Theriogenology Insight: 7(1): 25-34, April, 2017
DOI: 10.5958/2277-3371.2017.00012.2

Effect of Low dose Chronic Exposure to Deltamethrin and Lindane on Reproductive System of Male Mice

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ABSTRACT

In the present study, 198 Swiss albino male mice were exposed to daily oral doses of deltamethrin and lindane to study the effect of low dose chronic exposure to reproductive organs of male mice. Mice were exposed for 15, 30 and 60 days Doses of pesticides were selected on the basis of maximum residual limits (MRL) as well as the residues of pesticides found in various food commodities in the previous studies. Thus the three doses used in the study were 0.5, 1.0 and 1.5 mg/kg bwt/day for deltamethrin and 0.25, 0.5 and 0.75 mg/kg bwt/day for lindane. The highest dose of deltamethrin and lindane used in this study was $1/40^{th}$ and $1/200^{th}$ of the LD_{50} of these two pesticides, respectively. After the completion of experimental trial, the mice were sacrificed and testicular tissues were collected and preserved in neutral buffered formalin till analysis. The sections of tissues (testes) were taken and stained with haematoxylin and eosin to visualize the histopathological changes caused due to exposure of mice to the pesticides. The histological examination revealed the degenerative changes i.e. vacuolar degeneration of the spermatogenic cells, presence of necrotic cells and edema inside the seminiferous tubule and aspermatogenesis at all the dose and duration of exposure to each of the pesticide. The changes were more or less dependent upon the dose of pesticide as well as the duration of exposure to these pesticides. This was further confirmed by the residues of pesticides detected in these vital tissues through gas chromatography (GC) and confirmation with gas chromatography-mass spectrophotometry (GC-MS).

Keywords: Histopathology, pesticide, residues, testes

Pesticides are biologically active molecules that are commonly used to destroy unwanted organisms in the agricultural and residential environments. The usage of pyrethroid insecticides has been increasing and the pyrethroid insecticides are replacing the organophosphorus insecticides for residential control (Sudakin 2006). It has been employed as a substitute for organochlorines and carbamate insecticides. So, human exposure to pyrethroid insecticides has been increased (Khan *et al.* 2008). Pyrethroid insecticides are synthetic analogues of pyrethrins that are botanical insecticides extracted from the flower of the genus *Chrysanthemum*. These compounds have been modified to be more stable in sunlight and heat and are, therefore, more widely used especially outdoors. A subgroup of these compounds has been modified with α cyano side chain. This modification creates a compound that is significantly more resistant to degradation and potentially more toxic than other pyrethroids. Commonly used chemicals in this subgroup are deltamethrin, cypermethrin and fenvalerate (Roberts and Catherine 2012).

Deltamethrin is a type-II synthetic pyrethroid which is widely used in household and agricultural insect management programmes (Sharma *et al.*, 2013). Owing to its rapid metabolism and low toxicity to humans and other non-target animals in addition to its high potency on a large number of pests, it has become an insecticide of choice in most countries (Issam *et al.,* 2012).

Lindane (benzene hexachloride (BHC) is a monocyclic compound which is synthesized from the chlorination of benzene in the presence of ultraviolet light and gives admixture of the alpha, beta, gamma and delta isomers. The liver tissue seems to be the most sensitive organ following experimental lindane (γ-hexachlorocyclohexane) intoxication, with development of hypertrophy (Videla *et al.*, 1990). Whilst lindane poisoning may result in tremors, ataxia, convulsions, stimulated respiration and prostration and, in especially severe cases, degenerative hepatic and renal tubule changes, there has been speculation that such agents may also play a role in the aetiology of cancer (Dich *et al.,* 1997). Therefore, keeping in view the toxic effects of pesticides in various organs, the present study was designed to estimate the histopathological alteration in mice testes on subchronic low dose oral exposure to mice.

MATERIAL AND METHODS

Procurement of mice

The experiment protocols were approved by Institutional Animal Ethics Committee, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana (IAEC/14/179-212/22 dated 26-09-2014). Swiss albino male mice (8-10 week age) were purchased from department of Livestock Product Management, GADVASU, Ludhiana and Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar. These mice were kept at small animal house for two week for acclimatization to prevent transportation stress before start of the experiment.

Chemicals

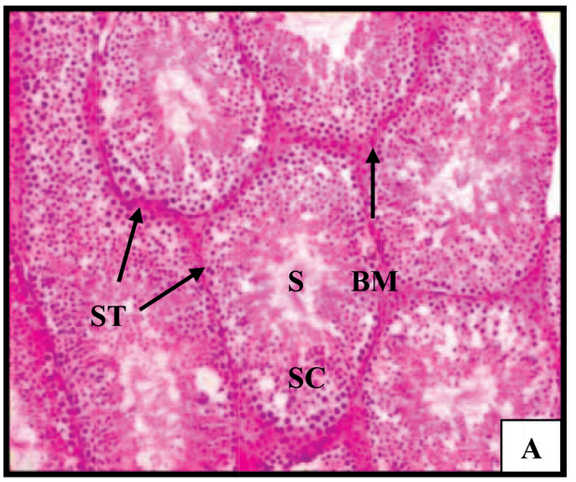
The technical grade lindane (Cat no. RM2651) was procured from HiMedia, India and deltamethrin (technical grade) with 98.50 % purity was obtained from Kilpest India Ltd, Bhopal, India. Pesticide solution was prepared by dissolving known amount of pesticide in groundnut oil. The solution was kept in refrigerator and was brought to room temperature before oral administration. The xylazine-ketamine combination anesthetic solution was prepared by mixing 0.5 ml (10 mg) xylazine (Xylazin®) and 2 ml (100 mg) Ketamine (Aneket®) in 7.5 ml of isotonic normal saline. All other chemicals used were of the highest grade available commercially.

Experiment design

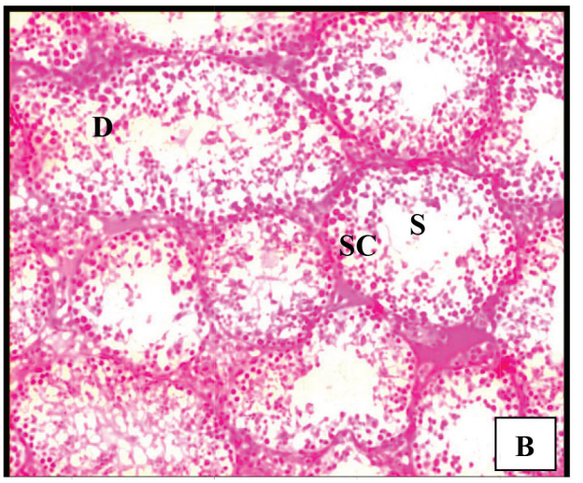
The mice (n=198) were randomly divided into three groups for each pesticide (Table 1).

Table 1: Experimental Schedule of mice

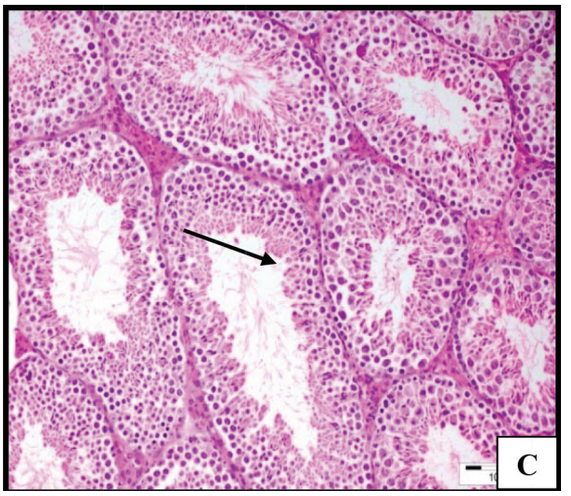
Pesticides	Groups	Doses	Number of mice		
			15 days	30 days	60 days
Deltamethrin	I	(1.5 mg/kg)	6	6	6
	II	(1.0 mg/kg)	6	6	6
	III	(0.5 mg/kg)	6	6	6
Lindane	I	(0.75 mg/kg)	6	6	6
	II	(0.50 mg/kg)	6	6	6
	III	(0.25 mg/kg)	6	6	6
Lindane + Deltamethrin	I	(1.5+0.75 mg/kg)	6	6	6
	II	(1.0+0.5 mg/kg)	6	6	6
	III	(0.5+0.25 mg/kg)	6	6	6
Positive Control	—	Cyclophosphamide	6	6	6
Negative Control	—	Groundnut oil	6	6	6
		Total	66	66	66
		Grand Total			198



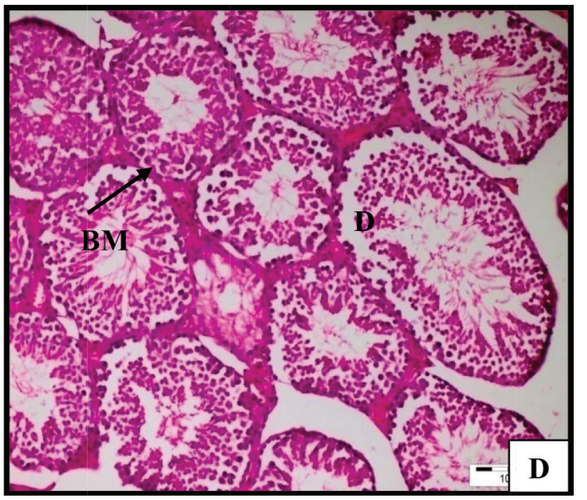
Testes of control mice; ST- seminiferous tubules, BM-basement membrane, SC-sertoli cell, S-sperms



Degeneration of seminiferous tubules (D); loss of sperms (S) in sertoli cells (SC)



Deltamethrin exposed testes in mice showing sloughed off germinal epithelium



Loss of basement membrane (BM) and degeneration of seminiferous tubules (D)

Fig. 1: H & E stained section (20X) of testes of Control (A), 1.5 mg/kg bwt (B), 1 mg/kg bwt (C) and 0.5 mg/kg bwt (D) after 60 days of deltamethrin exposure

After completion of trial periods (15, 30 and 60 day), animals were sacrificed under ketamine-xylazine anaesthesia and the samples were collected for various analysis. Mice were housed in laboratory animal cages with room temperature of around 18-22°C and 12:12 h light-dark cycle. The mice were provided feed (Ashirwad Industries, Chandigarh, Punjab, India) and drinking water *ad libitum*. The pesticides (dissolved in groundnut oil) were administered through oral route. Doses of pesticides were selected on the basis of maximum residual limits (MRL) as well as the residues of pesticides found in various food commodities in the previous studies. Thus the three doses used in the study were 0.5, 1.0 and

1.5 mg/kg bwt/day for deltamethrin and 0.25, 0.5 and 0.75 mg/kg bwt/day for lindane. The highest dose of deltamethrin and lindane used in this study was $1/40^{th}$ and $1/200^{th}$ of the LD_{50} of these two pesticides, respectively. LD_{50} of deltamethrin and lindane is 150 mg/kg bwt/day and 50 mg/kg bwt/day, respectively (Tos-Luty *et al.,* 2001).

RESULTS AND DISCUSSION

Histopathological alterations in testes of mice exposed to pesticides

In the present study, the mice were exposed orally to three doses each of lindane and deltamethrin for 15, 30 and 60 days. The three doses used were 1.5 mg, 1.0 mg and 0.5 mg/kg bwt for deltamethrin and 0.75 mg, 0.5 mg and 0.25 mg/kg bwt for lindane. After the completion of experimental trial, the mice were sacrificed and testicular tissues were collected and preserved in neutral buffered formalin till analysis. The sections of tissues (testes) were taken and stained with haematoxylin and eosin to visualize the histopathological changes caused due to exposure of mice to the pesticides. The histological examination revealed the degenerative change in the testes at all the dose and duration of exposure to each of the pesticide. The changes were more or less dependent upon the dose of pesticide as well as the duration of exposure to these pesticides. This is further confirmed by the residues of pesticides detected in these vital tissues.

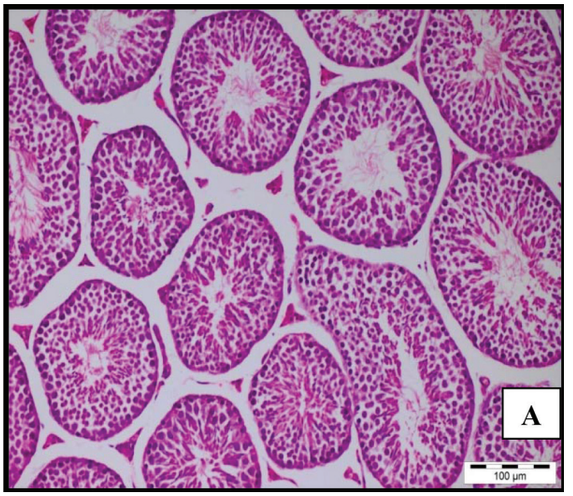
Histopathological alterations on exposure to deltamethrin

Normal histological structure of the testes was observed in the control group (Fig. 1A). In comparison to the control group severe testicular damage induced by deltamethrin was found in treatment group. These included; vacuolar degeneration of the spermatogenic cells, presence of necrotic cells and edema inside the degenerative seminiferous tubules and aspermatogenesis. The changes were mild at 15 and 30 days of exposure and more severe at 60 days of exposure. Exposure to dose 1 at 60 days has lead to degeneration of seminiferous tubules and loss of sperms (Fig. 1B). At dose 2, sloughing off of germinal epithelium was observed (1C). At dose 3, there was loss of basement membrane and degeneration of seminiferous tubules (Fig. 1D).

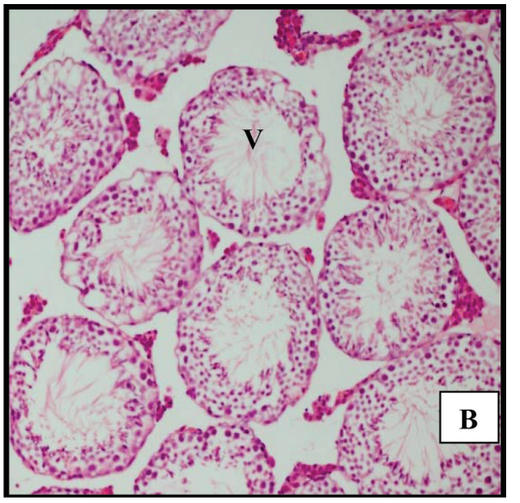
Thus, histopathological examination of tissues from testes of mice revealed various alterations on exposure to deltamethrin. These changes were dependent on the dose of the deltamethrin administered as well as the duration of exposure. Even the lowest dose of deltamethrin (0.5mg/kg bwt) and the shortest exposure period (15 days) were able to induce these histopathological alterations. Also these changes are in agreement with the studies conducted in the past on histopathology of deltamethrin. It should be noted that the cumulative effect of these pyrethroids, which can change the function of certain targets, should be taken seriously in light of the effects obtained following exposure of organisms to low doses accumulated during life. Once deltamethrin is introduced into the body it begins to set in target tissues due to its lipophilic properties. As one of the most toxic pyrethroid, deltamethrin is not fully metabolized or detoxified completely in the body and so it creates serious problems due to accumulation of its residue specifically in the lipophilic tissues.

The testicular damage caused by deltamethrin in the present study is consistent with the findings of Manna *et al.* (2005) who recorded edematous fluid accumulation between the seminiferous tubules and vacuole formation within the tubules after exposure of mice to deltamethrin at dose 15 times higher than that used in the present study (15 mg/kg bwt/d). The recorded symptoms were similar to those reported in previous studies on rats testicular toxicity (Clos *et al.,* 1994, Turner 2002, Hernandez *et al.* 2006, Rashid *et al.,* 2012).

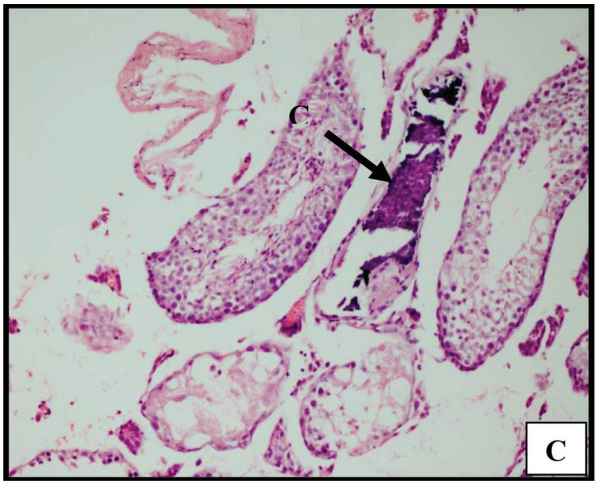
Deltamethrin is also characterized for the production of testicular apoptosis in male rats. It was found that administration of deltamethrin (1mg/kg daily for 21 days) to male rats resulted into testicular apoptosis (El-Gohary *et al.*, 1999). Chronic exposure to deltamethrin-based commercial formulation in male rats cause significant decline in serum testosterone, LH and FSH (Ismail and Mohamed 2012). Steroidogenesis is mainly regulated by pituitary gonadotropins such as LH and FSH hormones. Exposure to environmental contaminants has adverse effects on testicular function by decreasing pituitary LH secretion and reducing Leydig cell steroidogenesis. It has been reported that fenvalerate, another pyrethroid insecticide might inhibit progesterone production by attenuating cAMP generation and inhibiting



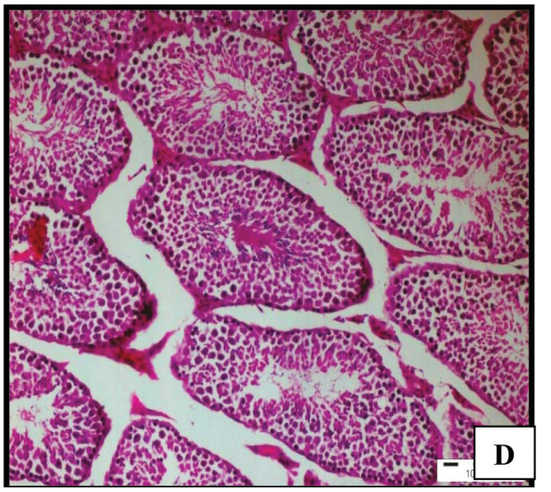
Testes of control mice



Testes of mice showing vacoulation (V) of seminiferous tubules



Testes of lindane exposed mice showing calcification (C)



Testes of lindane exposed mice showing testicular swelling

Fig. 2: H & E stained section (20X) of testes of Control (A), 0.75 mg/kg bwt (B), 0.5 mg/kg bwt (C) and 0.25 mg/kg bwt (D) after 60 days of lindane exposure

cytochrome P450 side chain cleavage complex (P450scc) (Qu *et al.,* 2008). More recently, Issam *et al.* (2009) demonstrated that deltamethrin-treated rats exhibited significant decline in testosterone and gonadotropins levels signaling the hormonal system as distinguished target for deltamethrin.

Another possible explanation would be increased corticosterone levels due to indirect action of deltamethrin on the hypothalamic-pituitary axis as postulated by Queiroz (1993). The elevated levels of corticosterone, may suppress the sensitivity of gonadotroph cells to GnRH and therefore may prevents gonadotrophin secretion (Kamel and Kubajak 1987). Recently, Taylor *et al.* (2010) demonstrated that following the exposure of mouse sertoli cells to pyrethroid compounds, the transcript levels of estrogen receptors has been increased suggesting that male fertility may be affected through molecular mechanisms involving estrogen receptors.

Histopathological alterations on exposure to lindane

Histopathological evaluation of testes of the lindane treated mice revealed some distorted seminiferous tubules and degenerative changes with reduced spermatozoa and increased lumen of seminiferous tubules. Marked vacoulation has been observed in seminiferous tubules at dose 1 of lindane exposure for 60 days (Fig. 2B). Calcification was observed at dose 2 of lindane exposure (Fig. 2C). Testicular swelling and edema was observed between the seminiferous tubule at dose 3 of lindane (Fig. 2D). In the present study even the lowest dose of lindane (0.25 mg/kg bwt/d) was found to induce testicular damage. The damage was dependent on dose and duration of exposure to lindane. The microscopic examination of sections of the testes of control mice revealed that the parenchyma of testis was formed of rounded seminiferous tubules having primary spermatogonial cells, spermatocytes and sperm in the seminiferous tubules of control mice (Singh and Sangha 2014).

Investigations had revealed (Chowdhury 1994) that exogenous lindane treatment diminishes serum testosterone level and it had been confirmed that lindane acts as an inhibitor on testicular steroidogenesis (Ronco *et al.,* 2001, Saradha *et al.,* 2008). In agreement of the present study, Simic *et al.* (2012) also reported irregularly shaped cells marked intercellular space between the spermatogenic cells and cell disorganization along with the decrease in testicular weight of lindane-treated rats.

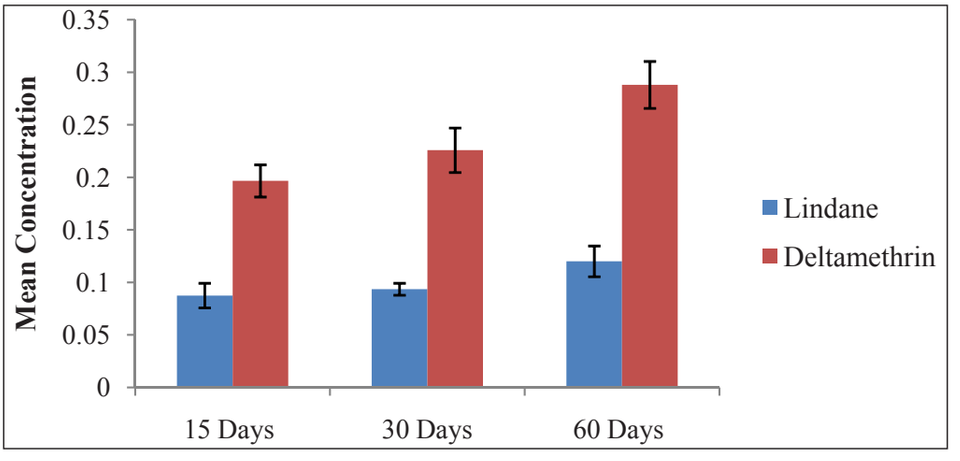


Fig. 3: Comparison of lindane and deltamethrin residues in Testicular fat at different durations of exposure

Thus, summarily, the findings of the present study on histopathological examination of testes of mice after low dose long term exposure to lindane and deltamethrin are in agreement with the studies conducted earlier. The histopathological changes on exposure to the combination of deltamethrin and lindane were similar to those observed on exposure to the individual pesticide. However, the doses used in this study were many times lower than those used in the earlier studies. So these finding are important on the understanding that the low doses of these two pesticides have the tendency to cause significant damage to reproductive system and their exposure for long term may prove harmful due to reproductive failure.

Analysis of pesticide residues in tissues of vital organs of mice

The pesticides used in the present study have lipophilic properties and thus a tendency to accumulate in the body. It is therefore, imperative to determine the concentration of each of the pesticide in the vital organs of mice to establish the correlation between the residual load of these pesticides and associated testicular damage as revealed by histopathological examination of these tissues. In the present study tissue samples i.e. testicular fat were collected after the completion of experimental trial and pooled to detect the level of lindane and deltamethrin residues. The samples were analyzed through gas chromatography (GC) and confirmed with gas chromatography-mass spectrophotometry (GC-MS). Gas chromatography coupled with mass spectrophotometry is a sensitive technique to detect the pesticide residue in any given sample even at very lower concentrations.

Limit of detection and recovery studies

The limit of detection of our method used was 1.5ng/g (0.015ppm) for lindane and 3ng/g (0.03ppm) for deltamethrin. The recovery percentage of lindane and deltamethrin varied from 72-79% and 75-81%, respectively. The retention time of the standard of deltamethrin and lindane and lindane on GC was 49.18 minutes and 8.715 minutes, respectively. To find out limit of detection of each pesticide, the samples were run in triplicates for six serial dilutions of each pesticide standard starting from 1ppm. For recovery percentage the samples were fortified with 1ppm concentration of pesticides standards and run in quintuplicate.

Residues of deltamethrin

The gas chromatography analysis indicated that the residues of deltamethrin were detected in the testicular tissues studied and their concentration was dose and time dependent. The mean residue levels in testes and testicular were found to be 0.197, 0.226 and 0.288 ppm, respectively, at 15, 30 and 60 days of oral exposure of deltamethrin to mice (Table 2).

Table 2: Mean residue levels (ppm) of deltamethrin and lindane in mice tissues at 15, 30 and 60 days of exposure

Treatment	Days	Testicular Fat
Deltamethrin	15	0.197 ± 0.015
	30	0.226 ± 0.021
	60	0.288± 0.022
Lindane	15	0.087 ± 0.012
	30	0.093 ± 0.006
	60	0.120 ± 0.015

Results are expressed in mean ± standard error

Results with common superscript differ significantly from each other

In all these measurements, it was observed that the concentration of the residues was maximum at 60 days exposure.

Residues of lindane

The mean residue levels of lindane in testicular fat were 0.087, 0.093 and 0.120 ppm, respectively, at 15, 30 and 60 days of exposure. The concentration of lindane residues was higher

at 60 days of exposure. A comparison between the mean residue concentration of lindane and deltamethrin in testicular fat, indicated that the deposition of deltamethrin was higher in the tissues as compared to that of lindane (Fig. 3) at all the durations of exposure. This could be linked to the difference in the dose rate of both of the pesticides. The dose rate of deltamethrin was almost double to the dose rate of lindane in the present study. There is no supporting study available in the literature that can explain the differences the deposition rates of these two pesticides. Yet the differential doses of these two pesticides can explain to some extent.

Deltamethrin, being a lipophilic chemical had highest residue levels in the fat. The accumulation was found to be dose and time dependent. The higher levels of deltamethrin residues in this study are consistent with a previous study conducted by Manna *et al.* (2005) who found the tissue residual concentration of deltamethrin at the concentration of 0.92, 0.74, 0.10, 0.09, 3.00 and 0.15 ppm in liver, brain, testis, kidney, lungs and heart, respectively following repeated oral administration for 30 days at the dose 15mg/kg bwt/d (approximately 15 times higher dose as used in our study).

The higher lindane bioaccumulation in testicular fat can be correlated to the fact that, the lindane being lipophilic in nature gets more accumulated in the high lipid containing organs of body. The ability of lindane to accumulate in various tissues of rodents had been reported in various studies conducted in the past. Dikshith *et al.* (1990) reported accumulation of hexachlorocyclohexane (HCH) in the fatty tissue, brain, liver and blood of mice after administration of single oral dose of technical HCH at levels of 5, 25, 50, 100 and 200 mg/kg bwt.

In another study, Lahiri *et al.* (1990) observed a dose and time dependent accumulation of lindane residues in vital organs of mice in adult female *Swiss Albino* mice after chronic feeding. Highest concentration was observed in abdominal fat followed by brain, kidney, femoral muscle, liver, adrenal and ovary. Junqueira *et al.* (1997) also observed the accumulation tendency of lindane in rat liver, whole blood, plasma and adipose tissue after administration of single dose orally. Bioaccumulation level of lindane in various tissues of *Channagachua* had been studied by Shingare *et al.* (2009) where fishes were collected from nearby agricultural area. Tissues like muscle, kidney and liver were used for quantification of bioaccumulation level of lindane. The concentration of lindane was found at 0.1432 µg/g in kidney, 0.0361 µg/g in muscle and 0.1419 µg/g in liver.

Thus, summarily, the pesticide residue data of lindane and deltamethrin in the present study shows that both of these pesticides have a tendency to accumulate in the vital organs of the mice even at the very low doses for shortest duration of exposure (15 days). The levels were found to be increasing with the increase in duration of exposure. These findings have a significance in this study since it is the residual load of these two pesticides which had possibly resulted into the testicular damage as observed by the histopathological examination of this organ.

CONCLUSION

From the present study it can be concluded that low dose long term exposure to pesticides can lead to significant damage to the reproductive system which may further become a cause of infertility or sterility. Further insights into the study can provide certain information about the deteriorating effects of pesticide exposure on male and female primary reproductive organs evan at further low doses of these pesticides.

ACKNOWLEDGEMENTS

Authors are highly thankful to GADVASU for providing research funding and facilitiesto complete the study. Authors are also thankful to DST-INSPIRE, for providing funds.

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