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Review on exposure, absorption and elimination of pyrethroids in humans

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Abstract
Insecticidal properties were found in the flowers of *Chrysanthemum cinerariifolium*. Toxicity of these flowers designated as Pyrithrum. Pyrethrum was intending to overcome the number of agro-medical pests like flies, mosquitoes, ticks etc. In regard of its properties, it is considered to be less persistent and readily degradable molecule in the atmosphere. Synthetically prepared analogue, Pyrethroids had tremendous effects on plant foliage and fruits. Human consumption of pyrethroid treated plants was significantly responsible for number of diseases. Occupational exposure to pyrethroids by the human, poses inhalation exposure, dermal and oral exposure or the combination of these various routes. Acute and chronic symptoms were the result of different exposures by pyrethroids. Following exposure, absorption and elimination or excretion of various pyrethroids from the body of human beings were extensively deliberated. Pyrethroids are responsible for respiratory effects, immunological or lymphoreticular effects, neurological effects, gastrointestinal effects, hematological effects and even cause death to the human being.

Keywords: Chrysanthemum cinerariifolium, Pyrethroids, Exposures, Chronic poisoning.

1. Introduction
Pyrethroids principally used against indoor and outdoor insect pest fauna. Molecules of four generations of pyrethroids include allithrin, resmithrin, permethrin, and cypermethrin, respectibely. Most hazardous and deadly exposure due to pyrethroids is by eating of contaminated fruits and vegetables. Inhalation of pyrethroids polluted air was significantly affects the immunological and neurological deviation in living organism. Dermal contact also plays an integral role for the exposure of these health hazard chemicals. Persistent and havoc pyrethroid molecules become a part of water and adversely affect the fishes fauna. Depending on the structures of different pyrethroid molecules it is classified as Type 1 and Type 2 pyrethroids. Cypermethrin, Deltamethrin, Fenvelrate, Cyfluthrin, Cyhalothrin etc., called Type 1 pyrethroid. Molecules of Type 2 pyrethroid include Allithrin, Bifenthrin, Resmithrin etc. Cinerin 1 and cinerin 2 are the constituent of natural pyrethrin 1 and pyrethrin 2, respectively [1, 2].

2. Inhalation exposure
2.2. Respiratory Effects
Respiratory effects in the human being through inhalation exposure due to pyrethrin are Hypersensitivity, neumonitis, pleuritic chest pain, nonproductive cough, and shortness of breath. These symptoms were reported in 24-year-old woman due to repeated indoor use of a pyrethrum-based insecticide. Treatment of conifer seedlings were done through Pyrethroids which also resulted hazardous and dangerous effect viz. dyspnea, increased nasal secretions, coughing and sneezing in the plant nursery workers [5]. People involved in the packing of deltamethrin and fenvalerate insecticides also suffered by sniffles and sneezes [6].
Office workers were affected by signs of respiratory irritation poses cough, shortness of breath and congestion. This reaction was due to the cypermethrin which is sprayed on the building 2 days prior to contact with the person. Cypermethrin contains xylene-based aromatic petroleum solvents named trimethylbenzene and paraffinic oils [3]. Symptoms worsened after the air-conditioning system was activated in an effort to clear the air. It was resulted that a part of the pesticide had been entered into ventilation ducts. In the potential influence of inert ingredients was not noted. Another similar study was conducted to evaluate the respiratory effect due to

inhalation of lambda-cyhalothrin among the 12 workers. They sprayed indoors, daily interviews following spraying on each of 6 consecutive days exposed 11 complaints by nasal irritation and 6 were through the throat irritation [4].

2.3 Immunological and Lymphoreticular Effects

24 year-old women was hospitalized due to subsequent use of indoor pyrethrum insecticide. She suffered in Hypersensitivity pneumonitis that having peculiar or distinguish characters. Levels of antibodies IgE, IgM and IgG were all prominent in this female patient. Suggestive treatment was used and a discharge after a week, a pulmonary challenge test to the insecticide give in an itchy and runny nose within 2 minutes following the initiation of exposure but there is no any symptom of cough or shortness of breath. Subsequent skin tests resulted in abrupt skin reactions and allergic pulmonary response against pyrethrum while not in the other chemicals. In a review of literature pertaining to pyrethrum [7], it was recorded that many individuals who were sensitive to ragweed were also sensitive to pyrethrum, showing directly proportional relation of ragweed and pyrethrum but that the sensitization effect arose mainly from a volatile oil enclosed in the pyrethrum extract, was not from the pyrethrins [7].

2.4 Neurological Effects

Termite management through cypermethrin by the workers was influenced by the experience of spraying. Workers applied insecticides against termite to prevent the building, hence ultimately they suffered shortness of breath, nausea and headache [3]. The symptoms were exacerbated when the air-conditioning system was activated to ventilate the area while, the levels of cypermethrin in the air were not calculated. Signs of neurotoxicity have been associated with acute occupational (inhalation and dermal) exposure to various pyrethroids during outdoor or indoor spraying [4, 8-11].

In 1987 and 1988 acute poisoning due to pyrethroids have been observed in the cotton workers from China [8]. About 27 % (696 of 2,588) of the workers showed symptoms such as paresthesia, severe headache, nausea, loss of appetite, blurred vision, dizziness and tightness. These symptoms were examined in the pyrethroid application workers [8].

It was investigated that increased peripheral nerve excitability in the cotton workers following 3 days of exposure by the deltamethrin during spraying [9]. Assessing of nerve excitability was conducted by treating two sequential electrical stimuli having equal intensity and time to the median nerve area of the wrist and footage the median nerve activity at the lateral side of elbow. Following, deltamethrin exposure, median nerve conduction measurements showed the significant increase in the supernormal epoch which is defined as a duration or time after the recovery of normal excitability during which an action potential produced by the second stimulus that is elevated in amplitude than that of first action potential. Some studies also investigated that the air concentrations of pyrethroids in the breathing region of the sprayers were calculated and ranged about 0.005 to 2.0 µg/m3 [9].

However, another study concluded that the air concentration was high at 24 µg/m3 [10]. Majorly source of exposure considered to be by the dermal in the sprayers although some workers showed the symptoms of laryngeal irritation and nasal [4]. Another study revealed that deltamethrin and fenvalerate were responsible for various symptoms like miliary red facial papules, paresthesia, sneezing, dizziness, fatigue, sniffles and facial in the workers involved in the packing of these insecticides. Air sampling highlighted the different pyrethroid levels which were in the range of 0.005–0.055 mg/m3 while, dermal contact was also obvious. This may result in the severity of various toxicity signs during summer months [6].

3. Oral Exposure

3.1 Death

Between1983-1988 study was conducted to estimate the acute pyrethroid poisoning in China. Results documented as about 573 cases with accidental poisoning. They were considered to great extent due to ingestion or consumption of pyrethroids [12]. There are four deaths reported, from which two were associated with occupational exposure. Furthermore, concluded that the death of a 30-year-old male about 2 days after he had consumed the 30 mL of deltamethrin [13]. In another similar kind of study, an adult male quickly developed the convulsions and died soon after having accidentally ingested an unidentified amount of 10% cypermethrin [14].

3.2 Gastrointestinal Effects

By the human beings ingestion of large quantity of pyrethroids may results in the following symptoms like epigastric pain, vomiting, nausea and diarrhea [12, 15].

3.3 Hematological Effects

Information concerning hematological effects through oral exposure by the pyrethroids in humans is limited. Leukocytosis was observed in 15% of 235 human cases of pyrethroids poisoning for which blood tests were carried [12]. However, in animal studies it was examined that hematological end points, no significant alterations were found. Furthermore, it was revealed that significantly decreased red blood cell count and hemoglobin contents.

3.4 Neurological Effects

Ingestion of pyrethroids through accidentally or intentionally can cause severe neurological problems in the human beings. Neurological or neurotoxic symptoms includes coma, muscular fasciculations, headache and convulsions [13, 15].

4. Dermal exposure

4.1 Death

Death cases by pyrethroids through dermal exposure are maximum in animals than that of human beings. An allergic reaction was observed in the dogs when they are subjected to washing with shampoo which contains the pyrethroids. There are two death case reports were to be found in dogs due to the dermal exposure of pyrethrins [12].

4.2 Dermal Effects

Farmer's growers of pyrethrin based plants also affecting by various signs or symptoms like skin irritation but their affecting level is too low. Paresthesia is contradictory between dermal or neurological, depicted the symptoms which cause the hurdles in normal functioning of the human beings. Paresthesia includes burning, numbness and itching like symptoms which are the indication from the normal state due to the pyrethroids [16].

4.3 Neurological Effects

Peoples involved directly in the production of pyrethroids or occupational people get affected by the paresthesia which is abnormal cutaneous sensation along with some other symptoms which can cause the hazardous affect in the human beings [17-21].

This effect is reported to be the outcome of a direct effect on intracutaneous nerve endings following dermal exposure to the

pyrethroids group of insecticides [20, 22]. Person involve in the application of fenvalerate, a pyrethroids insecticide, affect by the severe problems after some time of an application. Post application symptoms of fenvalerate included cutaneous sensation like itching, burning and numbness which is responsible for the deviation from the normal state in human beings [18].

In another study farmers were used fenvalerate to prevent or manage the attack on insect fauna in their crops. Resultantly, a short time after application of insecticides they were affected by the paresthesia. Various pyrethroid insecticides like permethrin, cypermethrin, flucythrinate and fenvalerate have been studied as to encourage different severity in the paresthesia responses [17]. They concluded as the mildest responses were represented due to the permethrin. Fenvalerate and cypermethrin produced significantly much more severe responses than that of permethrin [17].

Various signs and symptoms of mild acute pyrethroid poisoning poses the severe headache, nausea and dizziness. Paresthesia is also considered an additional. These different symptoms or signs have been related with acute occupational which may be inhalation or dermal exposure to the pyrethroids. These pyrethroids are applying either indoor or during outdoor as a spray [4, 8, 10, 11]. Different people worked in the packing of insecticide, subjected to the various symptoms like Facial paresthesia, dizziness, fatigue, sniffles and sneezes. Majorly these signs were the result of dermal exposure, inhalation exposure also responsible for these various symptom but having the slight role. Pyrethroids which are responsible for the symptoms include deltamethrin and fenvalerate [6].

Environmental factors play an integral role for the efficacy of insecticides. Pyrethroid efficacy increased during the summer month. In a case study it was revealed that toxicity of pyrethroids increased by the increase in temperature. Due to toxicity of pyrethroids various symptoms produced on the body of human being, resulted from the dermal exposure. Severity of the disease depend upon the level of exposure of human against the pyrethroids. Listless, consciousness symptoms were due to the mild pyrethroids poisoning while coma and convulsive symptoms are the results of acute pyrethroid poisoning [8, 9, 12].

4.4 Genotoxicity

Larva of Drosophila treated with the commercially available pyrethroid, permethrin results in the mutation. Mutation associated with the sex-linking and was lethal to the insect (Drosophila). Permethrin affect the DNA of insect by influencing both the spermatogonia and spermatocytes [23]. In another controversial study it was recorded that there is no any significant results in the mutation of insects due to the application of permethrin. For this study adult males were treated with permethrin insecticide that results in a non-significant way and concluded that there is no any significant differences in the frequencies of spontaneous mutation [24].

Cypermethrin, a pyrethroid, ingested to the insect to determine the mutation in the body of insect. Results revealed that there is a significant relationship in frequency of sex-linked mutation by ingestion of cypermethrin on the larval feeding [25]. However, again contradict study was resulted that due to application of cypermethrin against larval ingestion produced a non-significant relation in the mutation [26]. Vitro study concluded that commercial application of various available pyrethroids not resulted in the mutation of subjected insect while by the application of active ingredient of the pyrethroids May results in the mutational variability in the insect [27].

5. Absorption

5.1 Inhalation Exposure

Different studied revealed about the absorption of the pyrethroids which include permethrin, deltamethrin, cyhalothrin, cyfluthrin, cypermethrin, lambda cyhalothrin etc. in the body of human beings. Absorption inside body is a result from the occupational exposure through recognition of pyrethroid metabolites in urine [28-32]. [32] Reported that few insects have the plasma limit lower than the normal limit of detection (5 µg/L). It was confirmed by the study that cyfluthrin absorbed in the workers through the measurement of plasma cyfluthrin levels however, estimates of total exposure levels by cyfluthrin in these workers were not obtainable [33].

It was studied that by the increase of level of exposure to pyrethroid in humans, increased the level of pyrethroid metabolites in urine. Human get affected by the various pyrethroids through the several routes like inhalation, dermal etc while inhalation exposure responsible for absorption in the body. Absorption of pyrethroids through inhalation exposure was greatly influenced by time period of exposure to organism [32].

5.2 Oral Exposure

Pyrethroids like permethrin, cypermethrin, deltamethrin, resmethrin, fenvalerate etc are absorbed in the gastrointestinal tract through oral exposure. In a case study about 59-year-old male intentionally intended to suicide with permethrin about 600 ml of 20 % [15]. Patient was checked to determine the cis and Trans isomers of permethrin. It was noted that maximum plasma concentrations of permethrin found after 3-4 hours of ingestion. Cis and Trans both isomers were diagnose in the plasma. These results indicated that both isomers of permethrin are absorbed after the administration in the human beings. However the fraction of administered dose is difficult to determine in the exact amount.

Another experiment was performed on oral exposure of an intentionally demonstrated cyfluthrin its absorption and their metabolites in the urine. Results confined as minimum oral absorption of about 40%, depend on recovery of urinary metabolites of pyrethroid, cyfluthrin [32]. It was documented in another study which shown similar results by suicide due to cypermethrin. Following administration of this chemical in the body of male it was noted that absorption range about 36 to 63% due to subjected dose [34-36].

5.3 Dermal Exposure

Information regarding the absorption of pyrethroid due to dermal exposure in the human being was extensively studied in the literature. By the application of permethrin, absorption occurs inside the body of organisms. Several diseases take place due to this phenomenon as a result different sign and symptoms produced. Application of permethrin on the skin for treatment of scabies, results in the absorption inside the body. The proportional absorption of permethrin was about 0.5% of the applied dose that is depending upon the urinary excretion of the chemical, permethrin metabolites [19].

Repeatedly testing on the urinary excretion of pyrethroid metabolites persisted about 7-10 days following a single dermal/skin application. Results suggest that pyrethroids were stored in skin of the organism and gradually released from the body of organisms. Further it was investigated that penetration of permethrin in the body of organisms are depend upon the dose of insecticide, time exposure to the organisms and environmental conditions. By increasing the time of exposure, severity of symptoms will be increased however, dose also directly correlated with the symptoms. Only small fraction of

insecticides absorbs in the body of organisms when applied on the skin.

Absorption of cypermethrin in the body of human through dermal affect also revealed twice time in the literature. Studied showed that by the volunteer single dose in human is also result in absorption inside body through akin. Results noted that about 0.3-1.8% dose of cypermethrin was absorbed. Excretory metabolites of cypermethrin were investigated after 14 and 36 hours through urine. Finally, it was recommended that excretory metabolites highest after 24 hours of application [35, 36].

6. Elimination and Excretion

6.1 Inhalation Exposure

Elimination or excretion of various pyrethroids included, permethrin, resmethrin, fenvalerate, lambda-cyhalothrin, cyhalothrin, cyfluthrin etc., by urine which are come in body through inhalation exposure. Metabolites of the pyrethroids excreted through urine and it was also documented after research that few pyrethroids are completely excreted from the body of organism after 4 days of exposure [28-30]. Elimination from the body is varied for different chemicals. Some excreted quickly from the body while few require some time for their elimination through the urine. Excretion of cyfluthrin from the plasma, the elimination half-time is investigated which is between 0.5 and 2 hours [33]. However, an elimination of metabolites into the urine, the elimination half-times was about 5 hours for cyfluthrin but for cypermethrin it was 8 hours [28].

6.2 Oral Exposure

Removals of pyrethroids which are taken inside the body through ingestion inside humans depend upon the nature of the chemicals. Research finding investigated the removal of half-time of cis-permethrin from plasma after oral intake of the mix cis and Tran's isomers of permethrin in a suicide effort was averagely about 67 hours [15].

Experimental findings explained that trans-permethrin was excreted from the blood more rapidly than that of cis isomer, which is undetectable in blood following 25 hours of exposure. In humans exposed to single oral doses of Type II pyrethroids (not having cyno group like Bifenthrin, Resmethrin etc.) the excretion half-time depend upon the appearance of metabolites in the urine has been predictable to be between 6 and 13 hours [32, 35]. About 35–50% of the subjected dose was eliminated in the urine as metabolites during the first 5 days after dosing, with maximum urinary excretion rates pragmatic during the first 24 hours following administered dose [32, 34-37].

6.3 Dermal Exposure

Elimination and excretion of pyrethroids following by the skin or dermal exposure were extensively studied in the human being. Humans were exposed to a pyrethroid, cypermethrin, through skin which is absorbed inside the body of human beings. Excretion of cypermethrin showed that about only 0.1-1.2% of the cypermethrin were excreted of the administered dose through urine [35, 36]. Results concluded that maximum rate of urinary excretion noted between 12 and 36 hours after the administered [35]. Another, similar study was conducted for the removal of permethrin, used to treat the scabies. It was applied as dermal and their removal from the body take place through urinary. It was concluded that excretion persisting for about 7 days following exposure [19].

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