**Effect Co-exposure of Fipronil insecticide and Potassium- dichromate on liver of male albino rat**

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**ABSTRACT**

The current study aimed to investigate the effects of combined toxicity of Fipronil insecticide and Potassium- dichromate on liver of albino rats. The rats were randomly assigned into 5 equal groups (10 rats each). Group 1: controls received daily Filtered water orally. Group 2: control received day after day corn oil orally. Group 3: received FPN day after day at a dose of 10 mg/kg b. wt. orally. Group 4: received K2Cr2O7 daily via drinking water (700 ppm equivalent to 67 mg/kg b.wt) *.*Group 5: received FPN day after day (10 mg/kg b. wt orally) + K2Cr2O7 daily via drinking water (700 ppm equivalent to 67 mg/kg b.wt) for 28days. The results revealed that FPN and/or K2Cr2O7significantly increased serum levels of ALT, AST and decrease in total protein and albumin. In addition, there were substantial increases in the liver contents of MDA and NO, along with significant decreases in TAC. also, there is upregulation in TNF-α and IL-6. It can be concluded that FPN and/or K2Cr2O7 induce severe tissue damage in liver of male albino rats.

**Keywords: Fipronil, Potassium dichromate, TNF-α, IL-6, hepatotoxicity.**

**INTRODUCTION**

Pesticides are considered a source of environmental and health hazards causing irreparable complications for human and animal **(Jabłońska-Trypuć  *et al*., 2017)**. Fipronil (FPN) is a systemic insecticide belong to the second-generation phenylpyrazole with broad- spectrum activity widely used for the effective control of many agriculture and domestic pests. FPN has attract more attention for its effect on insects that are resistant to organophosphates, pyrethroids, and carbamate insecticides **(Kim *et al*., 2019) .** Its insecticidal action appears through antagonizing the gamma-amino butyric acid receptor as well as glutamate- activated chloride channels **(Zhao *et al.*, 2004),** leading to depression in the central nervous system and death **(Das *et al* ., 2006)**. Fipronil is extremely toxic to many non-target groups of animals, including aquatic invertebrates, fishes, birds, and mammals **(Mohammed *et al*., 2016)**, classified as a possible human carcinogen depend on increase in thyroid follicular cells tumors in both sexes of the rats**(Leghait *et al* ., 2009)***.*FPN can be metabolized in the environment into fipronil-desulfinyl intermediate, which is 9–10 times more harmful to mammals than FPN itself **(Tingle *et al*., 2003; Terçariol *et al*., 2011; Ferreira *et al*., 2012).**

Potassium-dichromate (K2Cr2O7) is one of the soluble hexavalent chromium compounds commonly used and found in effluents of more than 50 different industries around the world, including dye and textile manufacturing, leather tannery, wood processing, chromium plating, metallurgical and chemical industries, stainless steel factories, welding, cement manufacturing, ceramics, glass factories, and photographic (M. Costa & Klein, 2006)***.*** The toxic effects of chromium (VI) are usually associated with intracellular reduction resulting in the generation of toxic Cr intermediates, which are considered as strong oxidants leading to ROS generated in excess causing injury to cellular proteins, lipids and DNA, leading to oxidative stress**(Nordberg & Arnér, 2001)***.* Cr (VI) compounds have toxic, genotoxic, mutagenic, and carcinogenic effects on humans, animals, plants, and as well as in microbes **(Ackerley *et al*., 2004; Turpeinen *et al*., 2004)**

Humans and animals maybe co-exposed to fipronil and chromium in the environment potential interactions between fipronil and chromium have been rarely investigated. Hence, the goal of the present research work was to study Hematological aspect, and toxicological effect of Fipronil (FPN) and/or Potassium dichromate (K2Cr2O7) treatment on liver of male albino rat.

**2. Materials and methods:**

**2.1. Chemicals:**

Fipronil, (FPN ((BARS®, 50mg/mL): was purchased from AVZ, Ltd. (Moscow, Russia) as a commercial product formulated for veterinary use. Potassium Dichromate (K2Cr2O7): was supplied by El-Nasr pharmaceutical chemicals, Egypt.

**2.2. Experimental animal:**

A total of 50 male Wister Albino rats with an average body weight of (160 -200 g) were supplied by the Center of Laboratory Animal (Faculty of Veterinary Medicine, Benha University, Egypt).Then, They were kept in a well-ventilated place, and the temperature 25 ± 3 °C and relative humidity were ~ 60%. They were maintained under the 12:12 h light/dark cycle with free access to water and a normal pellet diet over the experimental period. Rats were acclimatized to the new laboratory conditions for 14 days before any treatment.

**2.3. Experimental protocol:**

In the present study male albino rats were randomly allocated into 5 equal experimental groups (10 rats each) and treated for 28 days. Group 1: controls received Filtered water orally by stomach tube dailly. Group 2: control received corn oil orally by stomach tube day after day. Group 3: received FPN at a dose of 10 mg/kg b. wt. orally by stomach tube day after day. Group 4: received K2Cr2O7 via drinking water (700 ppm equivalent to 67 mg/kg b.wt) daily *.*Group 5: received FPN (10 mg/kg b. wt orally day after day by stomach tube) day after day+ K2Cr2O7 via drinking water (700 ppm equivalent to 67 mg/kg b.wt) daily for 28days.

**2.4. Sampling:**

After 28 days, Blood samples were collected by puncture of retro orbital plexus from rats in each group. Blood received on disodium EDTA 10% solution (20 μl/ml blood) was used for hematological studies. Then, all rats were euthanized, and liver tissue were collected.

**2.5. Serum biochemical analyses**

The collected sera were used for assessing the liver function parameters, including AST, ALT, total protein, and albumin. AST, ALT estimated according to method of (Wilkinson, Baron, Moss, & Walker, 1972)***.***While, total protein was were evaluated as described by **(*Gornall et al., 1949)*** and albumin was determined colorimetrically according to the method described by ***(Paul et al., 1981)***

**2.6. Evaluation of oxidative stress markers**

Lipid peroxidation was measured by determination of MDA content in liver homogenates according to method adapted by **(satoh, 1978)**. Additionally, NO was determined according to method adapted by(Gallinelli et al., 2009) and (TAC) levels ,the analysis was done according to **(Sinha, 1972)**

**2.7. Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6)**

Both TNF-α and IL-6 levels were assessed in the liver homogenate using ELISA commercial Kit. The analysis was done according to the manufacturer’s protocol.

**2.8. Statistical Analysis**

all data were tested for normality and homogeneity. Then, one-way analysis of variance used to determine the statistical significance of differences among groups followed by Duncan's test as post hoc for making a multiple comparison using the Statistical Package for Social science Software (Version 25, SPSS Inc., Chicago, IL, USA). The values were expressed as the mean ± standard error of the mean. A significant difference was used at ≤ 0.05 probability level.

**3. Results**

**3.2. Effect on hematological parameters**

The present investigation indicated no significant variations in hematological indices (RBCs, Hb, and WBCs) of rats exposed to Fipronil (FPN) and/or Potassium dichromate (K2Cr2O7) for 28 days and have been presented in **Table 1** and **figure** **(1-3).**

**Table (1):** Effect of Fipronil (FPN) and Potassium dichromate (K2Cr2O7) and their combinations on hematological parameters. Data are expressed as the mean ± SE (n=5). Different superscript letters in the same row indicate statistical significance at P≤0.05.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Experimental groups | | | | | Parameters |
| FPN + K2Cr2O7 | **K2Cr2O7** | **FPN** | **Control**  **Corn oil** | **Control** |
| 8.36 ± 0.42 a | 8.37 ±0.33 a | 8.45 ± 0.22 a | 9.04 ± 0.54 a | 9.52 ± 0.86 a | **RBCs (106/cmm)** |
| 9.47 ± 1.13 a | 8.02 ± 0.84 a | 8.10 ± 0.68 a | 11.35 ± 2.08 a | 9.90 ± 1.46 a | **WBCs (109/L)** |
| 13.41 ± 0.41 a | 13.73 ± 0.31 a | 14.72 ± 0.43 a | 15.32 ± 1.24 a | 13.48 ± 0.30 a | **Hb(g/dl)** |

Fig. 1: total erythrocyte count of wistar rats following exposure to Fipronil (FPN) and/or Potassium dichromate (K2Cr2O7) for 28 days

Fig. 2: total leucocyte count of wistar rats following exposure to Fipronil (FPN) and/or Potassium dichromate (K2Cr2O7) for 28 days.

Fig. 3: Changes in hemoglobin level of wistar rats following exposure to Fipronil (FPN) and/or Potassium dichromate (K2Cr2O7) for 28 days

**3.1. Serum biochemical analysis**

As shown in **Table 1** FPN and/or K2Cr2O7 induced hepatoxicity as demonstrated by the elevation of serum liver biomarkers. The AST, ALT levels were substantially increased (P≤0.05) and significant decrease in total protein and albumin(P≤0.05) in response to FPN and/or K2Cr2O7 treatment compared to those of control rats.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameters | Experimental groups | | | | |
| control | Control corn oil | FPN | K2Cr2O7 | FPN + K2Cr2O7 |
| AST (U/L) | 39.25 ± 4.09 d | 48.88 ± 4.90 d | 94.76 ± 5.57 c | 114.19 ± 4.70 b | 141.00 ± 3.99 a |
| ALT (U/L) | 55.90 ± 3.65 c | 42.03 ± 1.91 c | 100.19 ± 4.88 a | 82.50 ± 4.59 b | 110.79 ± 5.78 a |
| TP (g/dL) | 6.66 ± 0.41 b | 7.71 ± 0.51 a | 4.65 ± 0.19 c,d | 5.45 ± 0.19 c | 4.08 ± 0.24 d |
| Albumin (g/dL) | 3.21 ± 0.16 a | 3.71 ± 0.54 a | 2.40 ± 0.19 b | 2.50 ± 0.14 b | 1.49 ± 0.13 c |

These data suggested that when FPN and K2Cr2O7 were used in combination, provide synergistic effect lead to more damage on liver of rats than either one alone.

Table 1: Effect of oral administration of Fipronil (FPN) and Potassium dichromate (K2Cr2O7) and their combinations on serum biochemical parameters. Data are expressed as the mean ± SE (n=7). Different superscript letters in the same row indicate statistical significance at P≤0.05.

**3.4. Hepatic oxidative damage parameters**

The effects of Fipronil (FPN) and/or Potassium dichromate on lipid peroxidation and liver oxidative parameters are shown in Table 2. Fipronil (FPN) and/or Potassium dichromate intoxicated rats showed significant increases (P≤0.05) in MDA and NO levels along with significant decreases (P≤0.05) in the TAC levels in liver tissues compared to those of control rats.

Table 2: Effect of oral administration of Fipronil (FPN) and Potassium dichromate (K2Cr2O7) and their combinations on oxidative damage parameters. Data are expressed as the mean ± SE (n=7). Different superscript letters in the same row indicate statistical significance at P≤0.05.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameters | Experimental groups | | | | |
| control | Control corn oil | FPN | K2Cr2O7 | FPN + K2Cr2O7 |
| MDA | 9.42 ± 0.76 c | 10.54 ± 0.89 c | 19.97 ± 2.55 c | 48.43 ± 6.24 b | 85.64 ± 3.02 a |
| NO | 10.95 ± 0.24 c | 9.33 ± 0.28 c | 18.95 ± 2.02 b | 19.86 ± 1.62 a,b | 23.42 ± 2.23 a |
| TAC | 3.89 ± 0.20 a | 2.66 ± 0.16 b | 1.49 ± 0.22 c | 1.32 ± 0.43 c | 0.75 ± 0.16 c |

**3.5. Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6).**

The expression of inflammatory cytokines (TNF-α) and IL-6) in liver tissue were significantly increased (P≤0.05) in response to Fipronil (FPN) and/or Potassium dichromate compared to the control.

Table 3: Effect of oral administration of Fipronil (FPN) and Potassium dichromate (K2Cr2O7) and their combinations on inflammatory cytokines. Data are expressed as the mean ± SE (n=7). Different superscript letters in the same row indicate statistical significance at P≤0.05.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameters | Experimental groups | | | | |
| control | Control corn oil | FPN | K2Cr2O7 | FPN + K2Cr2O7 |
| TNF-α | 14.78 ± 1.70 d | 17.04 ± 1.85 d | 44.23 ± 4.44 c | 74.94 ± 6.99 b | 141.00 ± 6.14 a |
| IL-6 | 2.85 ± 0.54 c | 1.29 ± 0.05 c | 3.31 ± 0.23 c | 6.96 ± 0.88 b | 12.50 ± 1.39 a |

**4. DISCUSSION:**

FPN is commonly used insecticide in agriculture and for public health purposes lead to more toxic effect in many nontarget species, including humans. Potassium dichromate is one of the most toxic chemical compounds Commonly released in the environment as a result of industrial and agricultural practices. Additionally, it is a common pollutant in aquatic and terrestrial ecosystems **( Costa *et al*., 2003).** Interestingly, humans and animals may be co-exposed to FPN and K2Cr2O7 under many circumstances resulting in existence of potentiated toxic effects as indicated by the current study.

Changing in hematological indices is a biomarker of physiological stress**(Rm & David, 2017)**. in which, FPN exposure in male Wistar rats at dose 6.46, 12.12 and 32.33mg/kg body weight for 90 days investigate variations in hematological indices of rats (increase in WBC, demolish the RBC concentrates and Hb) **(Rm & David, 2017) .**Moreover**,** Chronic exposure to K2Cr2O7 at dose 0.25 , 0.5 , 1mg/kg bw/day for 90 days induces anemia with decreased RBC count and hemoglobin concentration **(Saha *et al*., 2017)** .

In the present investigation, there is no significant variations in hematological indices of rats exposed to FPN and /or K2Cr2O7 for 28 days compared to control groups as shown in figure ( 1-3). Our result were not agree with those result of **(Rm & David, 2017; Saha *et al*., 2017)**. This may be due to variation in doses as well as short duration of exposure.

There are substantial evidences indicate that liver is targets for FPN and K2Cr2O7 intoxication **(Badgujar *et al*., 2015; Fatima *et al*., 2005)** as they are highly perfused organs with a high blood volume. In addition, the liver is the main site for xenobiotic metabolism as it contains numerous xenobiotic metabolizing enzymes **(Hogson *et al*., 2004).** So, the present study was designed to evaluate the effect of Fipronil and/or Potassium dichromate on liver function parameters, oxidative stress markers, and inflammatory cytokines (TNF-α and IL-6).

The present study showed that intoxication with Fipronil and/or Potassium dichromate markedly increased the levels of the serum hepatic enzymes (AST, ALT, total protein, and albumin). Transaminases (AST and ALT) used as an indicator of liver damage, and ALT is considered as a gold indicator for liver injury (McGill, 2016)***.*** The increased levels of these enzymes in serum may be due to loss of structural integrity of the liver as a result of their released into the blood circulation after the rupture of the plasma membrane **(Velmurugan *et al*., 2014).** Furthermore, hepatic damage influence the biosynthesis of total protein and albumin result in Declining in serum levels of total protein and albumin **(Kanwal *et al*., 2012)**. These findings were in agreement with those of several published studies on FPN and K2Cr2O7 intoxication **(Abdel-daim *et al*., 2018; Albasher *et al*., 2019; Ben Hamida *et al*., 2016; Elgawish *et al.*, 2019; Soudani *et al*., 2011).**

A strong body of evidence suggests that oxidative stress mechanisms are other mechanisms involved in both FPN and K2Cr2O7 induced toxicities ***(*Soudani *et al*., 2012*;* Abdel-daim *et al.,* 2018; Abdel-daim *et al.* 2019; Albasher *et al.,* 2019; Boşgelmez *et al.,*2019; Sarıca *et al.* 2019*).*** The major manifestations of oxidative distress in the biological system are LPO, protein oxidation, mitochondrial damage, decreased ATP production and DNA damage. Oxidative stress is initiated due to imbalance between oxidants (ROS) and cellular antioxidant components (enzymatic and non-enzymatic).

There is a variety of ROS such as OH•, O•‾, H2O2, NO, NOO‾, and others are produced during oxidative stress. Since, OH• is the most harmful and abundant radical **(Avery, 2011; Dasari et al., 2014; Sies et al., 2017; Yang, Liu et al., 2014)**. Additionally, it is the most harmful radical due to high rate of reactivity compared to other ROS **(Sies et al., 2017).** OH• is formed by Large amounts of through a Fenton’s reaction in presence of Fe2+ and when there are no enough GSH and CAT enzyme. It can diffuse in the cell and directly interfere with distant molecules such as cell membrane causing LPO and production of MDA as result of breakdown of the unsaturated fatty acids content of the lipid bilayer **(Avery, 2011).**

In the same line, our results revealed incidence of oxidative stress indicated by a remarkable increase in MDA level (LPO marker) along with reduction in TAC in response to FPN and/or K2Cr2O7 insult. These findings were in agreement with those of several published studies on FPN and K2Cr2O7 intoxication where the MDA levels ,NO were significantly increased ,while TAC decreased in liver tissue in response to FPN intoxication or K2Cr2O7 treatment **(Elgawish & Soliman, 2019; Soudani et al., 2011)*.***

Additionally, oxygen free radicals play a key role in initiation and progression of inflammation **(Turner et al., 2014).** combined action of free cytokines and free radicals activates endothelial cells and promotes synthesis of inflammatory mediators and adhesion molecules. finally, the ROS exert its toxic effect on the cell components at the inflammatory site resulting in loss of cell functioning and death **(Elmarakby et al., 2012).** The major findings of the present study are the significant up regulation to levels of IL-6 and TNF-α on liver tissues on FPN and K2Cr2O7 alone or in combination compared to control group. It was also observed that TNF-α was positively correlated with interleukins as Production of interleukins accompanied with increased production of TNF-α (Al Jameil et al., 2017).ALSO, There is a complex relationship between oxidative stress and TNF-α shown that TNF-α increases ROS and ROS increases TNF-α level **(Kuhad *et al*,. 2009)**. This explaining the up-regulation of the inflammatory cytokines (IL-2, IL-6 and TNF-α) in treated groups as FPN and K2Cr2O7 induced their toxicities mainly through oxidative stress. these finding agree with other studies on fipronil and K2Cr2O7**(Al Jameil *et al*. 2017; Elgawish *et al*., 2019; Khalil *et al*. 2019).**

**Conclusion**

The overall data indicated that FPN and/or K2Cr2O7 could induce severe tissue da-

mage in the liver mediated by oxidative stress and apoptotic mechanisms. TNF-α, and IL-6 which may contribute in liver injury.

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