



## **$\beta$ -cyfluthrin induced sub-acute nephrotoxicity in Swiss albino mice**

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### **ABSTRACT**

*$\beta$ -cyfluthrin is broadly used synthetic pyrethroid worldwide due to its low toxicity and high insecticidal potency against various pests. Literature accounts numerous data regarding its toxicity on various vital tissues. However, data emphasizing on  $\beta$ -cyfluthrin induced nephrotoxicity is limited. Hence, the purpose of the present study was to evaluate the effect of pyrethroid pesticide  $\beta$ -cyfluthrin on the physiology of kidney in male Swiss albino mice.  $\beta$ -cyfluthrin (13 mg/kg body weight) dissolved in corn oil was administered intragastrically for study duration of 21 days. At the end of the protocol, gravimetric indices (body weight and organ weight) and biochemical parameters (protein content, ATPase, SDH, ALPase, ACPase, urea and Creatinine) were estimated. Significant decrease in body weight, organ (kidney) weight, protein content, ATPase, SDH and ALPase activity was reported in the treated group when compared with the control animals. Further, ACPase activity, serum urea and Creatinine levels were seen to increase in  $\beta$ -cyfluthrin treated group. To conclude, overuse and long term application of chemical pesticide leads to harmful toxic implication on the vital tissues of the non-target organism. Therefore, proper measures are required for utilization of these chemicals.*

**Keywords:**  *$\beta$ -cyfluthrin, nephrotoxicity, pyrethroid, pesticide*

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### **INTRODUCTION**

Pyrethroids are group of synthetic insecticides which are structural analogs of pyrethrins, extract from *Chrysanthemum cinerarifolium*. With phase down of organophosphorus and organochloride pesticides due to their toxic implications towards humans and animals, pyrethroids took over the market accounting more than 30% of global insecticide usage [1]. These are being extensively used in agricultural, medical, aquatic systems and household pest control [2]. Alarming rise in population has also put a demanding pressure on cultivable land to increase crop production which has led to increase in utilization of this chemical pesticide [3]. Unregulated use of these chemicals has been associated with a number of problems like the presence of insecticide residues in food commodities, environmental pollution, development of insect resistance, and resurgence resulting in outbreak of secondary pests [4]. Thus, human exposure to pyrethroids can be through different modes which are unexpected and unavoidable. Although these being considered relatively safe for humans; many epidemiological data, clinical reports and laboratory studies indicates that pyrethroid exposure leads to neurotoxic effects in humans and animals [5]. As pyrethroid insecticides have high selectivity for insects and act on mammalian sodium channels, causing prolonged excitation and affecting the function of the central nervous system by increasing Na<sup>+</sup> membrane permeability and disrupting action potentials [6,7]. Calcium (Ca<sup>2+</sup>) channels, Ca<sup>2+</sup> enzymes and Ca<sup>2+</sup>/Mg<sup>2+</sup> ATPases are other biochemical targets of these insecticides [8].

$\beta$ -cyfluthrin (and the racemic mixture cyfluthrin) belongs to Type II category of pyrethroid classification. Its ISO approved common name is 3-(2, 2 Dichloro-vinyl)-2,2- dimethyl-cyclo propane-carboxylic acid cyano-(4-fluoro-3-phenoxy-phenyl)-methyl ester [9]. It is used to control a wide variety of both indoor and outdoor pests including roaches, silverfishes, fleas, spiders, ants, crickets, houseflies, ticks, mosquitoes, wasps and more. In addition to its household applications, cyfluthrin is also widely used in various public health programmes [10]. Ubiquitous and incessant long-lasting use of cyfluthrin has caused substantial pesticide problem in the water ecosystem, which have also affected aquatic products and human health [11,12]. Also, Ccancapa-Cartagena et al. [13] have reported presence of cyfluthrin in water, sediments and various biological samples. Like all synthetic pyrethroids, cyfluthrin is a

neurotoxicant. It causes hyperexcitation of the nervous system, which leads to convulsions and ultimately death [14]. It induces alterations in nerve membrane, causing abnormal sodium and potassium flow, resulting in repetitive discharges from the neurons, causing convulsions and also blockage of further nerve impulses [7]. Reports suggest that  $\beta$ -cyfluthrin causes neurotoxicity [15], hepatotoxicity [16], genotoxicity [17] and anti androgenic activity [18]. However, data regarding  $\beta$ -cyfluthrin effect on kidney is limited. As kidney is a highly specialized organ that maintains homeostasis by selectively excreting or retaining various substances according to specific body needs [19]. Also, this organ regulates metabolism and participates in endocrine system functions. The kidney can also discharge body metabolites and harmful exogenous substances [20]. Therefore, there is a need to focus on this vital tissue of mammalian system which can get adversely affected by getting exposed to various chemical and as it is highly susceptible to pesticide toxicity and damage. Hence, the present *in vivo* study was undertaken to investigate implication of  $\beta$ -cyfluthrin administration for a period of 21 days on the renal tissue of Swiss albino mice.

## MATERIAL AND METHODS

### Animals

Healthy, adult, pathogen free, colony bred male albino mice (*Mus musculus*) of Swiss strain weighing between 30-40 gm were obtained from IAEC registered supplier Cadila Pharmaceuticals, Dholka, Gujarat, INDIA. The experimental protocol and the number of animals used for the experiments were mentioned in a detailed proposal and approval was obtained as per the guidelines of the institutional animal ethics committee, under registration No. 167/GO/ReBi/S/99/CPCSEA from the Ministry of Social Justice and Empowerment, Government of India and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Chennai, India. All the animals were acclimatized for seven days prior to the commencement of experiment. The animals were housed in an air-conditioned animal house at a temperature of  $26 \pm 2^\circ\text{C}$  and exposed to 10–12 h of day light and relative humidity of 40%–50%. Animals were divided into control and treated groups and were caged separately. Standard chow (obtained from Amrut laboratory, Baroda, India) and water was provided *ad libitum*.

### Chemicals

Technical grade  $\beta$ -cyfluthrin of 95% purity was procured from Nanjing Essence Fine chemicals, China. All the other chemicals used in different assays were procured from HiMedia or Merck.

### Experimental Design

Pyrethroid insecticides are lipophilic in nature and are readily absorbed through gastro-intestinal tract than any other route. Therefore,  $\beta$ -cyfluthrin was dissolved in Corn oil and administered via feeding canula at a dose of 13 mg/kg body weight ( $1/20^{\text{th}}$  of  $\text{LD}_{50}$ ). The dose was determined on the basis of  $\text{LD}_{50}$  value of  $\beta$ -cyfluthrin in corn oil i.e.,  $260.01 \pm 30.73$  mg/kg body weight [21].

Animals were divided into following groups (6 animals per group).

Group I: Control (given distilled water and food *ad libitum*);

Group II: Vehicle Control (corn oil);

Group III:  $\beta$ -cyfluthrin treated (given 13 mg/kg body weight  $\beta$ -cyfluthrin dissolved in corn oil).

All the groups were treated for 21 days and at the end of experiment, animals were weighed and sacrificed using light ether anesthesia. Animals were dissected and tissue namely, kidney was dissected out. Tissue was weighed and homogenates were prepared accordingly.

### Gravimetric Parameters

#### Body and Organ weights

The body weight of control and all treated groups of mice were recorded weekly to the nearest gram on a digital balance (Reptech). Similarly, organ weights were recorded after euthanizing to the nearest milligram on digital balance (Aczet CY 224C).

### Biochemical Parameters

#### Total Proteins

Protein levels in the kidney of control and other treated groups of animals were estimated by the method of Lowry et al. [22]. The sample containing protein was treated with phenol reagent of Folin Ciocalteu, a deep blue colour developed, due to two reactions occurring simultaneously, i.e. the reaction of alkaline copper sulphate solution with peptide bonds and the reduction of phosphomolybdic and phosphotungstic acids by aromatic amino acids present in the protein. The blue colour developed is quantitatively proportional to the total proteins, which was measured on LABINDIA UV/VIS 3000+Spectrophotometer at 540 nm and expressed as mg/dL.

#### Succinate Dehydrogenase (SDH)

SDH activity was measured by the method of Beatty et al. [23]. The electrons released by the enzyme SDH from the substrate are taken up by an electron acceptor INT which is reduced to red coloured formazan.

After extracting it in ethyl acetate the colour intensity was measured at 420 nm against blank. SDH activity was expressed as  $\mu\text{g}$  formazan formed/15 minutes/mg tissue weight.

#### **Adenosine Triphosphatase (ATPase)**

The ATPase activity in kidney of control and all treated groups of animals was assayed by the method of Quinn and White [24]; while inorganic phosphate liberated was estimated using the method of Fiske and Subbarow [25]. Readings were taken at 660 nm on a LABINDIA UV/VIS 3000+ Spectrophotometer.

#### **Alkaline Phosphatase (ALPase)**

Alkaline Phosphatase (ALPase) activity was determined by the method of Bessey et al. [26]. The enzyme ALPase hydrolyses the substrate p-nitrophenyl phosphate into inorganic phosphate and p-nitrophenol. The quantity of p-nitrophenol released under standardized condition was measured at 410 nm. Enzyme activity was expressed as  $\mu$  moles p-nitrophenol released/30 minutes/mg protein.

#### **Acid Phosphatase (ACPase)**

Activity of ACPase was determined by the method of Bessey et al. [26]. ACPase catalyzes hydrolysis of p-nitrophenyl phosphate at pH 4.8, liberating p-nitrophenol and inorganic phosphate. The liberated p-nitrophenol combines with NaOH to form a yellow colored complex which is measured at 420 nm and is directly proportional to the enzyme activity. Enzyme activity was expressed as  $\mu$  moles of p-nitrophenol released/30 minutes/mg protein.

#### **Serum biochemical parameters**

Blood sample was collected from the retro-orbital sinus of mice from respective groups in EDTA vials. Serum samples were obtained by the centrifugation of blood at 6000 rpm for 6 min, and were then transferred to eppendorf tubes. Isolated sera were stored at  $-20^{\circ}\text{C}$  until further use. The levels of serum urea and Creatinine were measured using Skyla VB1 Veterinary Clinical Chemistry Analyzer.

#### **Statistical Analysis**

For each parameter, a minimum of 6 replicates were done and the results were expressed as Mean  $\pm$  Standard Error (S.E.). The data was then statistically analyzed by Analysis of Variance (One way - ANOVA) by Graph-pad Prism software version 8.0.1 taking significance at  $p < 0.05$ . Vehicle control and  $\beta$ -cyfluthrin treated groups were compared with control group.

### **RESULTS**

#### **Body weight**

In the present study, administration of  $\beta$ -cyfluthrin to Swiss albino mice for 21 days recorded a significant decline in body weight of  $\beta$ -cyfluthrin treated animals (Group III) when compared to control (Group I). While, vehicle control group (Group II) revealed non-significant changes when compared to control (Group I) [Table 1].

#### **Organ weight**

After treatment with  $\beta$ -cyfluthrin for 21 days, significant decrease in weight of renal tissue was observed in  $\beta$ -cyfluthrin treated group (Group III) when compared to control (Group I). However, non-significant alterations were seen in vehicle control (Group II) on comparison to control (Group I) [Table 2].

#### **Total Protein**

Table 3 represents the protein content in the kidney of control and treated groups.  $\beta$ -cyfluthrin administration for duration of 21 days significantly decreased protein content in kidney tissue of  $\beta$ -cyfluthrin treated group (Group III) upon comparison to control (Group I). Non-significant changes in the protein content were observed in vehicle control (Group II) when compared with control (Group I).

#### **Adenosine Triphosphatase (ATPase)**

Oral administration of  $\beta$ -cyfluthrin for 21 days revealed significant reduction in renal ATPase activity in  $\beta$ -cyfluthrin treated group (Group III) when compared to control (Group I). While, non significant alteration in ATPase activity was seen in vehicle control group (Group II) on comparison to control (Group I) [Table 4].

#### **Succinate dehydrogenase (SDH)**

SDH activity in  $\beta$ -cyfluthrin treated group (Group III) was observed to significantly decline in kidney tissue when compared to control (Group I) after administration of  $\beta$ -cyfluthrin for 21 days. Vehicle control (Group II) recorded non-significant alterations when compared to control (Group I) [Table 4].

#### **Acid Phosphatases (ACPase)**

Significant increase in the activity of ACPase enzyme was observed in renal tissue of Swiss albino mice after administration with  $\beta$ -cyfluthrin for 21 days in treatment Group III, when compared with control (Group I). Whereas, non-significant data was obtained in vehicle control (Group II) when compared to control (Group I) [Table 5].

**Alkaline Phosphatases (ALPase)**

Effect of  $\beta$ -cyfluthrin on the activity of ALPase is shown in Table 5. Renal ALPase activity significantly declined after treatment of  $\beta$ -cyfluthrin for 21 days in Group III. Vehicle control (Group II) revealed non-significant alteration in enzyme activity. Both Group II and Group III were compared with control (Group I).

**Urea**

Serum urea content was observed to increase significantly in  $\beta$ -cyfluthrin treated animals (Group III) when compared to control (Group I) after pesticide administration for 21 days. Whereas, non-significant result was obtained in vehicle control (Group II) when compared to control (Group I) [Table 6].

**Creatinine**

Table 6 represents serum Creatinine concentration in control as well as treated groups. Results obtained after 21 days of treatment with pyrethroid  $\beta$ -cyfluthrin in Swiss albino mice revealed significant elevation in serum Creatinine in animals treated with  $\beta$ -cyfluthrin (Group III). However, non-significant alteration in Creatinine content was seen in vehicle control (Group II). Both Group II and Group III were compared to control (Group I).

**Table 1: Body weight of control and treated animals for duration of 21 days.**

GROUPS		Body weight (grams)
I	Control	35.03 $\pm$ 0.43
II	Vehicle control	34.57 $\pm$ 0.59 <sup>ns</sup>
III	Treated	29.87 $\pm$ 0.49 <sup>**</sup>

N=6, Values are represented as Mean  $\pm$  S.E. \* $p$ <0.033, \*\*  $p$ <0.002, \*\*\* $p$ <0.001, ns – non-significant (compared to control) Analysis of Variance at  $p$ <0.05 level.

**Table 2: Organ weight (kidney) of control and treated animals for duration of 21 days.**

GROUPS		Organ weight (mg)
I	Control	335.6 $\pm$ 2.75
II	Vehicle control	336.3 $\pm$ 1.85 <sup>ns</sup>
III	Treated	291.4 $\pm$ 1.98 <sup>***</sup>

N=6, Values are represented as Mean  $\pm$  S.E. \* $p$ <0.033, \*\*  $p$ <0.002, \*\*\* $p$ <0.001, ns – non-significant (compared to control), Analysis of Variance at  $p$ <0.05 level.

**Table 3: Alteration in Protein content (mg/100 mg tissue weight) in kidney of control and treated animals after 21 days treatment.**

GROUPS		Protein
I	Control	11.82 $\pm$ 0.035
II	Vehicle control	11.80 $\pm$ 0.042 <sup>ns</sup>
III	Treated	11.04 $\pm$ 0.043 <sup>**</sup>

N=6, Values are represented as Mean  $\pm$  S.E. \* $p$ <0.033, \*\*  $p$ <0.002, \*\*\* $p$ <0.001, ns – non-significant (compared to control), Analysis of Variance at  $p$ <0.05 level.

**Table 4: Alteration in ATPase activity ( $\mu$ M of inorganic phosphate released / 30 minutes / mg protein) and SDH activity ( $\mu$ g formazan released/ 15 min/ mg protein) in kidney of control and treated animals after 21 days treatment.**

GROUPS		ATPase activity	SDH activity
I	Control	3.16 $\pm$ 0.037	286 $\pm$ 0.38
II	Vehicle control	3.15 $\pm$ 0.018 <sup>ns</sup>	285.7 $\pm$ 0.23 <sup>ns</sup>
III	Treated	3.03 $\pm$ 0.017 <sup>**</sup>	283.5 $\pm$ 0.41 <sup>**</sup>

N=6, Values are represented as Mean  $\pm$  S.E. \* $p$ <0.033, \*\*  $p$ <0.002, \*\*\* $p$ <0.001, ns – non-significant (compared to control), Analysis of Variance at  $p$ <0.05 level.

**Table 5: Alteration in ACPase activity ( $\mu$ M of p-nitro phenol released/ 30 min/ mg Protein) and ALPase activity ( $\mu$ M of p-nitro phenol released/ 30 min/ mg protein) in kidney of control and treated animals after 21 days treatment.**

GROUPS		ACPase activity	ALPase activity
I	Control	2.05 $\pm$ 0.028	1.55 $\pm$ 0.018
II	Vehicle control	2.07 $\pm$ 0.028 <sup>ns</sup>	1.54 $\pm$ 0.016 <sup>ns</sup>
III	Treated	2.18 $\pm$ 0.01 <sup>**</sup>	1.41 $\pm$ 0.013 <sup>***</sup>

N=6, Values are represented as Mean  $\pm$  S.E. \* $p$ <0.033, \*\*  $p$ <0.002, \*\*\* $p$ <0.001, ns – non-significant (compared to control), Analysis of Variance at  $p$ <0.05 level.

**Table 6: Alteration in Urea and Creatinine levels (mg/dL) in serum of control and treated animals after 21 days treatment.**

GROUPS		Urea	Creatinine
I	Control	48.53 ± 1.32	0.77 ± 0.024
II	Vehicle control	48.82 ± 1.58 <sup>ns</sup>	0.79 ± 0.022 <sup>ns</sup>
III	Treated	54.43 ± 1.27*	0.89 ± 0.021**

N=6, Values are represented as Mean ± S.E. \*p<0.033, \*\* p<0.002, \*\*\*p<0.001, ns – non-significant (compared to control), Analysis of Variance at p<0.05 level.

## DISCUSSION

Nowadays, to meet the increasing demand of food for increasing population and tackling the harsh climatic conditions, the farmers are prone to use high-yielding cultivars of crops to get higher yields [27], but these are highly susceptible to pests and diseases [28]. Therefore, pesticides employment is important and unavoidable in agro fields which can significantly increase crop productivity. However, long term utilization of pesticides causes severe environmental pollution and health hazards including severe acute and chronic human and animal poisoning [29]. Replacement of organophosphorus insecticides by pyrethroids have increased human exposure [30] as these are thought to be safer alternative and are used extensively for agriculture and public health program. But indiscriminate use of these chemicals stimulates pathological dysfunctions in various mammalian systems. The present study was undertaken to understand the toxic manifestation induced by  $\beta$ -cyfluthrin, a type-II pyrethroid insecticide on renal tissue of Swiss albino mice. As kidneys are organ for excretion and highly perfused organ which receive high blood volume, therefore, has been considered as target organ for toxic insults [31]. Pesticides induced alterations in various biochemical indices can be attributed to the effect of  $\beta$ -cyfluthrin in kidney and can therefore cause renal dysfunction. Thus, the article reports investigation on the renal tissue after  $\beta$ -cyfluthrin treatment for 21 days by performing various biochemical assays.

Changes in gravimetric indices of experimental animals such as body weight and organ weights are important criteria for toxicological studies of xenobiotic [32]. Oral administration of  $\beta$ -cyfluthrin for 21 days in the present investigation revealed reduced body weight and organ weight (kidney) in pesticide treated animals when compared to control. Decrease in body weight can be due to toxic implication of  $\beta$ -cyfluthrin on gastrointestinal tract which led to decline in food consumption. Similar decrease in body weight was reported by Al-Amoudi [33] in Wistar rats treated orally with lambda cyhalothrin for 30 days. Several other studies have also revealed reduced body weight in experimental animals after exposure to different pesticides [34,35].

The present investigation reported decrease in organ weight after treatment in  $\beta$ -cyfluthrin treated group. Increase or decrease of organ weight after exposure to any toxicant is the preliminary sign of toxicity of that particular toxicant. Shivanoor and David [36] also reported reduction in weight of kidney after deltamethrin treatment in rats.

Mechanisms of toxicity for most pesticides are stimulation of free radical production, induction of lipid peroxidation, and disturbance of the total antioxidant capability of the body [37]. Reactive oxygen species generated alters protein structure or function and amino acid side-chains can be irreversibly modified into aldehyde or ketone groups (carbonylation) which can lead to protein aggregation, inactivation or degradation, these changes in protein carbonylation process are a biochemical perturbation resulting from oxidative stress [38]. In the current investigation, protein content in the renal tissue was observed to significantly decrease after  $\beta$ -cyfluthrin exposure for 21 days experimental duration in Swiss albino mice. Similar decrease in protein content was seen by El-Demerdash [39] in rat kidney *in vitro*, kidney tissue was incubated at various dose concentration of fenitothion (organophosphate) plus lambda-cyhalothrin (pyrethroid). Decrease in protein content may be due to depletion of protein synthesis and enhanced proteolysis in the tissue.

Significant decrease in the activities of ATPase and SDH was observed in the present study after administration of  $\beta$ -cyfluthrin for 21 days in renal tissue of Swiss albino mice. ATPase as well as SDH indicates the energy metabolic status of the cell. ATPase was involved in oxidative phosphorylation and thus responsible for biosynthesis of ATP in mitochondrial membrane [40]. The activity of SDH parallels the number of mitochondria and is closely related to energy generation, which could reflect the function of mitochondria [41]. The activities of mitochondrial respiratory chain complexes are the most basic and most important indexes [42] that reflect the mitochondrial function and energy metabolism. Similar depletion in gill ATPase activity in common carp *Cyprinus carpio* was reported by Suvetha et al. [43] after cypermethrin treatment. Das and Mukherjee [44] also reported decreased ATPase and SDH activity in

liver, kidney and brain of *Labeo rohita* after cypermethrin treatment for 45 days duration at various dose concentrations.

Phosphatases are mainly localized at cell membrane. Any damage in the cells may result in alteration in phosphatases activity [45]. ALPase, are important critical enzyme in biological processes responsible for detoxification, metabolism and biosynthesis of energetic macromolecules for different essential functions. Any interference in this enzyme leads to biochemical alteration and impairment in the tissue and cellular function [46]. ALPase activity in renal tissue was observed to significantly decrease in pesticide treated group. Similar decrease in ALPase activity of gill and liver was recorded by Ansari and Ansari [45] after alphamethrin treatment in Zebra fish. Decrease in activity of ALPase indicate disturbance in the structure and integrity of cell organelles like endoplasmic reticulum and membrane transport system.

ACPase are lysosomal enzyme for hydrolysis of phosphorus esters in acidic medium. Present study revealed increased renal ACPase activity after 21 days administration of  $\beta$ -cyfluthrin. The increase in ACPase enzyme activity could be explained on the basis of enhancement of cell membrane permeability with disturbance in the trans-phosphorylation process as a result of cellular degeneration [47]. Singh et al. [48] also reported duration dependent elevation in ACPase activity of liver, kidney and testis after lambda-cyhalothrin treatment in *Clarias batrachus*.

The increased serum urea and Creatinine concentration in mice treated with  $\beta$ -cyfluthrin are in agreement with the results obtained by Shalaby and Abdel-Latif [49], similar increase in renal biomarkers urea and Creatinine was reported after  $\beta$ -cyfluthrin administration in albino rats for 30 days. Maalej et al. [50] also recorded similar increase after deltamethrin treatment in Wistar rats for 30 days. Urea is indicator of renal function which is routinely measured to assess the kidney health status while Creatinine is an important marker of the filtration function of the kidneys because it is chiefly excreted from the blood via glomerular filtration [51]. Abnormal increase in these renal markers is sign for impaired kidney function. Also, elevated serum urea and Creatinine levels can also be correlated with decrease in protein concentration due to increased protein catabolism in mammalian body or from more efficient conversion of ammonia to urea because of increased synthesis of enzyme involved in urea production [52].

## CONCLUSION

The results of the current investigation suggest that indiscriminate use of pyrethroid insecticide which is considered "safe pesticide" contradicts this notation and can potentiate adverse effects on vital tissues of the host.  $\beta$ -cyfluthrin, second generation Type-II pyrethroid insecticide administration for 21 days experimental duration in Swiss albino mice induced gravimetric and biochemical alteration in renal tissue of treated animals. Longer exposure to these chemicals can lead to chronic toxic manifestation to farmers and occupational workers; also residues of these compounds in food can pose risk to general population. Therefore, the study demands stringent laws and policies to be framed by regulatory bodies so that proper monitoring pesticide usage is possible. Further, future scope of research focuses on finding a potential mitigative agent which can effectively attenuate the toxicity induced by pesticide.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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