	1.793± 64**	3.255 ± 45**	N	N	0.235 ± 23**	0.629 ± 20**
12 – 15	N	0.632 ± 34**	1.232**± 53**	1.354 ± 48**	N	N	N	N
14 – 15	N	N	N	0.263 ± 14**	N	N	N	N

[1]Pregnant mice

[2]Non-pregnat

Nondeductible (N)

**Significantly different from control at P ≤ 0.01 by ANOVA with Tukey's test post –hoc

Pregnant mice treated on 6- 15 Gds. (10 continuously doses) had a dose dependent effects of IMI serum contents as well as non- pregnant as follows: 3.045, 5.932, 6.617 µg/ml for pregnant mice; 1.488, 2.900, 4.065 µg/ml for non-pregnant mice compared to the controls.

2. Maternal toxicity:

2.1. Maternal Signs of toxicity:

There were no deaths or abortions associated with single or repeated gestational exposure to all the treated groups compared to the control. Single oral dose or repeated exposure of IMI of 20 mg/kg body weight for pregnant in different gestational periods and non-pregnant in corresponding ages had not produced overt signs of toxicity in female mice but showed mild symptoms of toxicity like salivation, diarrhea, tremor, and weakness in all the treated groups. The clinical signs of toxicity appeared at 6 hr. after single or repeated doses and persisted up to 24 hrs. for single doses and progressed throughout the period of treatment for repeated dose group of 20 mg/kg/day. These signs were seen in 50 to 80 % of dams in all the single and repeated groups. No signs of toxicity appeared in single or repeated groups for 10 and 15 mg/kg/d compared to the control groups.

2. 2. Maternal body weights and weight gain:

There were no statistically significant differences in the weight of the dams and non-pregnant as well as the weight gains among all groups treated with only one day dose of 10, 15, and 20 mg/kg/day of imidacloprid (IMI) on the gestation days (Gds.) of 8, 10, 12, and 14 and the corresponding ages for non-pregnant compared to the control groups. Body weights recorded on the next day of treatment for both pregnant and non-pregnant (24 hours of treatment) (data not shown).

Tables 5 and 6 summarize the maternal body weights (mean ± standard deviation) recorded during different critical periods of pregnancy with different doses in terms of quantity and number. Statistically significant reduction on the maternal body weights (of pregnant mice treated with 20 mg/kg/day IMI on gestation days 8- 15 (8-contanously doses), 10- 15 (6 continuously doses), and 12 – 15 (4 continuously doses) were recorded compared to the controls and other treated groups. This reduction appeared on 18 Gd (Percent of reduction was equal to 12, 13, 7% of controls for the same previous critical gestational periods, respectively) (Table 5). No significant statistically differences on the maternal body weights were observed on all the treated groups of Imidacloprid on gestation day 14- 15 (two continuously doses) compared to the control (Table 5).

In the mice group treated with 15 and 20 mg/kg/day Imidacloprid on gestation days 6- 15 (10 continuously doses) to confirm the results, statistically significant decreases in the maternal body weights were observed. These decreases on maternal body weights appeared on Gd 18 by a percentage 5, 11% for 15 and 20 mg/kg/day, respectively (Table 5).

No statically significant differences in the body weights of non- pregnant mice on all the treated groups of 10, 15, 20 mg/kg/day at all the crossponding ages compared to the control groups (Table 6). Data are shown according to differences on the body weight on Gd 0.

Data of maternal weight gains are shown in Figure 2. There were a significant decrease in dams body weight gains in the highest IMI dose 20 mg/kg/day on all the treated groups of 8- 15, 10- 15, 12- 15, and 14- 15 Gds which started from the first day of the treatment through the end. The percentage of overall reduction (0-18 Gds.) on the 20 mg/kg/day was 39, 30, 19, and 19 % for mice treated on 8- 15, 10- 15, 12- 15, and 14-15 Gds., respectively compared to their corresponding control groups. Maternal body weight gain was decreased on the middle and highest groups of 15 and 20 mg/kg/day for the mice treated on 6- 15 Gds. The reduction also started from first treatment day, and it escalated to reach a maximum for gestation day 18. The percentage of reduction was equal to 13 and 35% for 15 and 20 mg/kg/day respectively compared to the control.

In the same manner, no statically significant differences in the body weight gains of non-pregnant mice on all the treated groups of 10, 15, 20 mg/kg/day at all the crossponding ages compared to the control groups (Fig.1).

2.3. Maternal Organ weights:

On the level of the effect of Imidacloprid on the absolute organ weights of pregnant female mice after cesarean section, the results present in Tables 7- 11. When compared with the control groups, significant decreases in the absolute weights of the brain were recorded in the 20 mg/kg/day, which treated in different pregnancy periods of 6-15, 8 -15, 10-15, 12-15 and 14-15 Gds. compared to the control groups and 10 mg/kg/day. Absolute weights of brain and kidneys decreased on the treated group of 20 mg/kg/d exposed on 14-15 Gds. compared to the control. No significant differences in all the absolute weights of non- pregnant

treated in the same crossponding ages compared to the controls.

No statistically significant differences in the relative organ weights for pregnant and non- pregnant mice on all the treated groups of 10, 15, and 20 mg/kg/d at the different gestational periods compared to the controls.

No statistically significant differences on Absolute or relative for pregnant and non- pregnant organ weights treated on Gds. 8, 10, 12, and 14 by one day treatment compared to the controls (Data not shown).

DISCUSSION AND CONCLUSION

Unlike prenatal exposure to IMI which has been examined in detail in the rodents and humans, the effects of the critical periods of gestation exposure of mammals to the distribution of IMI in tissues and serum blood has remained relatively unexplored. We sought to begin to fill this gap by investigating the effects of IMI content levels in the different tissues and serum blood on the critical periods of gestation on some maternal parameters compared to the non- pregnant mice.

Mild acute effects of IMI such as salivation, diarrhea, tremor, and weakness in the highest treated group of 20 mg/kg/d in pregnant and non-pregnant mice at critical periods of gestation were recorded This result were in consistent with the results of the studies of (Tamura, *et al,.* 2002, Proença, Teixeira *et al.*, 2005, Agarwal and Srinivas 2007, David, *et al.*, 2007, Lin, *et al.*, 2013) which indicated that repeated oral administration of imidacloprid at 5 and 10 mg/kg/day did not produce any signs of toxicity and mortality during all exposure periods of the pregnant and non- pregnant mice.

Table 5. Effects of Imidacloprid on body weights of female mice treated on different gestational days

	Doses (mg/kg/day)			
	0	**10**	**15**	**20**
	Body weight (g)			
Gds. (6- 15)[1]				
Number of Dams[2]	25	27	24	28
0	26.0 ± 0.1	26.7 ± 0.3	25.9 ± 0.6	26.9 ± 0.3
6	27.5 ± 0.4	28.1 ± 0.5	27.5 ± 0.4	28.2 ± 0.5
18	42.1 ± 0.5	42.4 ± 0.5	39.9 ± 0.6*	37.4 ± 0.5**
Gds (8- 15)[1]				
0	25.8 ± 0.2	26.5 ± 0.4	26.0 ± 0.1	26.7 ± 0.2
8	28.9 ± 0.3	29.3 ± 0.4	28.9 ± 0.1	29.4± 0.2
18	40.8 ± 0.5	41.2 ± 0.8	41.7 ± 0.6	35.9 ± 0.9**
Gds. (10-15)[1]				
0	26.8± 0.4	26.1 ± 0.5	25.9 ± 0.9	25.7 ± 0.4
10	31.0 ± 0.3	30.5 ± 0.2	30.8 ± 0.7	31.1 ± 0.5
18	40.2 ± 0.3	40.0 ± 0.9	39.9 ± 0.2	35.1 ± 0.2**
Gds. (12-15)[1]				
0	26.2 ± 0.1	27.3 ± 0.5	26.5 ± 0.4	25.9 ± 0.5
12	32.4 ± 0.2	33.4 ± 0.4	33.1 ± 0.3	32.9 ± 0.4
18	40.7 ± 0.6	40.9 ± 0.3	41.1 ± 0.4	37.8 ± 0.3**
Gds. (14-15)[1]				
0	25.8 ± 0.2	26.0 ± 0.5	26.5 ± 0.4	27.1 ± 0.3
14	35.6 ± 0.4	36.1 ± 0.3	35.9 ± 0.3	35.4 ± 0.3
18	41.0 ± 0.5	41.6 ± 0.2	40.9 ± 0.6	40.4 ± 0.4

[1]Gestation days

[2] Number of dams for each treated group (n= 10) except Gds (6-15).

*Significantly different from control at P ≤0.05.

**Significantly different from control at P ≤ 0.01

Table 6. Effects of Imidacloprid on body weights of non- pregnant mice treated on corresponding ages of pregnant

	Doses (mg/kg/day)			
	0	**10**	**15**	**20**
	Body weight (g)			
(10 doses)[1]				
Number of Dams[2]	25	27	24	28
0	25.0 ± 0.2	25.8 ± 0.4	27.0 ± 0.6	26.3 ± 0.4
6	25.5 ± 0.5	26.2 ± 0.8	27.5 ± 0.5	26.9 ± 0.3
18	26.9 ± 0.5	27.8 ± 0.3	28.9 ± 0.4	28.4 ± 0.3
(8 doses)[1]				
0	25.2 ± 0.1	26.1 ± 0.2	26.3 ± 0.3	25.8 ± 0.5
8	26.1 ± 0.4	27.2 ± 0.5	27.6 ± 0.3	26.7± 0.2
18	28.5 ± 0.5	29.5 ± 0.6	29.9 ± 0.5	29.2 ± 0.6
(6 doses)[1]				
0	25.6 ± 0.3	25.1 ± 0.7	25.3 ± 0.4	25.8 ± 0.2
10	27.2 ± 0.4	26.8 ± 0.5	26.9 ± 0.7	27.6 ± 0.4
18	28.0 ± 0.2	27.7± 0.6	27.7 ± 0.2	28.4 ± 0.2
(4 doses)[1]				
0	25.4 ± 0.1	26.6 ± 0.5	26.1 ± 0.2	26.0 ± 0.3
12	27.0 ± 0.1	28.0 ± 0.3	27.5 ± 0.2	27.5 ± 0.2
18	27.9 ± 0.5	29.0 ± 0.1	28.7 ± 0.5	28.9 ± 0.1
(2 doses)[1]				
0	25.5 ± 0.7	26.4 ± 0.4	26.5 ± 0.3	26.1 ± 0.6
14	27.3 ± 0.3	28.3 ± 0.3	28.4 ± 0.4	28.0 ± 0.1
18	28.8 ± 0.5	29.8 ± 0.3	29.8 ± 0.2	29.4 ± 0.4

[1]Corrosponding ages for non-pregnant

[2] Number of dams for each treated group (n= 10) except Gds. (6-15).

Data are shown according to differences on the body weight on Gd 0.

There were no effects on the weights and weight gains of the pregnant mice treated on different critical periods of pregnancy in all the treated groups (10, 15, and 20 mg/kg/day) by one day- treatment compared to the control. These results indicated that if pregnant mice were exposed to one day- treatment of IMI on any of the critical gestational days, the pregnant did not show any changes, whether in their body weight or appetite. These results were in consistent with our results for the IMI contents in brain, liver, and kidneys which indicated no detectable IMI accumulation

The reduction of the maternal weight gains was found to be decreased on 20 mg/kg/day for all the groups in the critical periods of gestation, whereas the length of exposure period was found to be increased. Among the treated mice in different gestation periods, the highest percentage of the maternal weight reduction was identified on 20 mg/kg/day for the treated groups of 8- 15 Gds., followed by 10-15 Gds., and then from 12-15 Gds. compared to the controls. The percentages of reduction in the maternal weight gains on these groups were as follows; 39, 30, 18, and 20% for 8- 15, 10- 15, 12, 15, and 14- 15, respectively of the controls. There was a direct relationship between the length of exposure to the IMI and the percentage of reduction in the maternal weight gains. In addition, the risk of exposure to the imidacloprid was also increased by maternal exposure on organogenesis critical period. These results are in consistent with the data reported that there was a significant decrease in the body weight gain of mice in the high dose group of 20 mg/kg/day(Zheng, *et al.*, 2020). In similar, significant toxic symptoms, together with significant decrease in weight gain appeared in rats exposed to 20 mg/kg/day of IMI (Kapoor, *et al.*, 2011). Exposure of pregnant mice on 6- 15 gestational days produced reduction on the body weight and weight gains on the middle and highest doses of imidacloprid compared to the control.

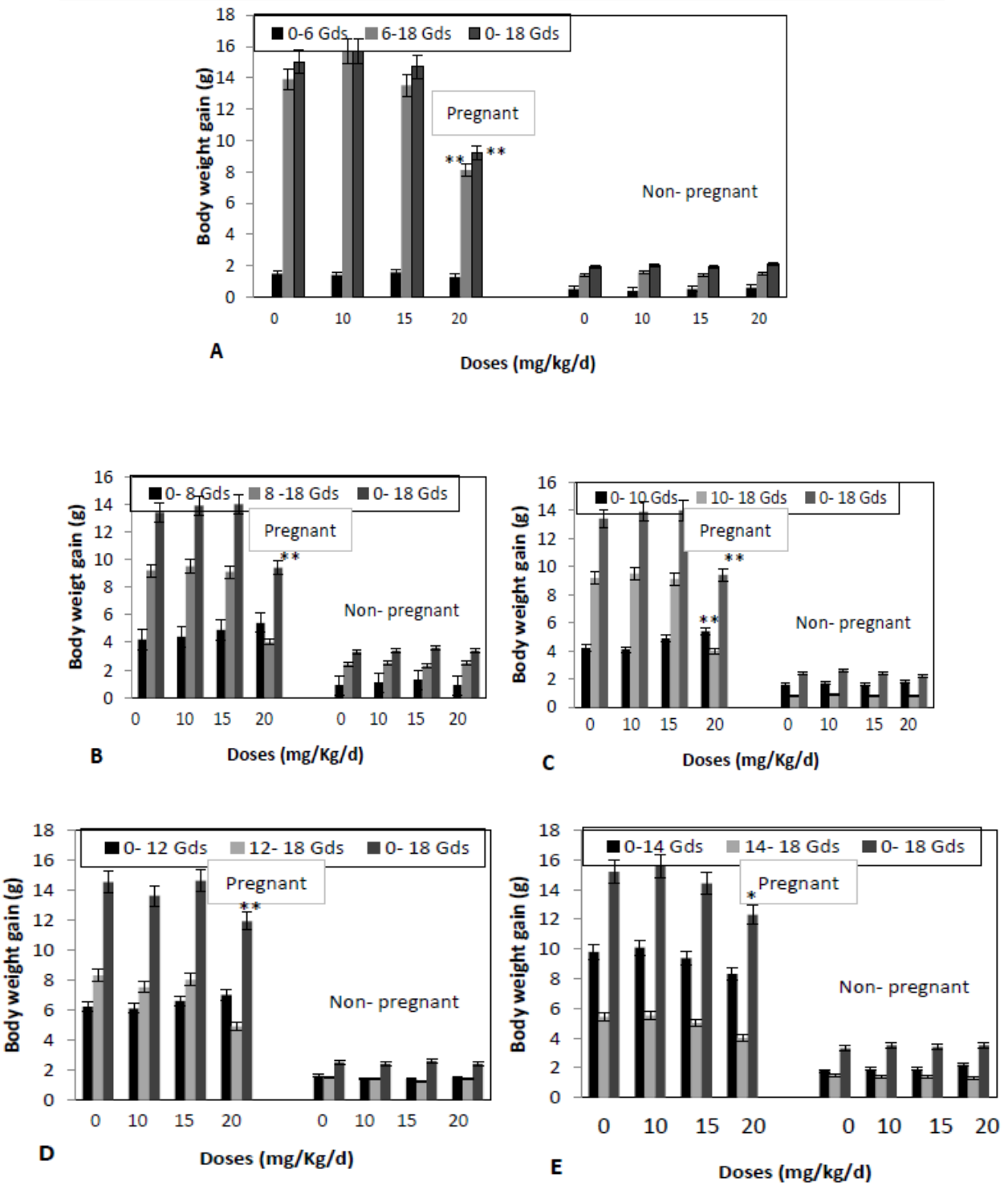

Fig. 1. Effects of IMI on the weight gains of pregnant mice treated on (A) 6- 15 Gds. (n = 30), (B) 8-15 Gds. (n= 10), (C) 10-15 Gds. (n= 10), (D) 12- 15 Gds. (n= 10), and (E) 14- 15 Gds. (n = 10) compared to non- pregnant mice in the same crossponding ages and number. Data are shown as mean ± SD. **Significantly different from control at P ≤ 0.01.

Table 7. Effects of Imidacloprid on organs weight of pregnant mice treated on gestational days 6 – 15 compared to non- pregnant.

	Doses (mg/kg/d)			
	0	**10**	**15**	**20**
Number of dams[1]	10	10	10	10
Terminal pregnant body weight (g)	42.1 ± 0.5	42.4 ± 0.5	39.9 ± 0.6*	37.4 ± 0.5**
Terminal non-pregnant body weight (g)	25.0 ± 0.2	25.8 ± 0.4	27.0 ± 0.3	26.3 ± 0.4
		Absolute organs weight (g)		
		Pregnant		
Liver	2.14 ± 0.03	2.19 ± 0.04	2.14 ± 0.04	2.26 ± 0.03
Kidneys	0.39 ±0.03	0.40 ± 0.02	0.39 ± 0.02	0.40 ± 0.03
Brain	0.43 ± 0.04	0.42 ± 0.03	0.41 ± 0.03	0.37 ± 0.04**
		Non- pregnant		
Liver	1.37 ± 0.05	1.43 ± 0.05	1.46 ± 0.03	1.44 ± 0.08
Kidneys	0.24± 0.03	0.27 ± 0.03*	0.28 ± 0.02*	0.24 ± 0.03
Brain	0.25 ± 0.03	0.27 ± 0.03*	0.27 ± 0.03*	0.26 ± 0.03
		Relative organs weight[2]		
		Pregnant		
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002
		Non- pregnant		
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002

[1]Number of pregnant females used in experiment

[2]Organ weight (g)/body weight (g)

*Significantly different from control at P ≤0.0

Table 8. Effects of Imidacloprid on organs weight of pregnant mice treated on gestational days 8- 15 compared to non- pregnant.

	Doses (mg/kg/d)			
	0	**10**	**15**	**20**
Number of dams[1]	10	10	10	10
Terminal pregnant body weight (g)	41.7 ± 0.6	41.2 ± 0.8	40.8 ± 0.5	35.9 ± 0.9**
Terminal non-pregnant body weight (g)	29.9 ± 0.6	29.5 ± 0.5	29.2 ± 0.5	28.5 ± 0.6
		Absolute organs weight (g)		
	Pregnant			
Liver	2.30 ± 0.08	2.27 ± 0.03	2.20 ± 0.05	2.22 ± 0.05
Kidneys	0.43 ±0.03	0.43 ± 0.02	0.40 ± 0.03	0.40 ± 0.03
Brain	0.44 ± 0.03*	0.42 ± 0.03	0.41 ± 0.03	0.37± 0.03
	Non- pregnant			
Liver	1.55 ± 0.05	1.60± 0.05	1.56± 0.03	1.58 ± 0.08
Kidneys	0.27± 0.03	0.27 ± 0.03	0.29± 0.02	0.33± 0.03
Brain	0.28 ± 0.03	0.28± 0.03	0.30 ± 0.03	0.28± 0.03
	Relative organs weight[2]			
	Pregnant			
Liver	0.05 ± 0.002	0.05± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002
	Non- pregnant			
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.002
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.001

[1]Number of pregnant females used in experiment

[2]Organ weight (g)/body weight (g)

*Significantly different from control at P ≤0.05.

Table 9. Effects of Imidacloprid on organs weight of pregnant mice treated on gestational days 10- 15 compared to non- pregnant.

	Doses (mg/kg/d)			
	0	**10**	**15**	**20**
Number of dams[1]	10	10	10	10
Terminal pregnant body weight (g)	40.2 ± 0.3	40.0 ± 0.2	39.9 ±0.2	35.1 ± 0.2
Terminal non-pregnant body weight (g)	28.0 ± 0.2	27.7± 0.6	27.7 ± 0.2	28.4 ± 0.2
		Absolute organs weight (g)		
	Pregnant			
Liver	2.20 ± 0.06	2.23 ± 0.04	2.29 ± 0.04	2.20 ± 0.03
Kidneys	0.40 ±0.04	0.42 ± 0.05	0.44 ± 0.02	0.42 ± 0.04
Brain	0.41 ± 0.03	0.41 ± 0.03	0.43 ± 0.03	0.39 ± 0.03*
		Non- pregnant		
Liver	1.53 ± 0.04	1.54± 0.08	1.58± 0.04	1.52 ± 0.03
Kidneys	0.27± 0.05	0.29 ± 0.03	0.30 ± 0.05	0.33 ± 0.03
Brain	0.28± 0.04	0.28 ± 0.08	0.29 ± 0.04	0.31 ± 0.03
		Relative organs weight[2]		
	Pregnant			
Liver	0.05 ± 0.002	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002
		Non- pregnant		
Liver	0.05 ± 0.002	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002

[1]Number of pregnant females used in experiment

[2]Organ weight (g)/body weight (g)

*Significantly different from control at P ≤0.05.

Table 10. Effects of Imidacloprid on organs weight of pregnant mice treated on gestational days 12- 15 compared to non- pregnant.

	Doses (mg/kg/d)			
	0	**10**	**15**	**20**
Number of dams[1]	10	10	10	10
Terminal pregnant body weight (g)	40.7 ± 0.6	40.9 ± 0.3	41.1 ± 0.4	37.8 ± 0.3
Terminal non-pregnant body weight (g)	27.9 ± 0.5	29.0 ± 0.1	28.7 ± 0.5	28.9 ± 0.1
	Absolute organs weight (g)			
	Pregnant			
Liver	2.23 ± 0.03	2.20 ± 0.03	2.15 ± 0.03	2.22 ± 0.03
Kidneys	0.39 ±0.04	0.42 ± 0.02	0.41 ± 0.03	0.43 ± 0.03
Brain	0.40 ± 0.03	0.40 ± 0.03	0.41 ± 0.03	0.38± 0.03*
	Non- pregnant			
Liver	1.54± 0.03	1.58± 0.03	1.50± 0.04	1.51 ± 0.04
Kidneys	0.27± 0.04	0.30 ± 0.02	0.28± 0.03	0.32 ± 0.03
Brain	0.27± 0.03	0.27± 0.03	0.28 ± 0.03	0.27± 0.03
	Relative organs weight[2]			
	Pregnant			
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002
	Non- pregnant			
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002

[1]Number of pregnant females used in experiment

[2]Organ weight (g)/body weight (g)

*Significantly different from control at P ≤0.05

Table 11. Effects of Imidacloprid on organs weight of pregnant mice treated on gestational days 14- 15 compared to non- pregnant:

	Doses (mg/kg/d)			
	0	**10**	**15**	**20**
Number of dams[1]	10	10	10	10
Terminal pregnant body weight (g)	41.0 ± 0.5	41.6 ± 0.2	40.6 ± 0.2	39.4 ± 0.4
Terminal non-pregnant body weight (g)	25.5 ± 0.7	26.4 ± 0.4	26.5 ± 0.3	25.5 ± 0.7
		Absolute organs weight (g)		
	Pregnant			
Liver	2.22 ± 0.03	2.18 ± 0.04	2.25 ± 0.04	2.16 ± 0.03
Kidneys	0.40 ±0.04	0.42 ± 0.02	0.40 ± 0.03	0.39 ± 0.03*
Brain	0.41 ± 0.03	0.42 ± 0.03	0.42 ± 0.03	0.39± 0.03*
		Non- pregnant		
Liver	1.57± 0.03	1.58± 0.03	1.50± 0.04	1.51 ± 0.04
Kidneys	0.28 ±0.04	0.30 ± 0.02	0.29 ± 0.03	0.29 ± 0.03
Brain	0.29 ±0.03	0.20 ± 0.03	0.29 ± 0.03	0.29 ± 0.03
		Relative organs weight[2]		
	Pregnant			
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002
		Non- pregnant		
Liver	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001	0.05 ± 0.001
Kidneys	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01 ± 0.001
Brain	0.01±.001	0.01±0.001	0.01 ± 0.001	0.01± 0.002

[1]Number of pregnant females used in experiment

[2]Organ weight (g)/body weight (g)

*Significantly different from control at P ≤0.05.

Therefore, the effects on the 15 mg/kg/day appeared whereas the exposure length was extended to all the days of organogenesis. These results are in consistent with previous studies indicated that oral administration of imidacloprid of mice at 15 or 20 mg/kg/day significantly reduced body weight, whereas mice exposed to 5 and 10 mg/kg/ day revealed no change in body weight when fed chow diet(Bhardwaj, *et al.,* 2010, Arfat, *et al.,* 2014). It is obvious that recording of the maternal body weight provides information on general health level of pregnancies which can also be important interpretation of reproductive effects (Aly, *et al.*, 2009). Although the maternal body weights were reduced for the critical gestational period, no changes in non-pregnant body weights or weight gains were recorded on all the treated groups.

The present study analyzed the concentration of IMI in different organs (brain, liver, and kidneys) and serum blood. The findings of the study indicated that IMI was easily absorbed after oral administration as indicated by its presence in fatal organs and blood (Kapoor, *et al.*, 2014).

The different gestational ages for one day treatment had no noticeable effects on the accumulation of the IMI in the different organs. However, there were no significant differences were observed in IMI biodistribution between pregnant and non-pregnant at different gestational ages. No organ IMI contents were observed on all the treated pregnant on the tested selected gestational days (8, 10, 12, and 14 Gds.) and non- pregnant mice in corresponding ages on one day treated groups of 10, 15, and 20 mg/kg/d. These results are consistent with the results indicated that imidacloprid was rapidly absorbed and distributed throughout the body and more than 90 % of IMI was eliminated in the urine and feces in the first 48 hours following exposure (Nabiuni, *et al,*. 2015). By increasing the gestational ages in parallel with the exposure period length, the highest percentages of the IMI contents were found in the brain and liver tissues compared to its presence in the kidney tissue on the medium and high doses (15 and 20 mg/kg/day) of the IMI and on all tested gestational ages (8-15, 10- 15, 12-15, and 14 –15 Gds.). The concentration of IMI was maximum attained at 6- 15 Gds post dosing in organs liver and brain and serum blood compared to the kidneys' IMI content in dose dependent manner.

It is not clear if the toxicity of IMI in pregnant mice is due to the parent compound or its metabolite, IMI is highly absorbed in the pregnant mice organs, especially liver and brain as well as the blood. Administration doses, blood and brain concentration of IMI are predictors of maternal weight changes in pregnant mice. The entry of IMI into mouse brain as confirmed by an ex vivo suggesting potential effects on mammals (Chao and Casida 1997). Furthermore, chao reported the accumulation of IMI or its metabolites in mouse brain. Toxicity signs of IMI were evident within 24 hrs. following oral administration, might be due to rapid and complete absorption (Bai, s *et al.,* 1991, Nauen, *et al.,* 2001, Solecki, 2001, Tomizawa and Casida, 2005).

Pregnant is well known to be sensitive to IMI, through our results, it was found that pregnant mice had much higher retention of the IMI in the organs and blood than non-pregnant mice. These results are confirmed by the presence of the IMI at a high concentration on the highest dose group 20 mg/kg/d for all the critical gestational periods in the different organs and blood of pregnant mice compared to non-pregnant. It is also clear that the percentage of IMI in the blood increased by increasing the treatment period (a positive relationship). Therefore, it could link between the presence of the IMI in a high percentage in the organs and blood of pregnant mice with the effects of the different gestational periods. All these factors together can be linked to toxic effects that appeared for the pregnant such as weights reduction and signs of toxicity compared to the non-pregnant. Despite IMI showed higher accumulation in brain and liver according to the period of pregnancy, relatively low amounts were determined in the kidneys. Accumulation of IMI in organs and blood of the pregnant and non-pregnant did not initiate inflammation or abnormality in the morphology of all the examined organs as well as in the relative organ's weights in all the treated groups on different exposure periods. For non-pregnant mice, an accumulation of IMI in the organs and blood was much lower than that of pregnant, which was significantly reflected in the accompanying effects. Where there were no effects on all the toxicity parameters for the non-pregnant group.

In conclusion, we have demonstrated that the biodistribution of IMI in pregnant mice is gestational periods-and dose dependent, with dose dependent. However, there were significantly differences were observed in IMI distribution between non- pregnant and pregnant mice of different gestational ages. Clearance of IMI from pregnant and non- pregnant after one treatment day at different gestational ages revealed that IMI being excreted quickly through urine frome non-pregnant mice. Pregnant status again proved to have effects on IMI clearance and accumulation. Exposure to the IMI appeared to have adverse effects on body weights, weight gains and caused signs of toxicity in dose and gestational ages dependent in pregnant mice compared to non-pregnant. Imidacloprid is considered as moderately toxic (WHO) and classified by EPA as toxicity class II and class III agents because it blocks specific neuron pathway that is more abundant in insects

than warm blooded animals. Hence it is more selective to insects than mammals (EPA 1994, Handbook 1995). This study highlight some important role of different gestational ages- associated biodistribution and biological effects of IMI in pregnancy compared to non-pregnant, and lay a foundation for the use of IMI as a pesticide during the critical pregnancy periods.

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الملخص العربي

تأثير الايميداكلوبريد وعمر الحمل على التوزيع الحيوى والسميه الاومية فى الفئران الحوامل مقارنه بغير الحوامل

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يستخدم الإيميداكلوبريد على نطاق واسع لحماية المحاصيل في جميع أنحاء العالم منذ العقد الماضي بسبب ثبات التربة المنخفض ونشاطه المرتفع كمبيد حشرى وانخفاض معدل تطبيقة للغاية. ومع ذلك، هناك حاليا معلومات محدودة بشأن تأثير الحمل على التوزيع الحيوي والسمية. في هذه الدراسة، تم دراسة التوزيع الحيوي والتأثيرات السامة المحتملة للإيميداكلوبريد في الفئران الحوامل ومقارنتها بغير الحوامل في مختلف أعمار الحمل الحرجة (Gds و٨ و١٠ و١٢ و١٤) بتركيزات ١٠ و١٥ و٢٠ ملجم / كجم / يوم، ثم أيضا تسجيل تأثيرات الإيميداكلوبريد على التوزيع الحيوي على الفئران الحوامل التي تم إعطاؤها جرعات متكررة من ١٠ و١٥ و٢٠ مجم / كجم / يوم الإيميداكلوبريد في أيام الحمل الحرجة المختلفة (٦-١٥، ٨-١٥، ١٠-١٥، ١٢-١٥، و١٤-١٥) مقارنة بغير الحوامل. لم يلاحظ أي تغيرات كبيرة في التوزيع الحيوي بين الفئران غير الحوامل والحوامل التي أعطيت في اليوم ٨ و١٠ و١٢ و١٤ من الحمل على جميع المجموعات من ١٠ و١٥ و٢٠ مجم / كجم/يوم. ظهرت التأثيرات السامة للـ IMI على علامات السمية ونقص وزن الجسم الوزن المكتسب في جميع أيام الحمل المختلفة التي إعطيت بجرعات متكررة مقدارها ٢٠ مجم / كجم مقارنة الحوامل وغير الحوامل. كما كانت هناك علاقة موجبة بين تراكم IMI في أعمار الحمل المختلفة والتأثيرات السمية للأم. أشارت هذه النتائج إلى أن أنماط التوزيع الحيوي للأم لـ IMI في الفئران الحوامل تعتمد على الجرعة وطول التعرض وأعمار الحمل.

الكلمات المفتاحية: تشوهات الأجنه، السمية التكشفية، الأيميداكلوبريد.