

# Review: Health Implications Due To Long-Term Use Of Pyrethroid Based Liquid Mosquito Repellent

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**Abstract:** Mosquito repellents are using as residential insecticides in developing countries. Because mosquitoes are vector of many diseases like malaria, dengue, yellow fever, filariasis and other viral diseases. So, it is constrain to use mosquito repellents. The mosquito repellents which are popularly made up of chemicals and use in a common house these are used at least for 8-10 hours per day. Further human beings are may come under its exposure either directly or indirectly (through the mother to her baby) in pregnant women. Use of these SMR (synthetic mosquito repellent) in last decade, has been increased in India mainly in liquid form, a bottle containing liquid mosquito repellent and a graphite rod at center which produces fumes on heating. These fumes of synthetic mosquito repellent may cause adverse effect on human health, cause breathing problems due to dysfunction of alveoli in lungs, may intrude into the brain by open up the developing blood-brain barrier and can cause functional loss in the developing baby. Neurotoxic effects like oxidative stress, headache, lethargy, dizziness, nausea, silliness and body ache may also be seen in such patients. Information regarding negative impact of these mosquito repellent on human health is not sufficiently available.

**Index Terms:** Mosquito repellents, insecticides, exposure, neurotoxic.

## 1 INTRODUCTION

Repellents are the substances that show their effectiveness in short or at a long distance and prevent human beings from biting of arthropods (Choochote, et al, 2007). Due to change in environment and increase in population mosquito population in developing countries are also increased and make them susceptible for diseases. This is because mosquitoes are vector of many diseases like malaria, dengue, yellow fever and filariasis out of these Malaria is a measure cause of death in many countries (Akhigbe, et al, 2011). The mosquito repellents which are being used may be synthetic or may be herbal. But synthetic mosquito repellents are more common to use. These synthetic mosquito repellent are available in different forms as like coil, mat, vaporizers, lotion etc. in the market. Other repellent devices are also available like buzzer and electronic device. But use of liquid mosquito repellent has been increased in last decade. The liquid mosquito repellent containing synthetic pyrethroids like allethrin, d-transallethrin, S-bioallethrin are using in most of mosquito repellent. They contribute upto 25% in world's insecticide market (Shafter, et al, 2005). Allethrin is using as the main constituent of mosquito repellent for long term exposure to humans (Anvita, et al, 2006). The graphite rod present in the bottle of liquid mosquito repellent produces fumes on heating and these fumes chock the chemo-sensor of mosquito. So they are unable to identify human being. These contain allethrin group of compounds mainly and its marketing in India and other countries is well organized. Allethrin is a common pyrethroid and human beings are using these liquid mosquito repellent at least for 8-10 hours per day. Due to which they cause adverse effect on human health. But there is a lack of knowledge about that the allethrin induce harmful effect on humans due to their long term use. They often using in sleeping quarters and also in day time. Because their vapors containing particulates (<1µm), metal fumes and vapors may reach to alveolar region of the lung on chronic and pronged exposure there by effecting lung functions in humans. So, it is needed to be focus on long term exposure may be directly or indirectly (through the mother). Due to this toxicity occurs in rodents

at adulthood stage and during development especially in humans. Altering in learning and memory function were also studied in rats. injection of allethrin in rats cause severe poisoning syndrome with tumors. Pyrethroids are absorbed by small dust particles also on other surfaces and make this potent toxicant. Suspected illness and injury due to this reported in Oregon since 1987. In a study performed by Sharma 1994, 11.8% people using repellent complained of ill health effect like running nose and wheezing. The toxicity induced by pyrethroids is because of its lipophilic nature. Cypermethrin which is a complex pyrethroid insecticide add to body fat, skin, liver, kidney, adrenal gland, ovary and brain due to its lipophilic nature. Allethrin used in mat and vaporizer cause increase blood brain barrier and biochemical changes and causing health risk, mainly at early age. Biochemical changes developed in erythrocytes membrane of humans due to allethrin (Narendra, et al, 2008). They also noticed reduction in phosphatidyl serine (PS) in human blood and decrease in membrane cholesterol.

## 2. Adverse Effect of Pyrethroid Based Liquid Mosquito Repellent

### 2.1 Biochemical Changes

It was shown that inhalation of liquid mosquito repellent effect blood brain barrier which is a protecting membrane that prevents most of substances from passing into the brain. A lot of functions are affected by damage in blood brain barrier in developing rats. In a study it has been observed that these affect 2 year old pups which were exposed to (postnatal days (PND) 2-9) liquid mosquito repellent continuously for 8 days, 18 hours per day. It has been observed that remarkable increase in blood brain barrier permeability and purpose the retarded maturity of blood-brain barrier. The level of glutathione in brain also decreased (17%) were also affected by liquid mosquito repellent in rats. Due to oxidative damage of end products of lipids e.g. lipid hydro peroxides and conjugated dines were increased in brain and kidney respectively. Oxidative product of proteins such as protein carbonyl was increased

remarkably in liver and kidney. It means due to inhalation of liquid mosquito repellent in rats oxidative damage occurs. But in neonatal rats biochemical changes in blood-brain barrier and oxidative damage were set up to completely except increase in glutathione (28%) level in brain. Shrivastava, et al, (2006) test toxicity of allethrin based liquid mosquito repellent (36% w/w) allethrin 8 hours per day continuously for ninety days. No sign of death were observed in those days and all pus were alive. But remarkable increase in relative weight of liver and adrenal in males, brain and thyroid in females were observed. Regarding their enzymes moderate changes were observed in activities of liver and serum alkaline phosphatase (ALP), testicular glucose 6-phosphate dehydrogenase (G-6 PDH) and epididymas orbital dehydrogenase (SDH). Narendra, et al, (2008) in his study has examined that allethrin alters erythrocytes membrane of humans by declining concentration of phosphotidyle serine (PS) and cholesterol concentration. Allethrin vapours released from mosquito repellent brings a significant change in lung, liver and kidney of adult rats (*Rattus rattus*) and declined in blood glucose level, cholesterol level and total protein amount were also observed (Kamble, 2012). Elevated level of creatinine and uric acid in serum and remarkable declined  $T_4$  level in plasma were noticed in male wistar rats treated with lambda-cyhalothrin (Marzouk, et al, 2012). Due to pesticides lipid peroxidation level was altered in rats (Noaishi, et al, 2013). Allethrin induce the production of ROS (reactive oxygen species) and enhance the lipid peroxidation level and also change the level of antioxidant enzymes in testicular carcinoma cells (LC540) in rats. These cells showed the characteristics of apoptosis (Madhubabu and Yenugu, 2014).

## 2.2 Reproductive Changes

Cypermethrin is potent to cause lung tumor in female mice and production of degenerated sperms in male rats. Oral dose of chlorpyrifos in albino rats reduced the number of sperms in epididymis and testes and sialic acid amount in testes also develop distorted changes in seminiferous tubules Joshi, et al, (2007) and similar changes were obtained after exposure of cypermethrin in adult Sprague Dawley rats. So, cypermethrin affect the fertility in male and implantation in females. Cypermethrin alter the developing germ cells (having mature sperms) and atrophy of leyding cells. It also provokes vacuole formation in early stages of germ cells (Al-Shaikh 2013). Mixture of different pesticides reduces the motility of sperms in male Lewin rats (Perobelli, et al, 2013). Cypermethrin also cause alterations in estrous cycle in female albino rats (Sangha, et al, 2011) similar results were obtained by Pascotto, et al, 2015. It also reduces the weight of reproductive organs, number of sperms and level of reproductive hormones Joshi, et al, (2011). Degeneration of ovarian follicles and decrease in concentration of proteins (38%), lipids (20%), phospholipid (18%), cholesterol (37%), acid (49.2%) and alkaline phosphatase (41%) while enhance the activity of lactate dehydrogenase (37.9%) and decreased level of 3  $\beta$ -hydroxysteroid dehydrogenase (31.3%) in ovary of female was observed in rats treated by cypermethrin which indicates changes in level of hormones in female rats (Sangha, et al, 2013). Elevated level of lipid peroxidation in caput, cauda and testes and elevated level of allethrin in

different concentration. It also cause destruction in testes and epididymis detriotion in epithelial cell lining, seminiferous tubules and ruin the spermatids in adult male rats (Madhubabu and Yenugu, 2013). Remarkable changes in sperm count, sperm motility and reduction in number of sperm produced and movement of sperms and germinal cell layer in seminiferous tubules was not completely matured, spermatozoa were absent in lumen and epididymis cells. These all changes were observed to due to exposure of liquid mosquito repellent and in dose dependent manner. These all changes may leads to infertility in males (Benedict, et al, 2017).

## 2.3 Histological changes

Male albino Wistar rats were treated with cypermethrin (170mg/kg) dose given to one time (~2/3 L/D 50) and (75 mg/kg) dose of cypermethrin in continuous daily continued for 5days. There were no sign of death in rats and no drastic changes were examined in any group. But a very few animals (3/12) were observed with insignificant secondary symptoms of neurotoxicity those were treated to cypermethrin one time. In both one time and continual treatment of cypermethrin elevated level of lipid peroxidation was identified in liver and brain tissues. But not in brain tissues observed after 24 hour of single dose. More changes observed in lipid peroxidation level in liver tissues treated with one time high dose of cypermethrin and lower in continual dose. The increasing level of conjugated dines and impaired glutathione level were also observed in both liver and brain but impairment of one time cypermeyhtrin dose was not greater than 24 hours. No changes were observed in GST (Glutathione - S- transferase) reactivity in both the tissues. All these points indicate that oral treatment of cypermethrin induces remarkable oxidative stress in liver and brain tissues. It has been shown that there is a remarkable relation between elevated level of lipid peroxidation and apprise level of antioxidant enzymes. But this is not clear in 'in vivo'. Type -1 pyrethroid by placing itself close to hydrophobic area disrupt the arrangement which makes membrane more fluidy and Type-2 pyrethroid patronize sixth acyl chain due to which binding of this chain become delicate. It was observed that permethrin that is a Type-1 pyrethroid suppress the expression of C-fos mRNA in cerebella of mice and expression of BDNf mRNA has reduced in cerebella of newborn mice in the lactational influence disclosure. Pyrethroids also reduce the operant activity in a dose dependent manner. According to a study on lymphoma cells of mouse and liver cells of rats and mouse esbiothrin and bioallethrin did not show any mutation in, in vitro conditions. But another pyrethroid deltamethrin induce alteration in chromosome and block the mitotic index in bone marrow of rat and did not show any deadly dominant mutation in mice (Chauhan, et al, 2007). Pyrethroid based mosquito repellent inhalation during early developmental period may leads to contrary function of nervous system like cholinergic dysfunction which leads to learning and memory shortfall in rats (Sinha, et al, 2006). Mixture of cypermethrin and endosulfan in 1:1 ratio cause bleeding in liver and kidney in albino rats (Raj, et al, 2013), vacuolization in liver cells (Mamun, et al, 2014). Endosulphan injection induces swelling in renal corpuscles; destroy tubular structure in kidney and necrosis of renal papilla in albino rats (Sabiha, et al, 2014). Experimental 5

groups of Sprague Dawley rats were exposed with (25µg beta- estradiol 3 benzoat, spiral mosquito coil, 3ml liquid mosquito repellent containing transfluthrin 0.162mg and propoxur 4.05mg/ml) respectively up to 20 days continuously. Appearance of germs and leydig tumor cells in animals treated with 4ml liquid mosquito repellent were shown which were characterized by abnormal characteristics of these cells having large nucleus, asymmetric size and shape, spectacular nucleoli, deep colored scrumpy cytoplasm. All these points indicate the malignancy of normal germ cell and leydig cells to tumor cells (Winarni, et al, 2016). Histological impairments like degeneration of outer molecular and inner (grey matter) granular layer of cerebellum and depreciate density of cells in purkinje cell layer were observed by Hasan, et al,(2017) and inhalation of parallethrin in Charles Foster rats restrict the actual pattern of cerebellum cortex (Alam, et al, 2017).

#### 2.4 Hematological changes

Cypermethrin affect the antioxidant enzymes. It declines the glutathione peroxidase (GPx) reactivity but superoxidase dismutase (SOD) and catalase enzyme reactivity was not so much effected in erythrocytes and no remarkable hemoglobin oxidation was reported. Cypermethrin also cause damage in D1- and D2- like receptors of renal dopamine. Cypermethrin declined RBC count, hematocrit (Ht) value, thrombocyte and mean corpuscular haemoglobin (MCH) value (Sayim, et al, 2005).Increased amount of W.B.C, lymphocytes, RBC, hemoglobin packed cell volume, platelets, mean corpuscular volume and mean corpuscular hemoglobin were reported after 24, 48, and 72 hours continuous inhalation of parallethrin 1.6% w/w. But depreciation in neutrophils and in monocytes reduction in 24, 48 and 72 hours but after 72 hours they became normal (Al-Damegh2013).Due to exposure of electric liquid mosquito repellent neutrophil amount declined, WBC amount, packed cell volume were enhanced(Benedict, et al,2017).

#### 2.5 Behavioral changes

Pyrethroid based mosquito repellent inhalation during early developmental period may leads to contrary function of nervous system like cholinergic dysfunction which leads to learning and memory shortfall in rats (Sinha, et al, 2006).Repeated dose of cypermethrin cause toxicity in albino rats like diarrhea, lower feed intake, body weight loss, ataxia and salivation (Grewal, et al, 2010). Results on behavioral changes and changes in physical activity due to mosquito repellent 20 albino rats were exposed to 3.2% w/v prallethrin vapours 12 hours per day and sustained up to for 180 days indicates that significant changes in spontaneous motor activity, forced locomotor activity and swimming endurance test were missing. So, no behavioral changes observed (Hasan and Maheswari, 2013).

#### 2.6 Effect on Humans

Exposure of parallethrin based mosquito repellent induce the formation of micronuclei, fragmented nuclei, cells to be binucleated and dissolution of cell nucleus started in South Indian human volunteers (Kripa, et al, 2013).Multiplication of human corneal epithelial cells (HCE) cells hindered by allethrin according to the concentration of dose and trigger apoptosis in (HCE) cells (Gupta, et al, 2013). Transfluthrin

cause jaundice, red coloured urine and irritability in 14 year old boy after drinking of 15 ml transfluthrin 0.88% w/w. Blood pressure, pulse rate and respiratory rate was also increased due to that (Sachdev, et al, 2015).Pyrethroid possess lower frequency of mutation and degenerate the DNA in Hep G<sub>2</sub> Cells (Human Hepatocarcinoma Cell line) (Oztas, et al, 2015).Allethrin and parallrethrin induce cell death and enhance mRNA expression and production of ROS in human airway NCI-292 epithelial cells (Na, et al, 2018).

### 3 CONCLUSIONS

Although the liquid mosquito repellents are easy to use and abundantly available but from above all the points we can conclude that the pyrethroid containing liquid mosquito repellent may affect adversely due to their long term exposure. It causes histopathological, neurological, physical, hematological and other adverse changes in rats, which is appropriate model to study any problem related to human beings. So, it is need to educating the peoples about the risk and problems by long term use of pyrethroid containing liquid mosquito repellent

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