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# An Evaluation of Hepatotoxicity, Nephrotoxicity, and Genotoxicity Induced by Acute Toxicity of Hexavalent Chromium and Comparison of the Possible Protective Role of Selenium and Vitamin E on These Effects

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**Abstract:** Introduction Hexavalent chromium Cr (VI) is a strong oxidizing toxic agent. It penetrates cell membrane and quickly reduced with production of reactive intermediates and reactive oxygen species that react with the DNA causing anomalies in the cell structure. Vitamin E (vit. E) is a lipid soluble antioxidant preventing damage to membranes also selenium (Se) is an essential micronutrient with an antioxidant activity. Aim of the present study was to evaluate the hepatotoxicity, nephrotoxicity, and genotoxicity induced by acute Cr (VI) toxicity. Also, to evaluate and compare the possible protective role of vit. E and Se against that toxicity. Methodology: This study was carried out on 60 adult male albino rats divided into 10 rats of six groups, negative control group, selenium control group (0.5 mg/kg IP for 5 consecutive days), vitamin E control group (125 mg/kg orally for 14 days), Cr (VI) group (10 mg/kg single dose IP), Cr (VI) + Selenium group and hexavalent chromium + Vitamin E group. Liver and kidney function tests, total protein, oxidative stress, antioxidant markers and genotoxic analysis were done to all groups. Result: Acute Cr(VI) toxicity resulted in increased levels of the studied liver, kidney , oxidative stress markers, all forms of chromosomal aberrations and elevation of DNA damage. It decreased levels of total protein and antioxidant markers. Treatment with Se or vit. E resulted in improvement in all these effects. Conclusion& recommendation: Cr (VI) is a hepatotoxic, nephrotoxic, and genotoxic. Se or vit. E has the ability for reduction of these deleterious effects. So it is recommended to do regular medical examination of workers exposed to hexavalent chromium for early detection of any health problem and afford dietary supplementation with vitamin E and selenium.

**Key words** Hexavalent chromium, Hepatotoxicity, Nephrotoxicity, Genotoxicity, vitamin E (vit. E) and selenium (Se).

## Introduction

Metals are major environmental pollutants (Holland and Avery, 2009). Human exposure to these heavy metals has risen dramatically due to their extensive use even in domestic applications. (Tchounwou et al., 2012). Chromium (Cr) is one of the eight metals in top of priority list of the toxic substances (ATSDR , 2011).

Chromium has two valence states: trivalent chromium Cr(III) and hexavalent chromium [Cr(VI)] (Stout et al., 2009). Chromium (III) compounds are found in foodstuffs and are essential micronutrients (He et al., 2007), do physiological functions as lipid, protein, and glucose metabolism (IPCS, 2006), it is safe and has no toxic effects due to its poor ability to enter cells (Zhitkovich, 2011).

Chromium (VI) compounds are toxic to humans, animals and even aquatic organisms. They are used in many industries as electroplating, leather tanning, and stainless-steel production (Yarkandi, 2014), but it is highly toxic causes multiorgan toxicity as hepatotoxicity, renal damage, and genotoxicity (Rana, 2008). Inside cells, Cr (VI) is reduced to Cr(III) by a variety of chemical reductants with production of reactive intermediates causing cellular damage and generation of reactive oxygen species (ROS) (Myers, 2012) that enhances oxidative stress and exert a cytotoxic effect and many diseases as renal disorders, liver disorders, inflammation and others (Soudani et al., 2011).

Vitamin E (lipid soluble antioxidant) could prevent membranes or proteins damage by scavenging ROS (Traber and Atkinson, 2007), attenuate the oxidative stress and restore the level of anti-oxidants including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) (Bharrhan et al., 2010).

Selenium is an one of the essential micronutrients with antioxidant activity (MacFarquhar et al., 2010) counteracts the free radicals , preserve the structure and function of DNA, proteins and chromosomes against the injury of oxidation (El-Demerdash, 2004).

So the aim of the present study was to evaluate the hepatotoxicity, nephrotoxicity and genotoxicity induced by acute Cr(VI) toxicity. Also, to evaluate and compare the possible protective role of vitamin E (vit. E) and selenium (Se) against that toxicity.

# Methodology

## The experimental animals

60 adult male albino rats with average weight about 150–240 grams (g) for each rat, were used in this study. The animals were obtained from Helwan animal breeding farm, Cairo, Egypt. They were maintained in special cages in a well-ventilated animal house at normal temperature (22°C ± 5°C) under a 12:12-hour light–dark cycle. They were fed with normal feeding and water. They were kept under suitable conditions for one week for adaptation before the start of the experiment.

Handling of the animals followed the rules for the experimental research ethics approved by Research Ethics Committee at faculty of Medicine for Girls Al-Azhar University.

### Groups of animals

**Group (1)** [Negative [-ve] control group]: rats were received normal feeding and distilled water only for 14 days.

**Group (2)** [Selenium control group]**:** rats were given selenium (intraperitoneal [IP]) at a dose of (0.5 mg/kg ] bodyweight (b.wt.) dispersed in distilled water daily for 5 consecutive days according to ***Peng et al., (2007)*.**

**Group (3)** [Vitamin E control group]**:** rats were given vitamin E [vit. E] (α-tocopherol) daily by (oral gavage) at a dose of (125 mg/kg b.wt.) for 14 days according to ***Arreola-Mendoza et al.,(2006)*.**

**Group (4)** [Hexavalent chromium [Cr(VI)] group]: rats were given a single dose of potassium dichromate ($K_2Cr_2O_7$) (IP) (10 mg/kg b.wt.) dissolved in distilled water according to ***Balakrishnan et al., (2013b)*.**

**Group (5)**[Cr(VI) + Se group]**:** rats were given a single dose of $K_2Cr_2O_7$ (IP) (10 mg/kg b.wt.) dissolved in distilled water, and were also given selenium (IP) at a dose of (0.5 mg/kg b.wt.) dispersed in distilled water daily for 5 consecutive days according to ***Hassanin et al., (2013)*.**

**Group (6)**[Cr(VI) + vit. E group]: rats were received a single dose of $K_2Cr_2O_7$ (IP) (10 mg/kg b.wt.) dissolved in distilled water, with vit. E daily by (oral gavage) at a dose of (125 mg/kg b.wt.) for 14 days ***Balakrishnan et al., (2013b)***.

### Chemicals:

1. Hexavalent Chromium [Cr(VI)] in its synthetic-form potassium dichromate (K2Cr2O7).
2. Selenium in the form of selenium dioxide .
3. Vitamin E (α-tocopherol) in the form of oil.

- Both Cr(VI) and selenium were purchased from Arab Company for Drug Industries and Medical Appliances, Abidin, Cairo, Egypt.
- Vitamin E (α-tocopherol) was purchased from Cairo Company for Pharmaceutical and Chemical Industries, Shubra Cairo, Egypt.
- potassium dichromate (K2Cr2O7) solution was prepared by dissolving 140 mg of K2Cr2O7 in 70 ml of distilled water to give the estimated dose for each rat.
- Selenium solution was prepared by dissolving 7 mg of Selenium in 28 ml of distilled water to give the estimated dose for each rat.

### Collection and preservation of the samples

Twenty four hours after the last dose; blood samples were taken from the medial canthus of the eyes of rats .The samples were collected in clean dry test tubes and left at room temperature for 20 minutes to clot. Samples were centrifuged at 4,000 rpm for 15 minutes to separate the sera.

The sera were then stored at -20 °C for subsequent assaying of Liver function tests (AST, ALT, ALP, total bilirubin), total protein, kidney function tests (urea, creatinine), oxidative stress markers (MDA), antioxidant markers (GSH, CAT, SOD).

Then all animals were sacrificed while they were under anesthesia by diethyl ether inhalation. Liver and both femurs were dissected.

Parts of the livers were washed with phosphate–buffered saline (PBS) to remove any red blood cells or clots, then stored at -20°C for subsequent assaying of oxidative stress marker [the liver malondialdehyde (MDA)] by using commercial kits.

Also, some parts of the livers are kept in normal saline and freezed for measuring deoxyribonucleic acid (DNA) damage by the comet assay.

The bone of the femora were kept in the normal saline then stored at 20°C, the bone marrows were used for estimation of chromosomal aberrations.

All the previous parameters were done at cell Biology Department of National Research Center in Dokki (Cairo) and were done by using commercial Kits, which were purchased from Bio diagnostic company, Dokki, Giza, Egypt.

# Statistical Analysis

All the data were tabulated and expressed as the mean ± standard deviation (S.D.) values. Comparing the values for different treated groups with the values for controls were done using one-way ANOVA test.

Independent sample t-test were used to compare between the means of two studied groups. Probability (P-value), P-value ≤0.05 was considered significant, P-value ≤0.001 was considered as highly significant and P-value >0.05 was considered insignificant. Data were

analyzed using Statistical Program for Social Science (SPSS).

## The results

**1) Biochemical studies**

**a) Liver function tests:**

Cr (VI) resulted in elevation of the serum level of AST, ALT, ALP and total bilirubin as compared with the control. Administration of selenium (Se)or vitamin E (vit. E) with Cr(VI) resulted in lowering of serum level of AST, ALT, ALP and total bilirubin as compared to Cr(VI) toxic groups ,treatment with vit. E. showed more reduction in the serum level of AST, ALT and total bilirubin than treatment by Se (Table 1).

**b) Total protein in the serum:**

Cr (VI)produced reduction in the serum level of total protein as compared to the control. Administration of Se or vit. E with Cr(VI), resulted in elevation of the serum level of total protein as compared to Cr(VI) toxic group with no significant differences between them (Table 2).

**c) Kidney function tests:**

Cr(VI) resulted in elevation of the serum level of urea and creatinine as compared to the control group. Co-administration of Se or vit. E with Cr(VI) showed significant decrease of urea concentration and creatinine level in the serum as compared to Cr(VI) toxic group with better effects observed with vit. E. (Table 3).

**d) Oxidative stress markers:**

Cr(VI) resulted in elevation of the level of liver malondialdehyde (MDA) as compared to the control group. Treatment by Se or vit. E with Cr(VI) induced reduction in the level of liver MDA as compared to Cr(VI) toxic group with no significant difference between them (Table 4).

**e) Antioxidant markers:**

Administration of Cr(VI) produced increase in superoxide dismutase (SOD) activity and decrease in the serum level of GSH and catalase activity as compared to the control. Treatment by Se or vit. E with Cr(VI) revealed reduction in SOD activity and increase in the serum level of reduced GSH and catalase activity as compared to Cr(VI) toxic group, treatment by vit. E produced more improvement in SOD activity and catalase activity than the treatment by Se, with no significant difference between them as regards GSH (Table 5).

**Genotoxic analysis (cytogenetic evaluation)**

**a) Comet assay (The single cell Gel Electrophoresis [SCGE]):**

Cr(VI)revealed elevation of DNA damage as indicated by increase in comet tail length (photo 2) as compared to the control(photo 1). Treatment by Se or vit. E resulted in decrease in DNA damage as compared to Cr(VI) toxic group, with no significant differences between them (Table 6).

**(b) Chromosomal aberrations study:**

Cr(VI) toxicity resulted in increase in all forms of chromosomal aberrations including Gap, Break, centromeric attenuation (C.A.), end mitosis(E. mitosis), deletion (Del.), fragments (Frag.) and end to end chromosome fusion (E to E) ( photo 5-10). Treatment Se or vit. E resulted in decrease in all forms of chromosomal aberrations, with no significant difference between them (Table 7&8).

**Table (1)**: **Statistical analysis of the mean values ± S.D. for the effect of acute toxicity by Cr(VI) on liver function tests of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests .**

| Groups n= 10 rats / group | | AST (U/L) | ALT (U/L) | ALP (U/L) | Total Bilirubin (mg/dl) |
|---|---|---|---|---|---|
| | | Mean ± S.D. | Mean ± S.D. | Mean ± S.D. | Mean ± S.D. |
| Control | | 48.95 ± 2.00 | 52.47 ± 1.58 | 224.76 ± 3.01 | 0.29 ± 0.04 |
| Se | | 48.80 ± 1.54[a] | 51.43 ± 2.04 [a] | 217.94 ± 6.02 [a] | 0.29 ± 0.03 [a] |
| Vit. E | | 47.79 ± 1.91[a] | 50.82 ± 1.16 [a] * | 217.04 ± 5.34 [a] | 0.29 ± 0.02 [a] |
| Cr(VI) toxicity<br>% change from control | | 90.34 ± 1.73[a]**<br>↑84.55% | 101.05 ± 2.24[a]**<br>↑92.59% | 809.55 ± 32.40 [a]**<br>↑260.18% | 3.17 ± 0.52 [a]**<br>↑993.05% |
| Cr(VI)+Se<br>% change from Cr(VI) | | 63.03 ±1.36[b]**<br>↓30.23% | 71.97 ± 1.78 [b]**<br>↓28.78% | 523.39 ± 65.26 [b]**<br>↓35.35% | 1.29 ± 0.28 [b]**<br>↓59.31% |
| Cr(VI)+vit.E<br>% change from Cr(VI) | | 60.84 ± 1.50 [b]**<br>↓32.65% | 66.21 ± 1.32 [b]**<br>↓34.48% | 498.53 ± 54.90 [b]**<br>↓38.42% | 1.00 ± 0.11 [b]**<br>↓68.45% |
| One Way ANOVA | F | 930.306 | 1263.315 | 412.490 | 206.693 |
| | P-value | 0.000** | 0.000** | 0.000** | 0.000** |
| Independent t-test | t-value | 3.415 | 8.200 | 0.922 | 2.987 |
| | p-value | 0.003** | 0.000** | 0.369 | 0.008** |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; n= number; AST= aspartate aminotransferase; ALT= alanine aminotransferase; ALP= alkaline phosphatase; S.D.= standard deviation; a= [Se, vit. E, Cr(VI) ] compared to the control group; b= the treated groups compared to Cr(VI) ; *= significant (P≤0.05); ** = highly significant (P≤0.01).*

**Table (2)**: **Statistical analysis of the mean values ±S.D. for the effect of acute toxicity by Cr (VI) on the total protein level in the serum of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests.**

| Groups n = 10 rats /group | | Total protein (g/dl) Mean ± S.D. |
|---|---|---|
| Control group | | 12.89 ± 0.87 |
| Se group | | 13.65 ± 1.00 [a *] |
| Vit. E group | | 13.69 ± 0.96 [a *] |
| Cr(VI) toxicity<br>% change from control | | 3.71 ± 0.60 [a **]<br>↓71.20% |
| Cr(VI)+Se<br>% change from Cr(VI) | | 9.36 ± 0.77 [b **]<br>↑152.28% |
| Cr(VI)+vit. E<br>% change from Cr(VI) | | 10.03 ± 0.70 [b **]<br>↑170.22% |
| One Way ANOVA | F | 214.695 |
| | P-value | 0.000** |
| Independent t-test | t-value | -2.020 |
| | p-value | 0.059 |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; n= number; S.D.= standard deviation; a= [Se, vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI); *= significant (P≤0.05); **= highly significant (P≤0.01).*

**Table (3)**: **Statistical analysis of the mean values± S.D. for the effect of acute toxicity by Cr(VI) on the Kidney function tests of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests.**

| Groups n= 10 rats / group | | Urea concentration (mg/dl) Mean ± S.D. | Creatinine (mg/dl) Mean ± S.D. |
|---|---|---|---|
| Control group | | 24.52 ± 1.50 | 0.64 ± 0.04 |
| Se group | | 23.30 ± 1.21 [a] | 0.62 ± 0.06 [a] |
| Vit. E group | | 22.84 ± 1.20 [a *] | 0.61 ± 0.05 [a] |
| Cr(VI) toxicity<br>% change from control | | 72.12 ± 1.83 [a **]<br>↑194.13% | 2.01 ± 0.20 [a **]<br>↑214.61% |
| Cr(VI)+Se<br>% change from Cr(VI) | | 51.61 ± 1.98 [b **]<br>↓28.44% | 0.94 ± 0.05 [b **]<br>↓53.36% |
| Cr(VI)+vit.E<br>% change from Cr(VI) | | 42.35 ± 1.53 [b **]<br>↓41.27% | 0.87 ± 0.04 [b **]<br>↓56.57% |
| One Way ANOVA | F | 1615.437 | 338.635 |
| | P-value | 0.000** | 0.000** |
| Independent t-test | t-value | 11.694 | 3.078 |
| | P-value | 0.000** | 0.006** |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; n= number; S.D.= standard deviation; a=[Se,vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI);*= significant (P≤0.05); **= highly significant (P≤0.01).*

**Table (4)**: **Statistical analysis of the mean values± S.D. for the effect of acute toxicity by Cr(VI) on the liver MDA of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests**.

| **Groups n= 10 rats / group** | | **MDA (g/dl) Mean ± S.D.** |
|---|---|---|
| **Control group** | | 7.86 ± 0.73 |
| **Se group** | | 7.55 ± 0.63 [a] |
| **Vit. E group** | | 7.19 ± 0.87 [a] |
| **Cr(VI) toxicity % change from control** | | 23.16 ± 1.72 [a **] ↑194.66% |
| **Cr(VI)+Se % change from Cr(VI)** | | 10.65 ± 1.17 [b **] ↓54.02% |
| **Cr(VI)+vit. E % change from Cr(VI)** | | 10.01 ± 0.74 [b **] ↓56.78% |
| **One Way ANOVA** | **F** | 339.800 |
| | **P-value** | 0.000** |
| **Independent t-test** | **t-value** | 1.462 |
| | **P-value** | 0.161 |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; MDA= malondialdehyde;n= number; S.D.= standard deviation; a= [Se,vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI);*= significant (P≤0.05); **= highly significant (P≤0.01).*

**Table (5)**: **Statistical analysis of the mean values ± S.D. for the effect of acute toxicity by Cr(VI)on antioxidant markers of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests.**

| **Groups n= 10 rats / group** | | **SOD activity (u/l) Mean ± S.D.** | **GSH (mg/dl) Mean ± S.D.** | **Catalase activity (u/l) Mean ± S.D.** |
|---|---|---|---|---|
| **Control** | | 22.01±1.75 | 28.26±1.52 | 741.06±54.74 |
| **Se** | | 22.00±1.50 [a] | 29.99±1.58 [a *] | 779.97±45.87 [a *] |
| **Vit. E** | | 21.71±1.58 [a] | 31.16±1.32 [a **] | 821.05±23.87 [a **] |
| **Cr(VI) toxicity % change from control** | | 82.09±2.24 [a **] ↑272.97% | 10.35±0.96 [a **] ↓63.37% | 282.84±34.42 [a **] ↓61.83% |
| **Cr(VI)+Se % change from Cr(VI)** | | 53.49±2.43 [b **] ↓34.84% | 20.77±1.48 [b **] ↑100.68% | 516.48±50.00 [b **] ↑82.61% |
| **Cr(VI)+vit.E % change from Cr(VI)** | | 49.93±1.36 [b **] ↓39.18% | 21.78±1.84 [b **] ↑110.43% | 621.55±31.27 [b **] ↑119.75% |
| **One Way ANOVA** | **F** | 175.787 | 282.212 | 237.760 |
| | **P-value** | <0.001** | <0.001** | <0.001** |
| **Independent t-test** | **t-value** | 4.052 | -1.354 | 0.193 |
| | **P-value** | 0.001** | -5.634 | 0.000** |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; n= number; SOD= Superoxide dismutase; GSH=reduced glutathione; S.D.= standard deviation; a= [Se,vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI); *= significant (P≤0.05); **= highly significant (P≤0.01).*

**Table (6)**: **Statistical analysis of the mean values± S.D. of comet tail length for DNA damage of acute toxicity by Cr(VI) of adult male albino rats (n=60) and the possible protection by Se or vit. E and comparison between the studied groups using one way ANOVA and independent t-tests.**

| Groups n= 10 rats / group | | comet tail length (uM) of DNA damage |
|---|---|---|
| | | Mean ± S.D. |
| Control group | | 12.95 ± 1.19 |
| Se group | | 12.89 ± 1.16 [a] |
| Vit. E group | | 12.54 ±2.21 [a] |
| Cr(VI) toxicity<br>% change from control | | 29.05 ±5.42 [a **]<br>↑124.32% |
| Cr(VI)+Se<br>% change from Cr(VI) | | 19.95±3.45 [b **]<br>↓31.33% |
| Cr(VI)+vit. E<br>% change from Cr(VI) | | 18.83 ±3.11 [b **]<br>↓35.18% |
| One Way ANOVA | F | 15.341 |
| | P-value | 0.000** |
| Independent t-test | t-value | 0.763 |
| | P-value | 0.456 |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium;DNA=Deoxyribonucleic acid; n= number; S.D.= standard deviation; a= [Se,vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI);*= significant (P≤0.05); **= highly significant (P≤0.01).*

**Table (7)**: **The numbers, mean percentages and mean values ± S.D. of the effect of acute toxicity by Cr(VI) on the chromosomes in the bone marrow cells of adult male albino rats (n=60) and the possible protection by vit. E or Se.**

| Chromosomal aberration | | Groups (n=10rats/group) | | | | | |
|---|---|---|---|---|---|---|---|
| | | control | se. | vit. E | Cr(VI) toxicity | Cr(VI) + Se | Cr(VI) +vit.E |
| Gap | n & % | 6 (1%) | 3 (0.5%) | 2 (0.333%) | 31 (5.166%) | 14 (2.33%) | 12 (2%) |
| | Mean±S.D. | 0.6±1.074 | 0.3±0.674[a] | 0.2±0.421 [a] | ↑3.1±1.523 [a**] | ↓1.4±0.669 [b**] | ↓1.2±0.918 [b**] |
| Break | n & % | 4 (0.667%) | 3 (0.5%) | 1 (0.167%) | 35 (5.833%) | 16 (2.66%) | 13 (2.16%) |
| | Mean± S.D. | 0.4±.699 | .03±0.483[a] | 0.1±0.316 [a] | ↑3.5±1.433 [a**] | ↓1.6±1.264[b**] | ↓1.3±0.823 [b**] |
| C.A. | n & % | 8 (1.33%) | 5 (0.833%) | 4 (0.667%) | 39 (6.5%) | 15 (2.5%) | 11 (1.83%) |
| | Mean± S.D. | 0.8±1.135 | 0.5±0.849[a] | 0.4±0.699 [a] | ↑3.9±1.663 [a**] | ↓1.5±1.081 [b**] | ↓1.1±0.875 [b**] |
| E. mitosis | n & % | 1 (0.16%) | 0 | 0 | 28 (4.66%) | 8 (1.33%) | 7 (1.16%) |
| | Mean± S.D. | 0.1±0.316 | 0 | 0 | ↑2.8±1.229 [a**] | ↓0.8±1.032 [b**] | ↓0.7±0674 [b**] |
| Del. | n & % | 0 | 0 | 0 | 18 (3%) | 9 (1.5%) | 6 (1%) |
| | Mean± S.D. | 0 | 0 | 0 | ↑1.8±1.032 | ↓0.9±0.994 [b**] | ↓0.6±0.699 [b**] |
| Frag. | n & % | 0 | 0 | 0 | 16 (2.66%) | 7 (1.16%) | 5 (0.833%) |
| | Mean± S.D. | 0 | 0 | 0 | ↑1.6±0.699 | ↓0.7±1.059 [b**] | ↓0.5±.0.707 [b**] |
| E to E | n & % | 0 | 0 | 0 | 12 (2%) | 4 (0.667%) | 5 (0.833%) |
| | Mean± S.D. | 0 | 0 | 0 | ↑1.2±0.418 | ↓0.4±0.699 [b**] | ↓0.5±0.707 [b**] |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; C.A.= centromeric attenuation; E. mitosis= end mitosis; Del.= deletion; Frag.= fragments; E to E = end to end chromosome fusion; n= number;S.D.= standard deviation; a= [Se,vit. E, Cr(VI)] compared to the control group; b= the treated groups compared to Cr(VI) ; *= significant (P≤ 0.05); **= highly significant(P≤ 0.01).*

**Table (8): Statistical analysis by independent t-test to compare between the possible protective role of Se or vit. E on acute toxicity by Cr(VI) as regards chromosomal aberrations in the bone marrow cells of adult male albino rats (n=60) using independent t-test.**

| Chromosomal aberration | Cr(VI) +Se | | Cr(VI) + vit.E | | Independent t-test | |
|---|---|---|---|---|---|---|
| | n | Mean ± S.D. | n | Mean ± S.D. | t-value | p-value |
| **Gap** | 14 | 1.4±0.669 | 12 | 1.2±0.918 | 0.641 | 0.527 |
| **Break** | 16 | 1.6±1.264 | 13 | 1.3±0.823 | 0.737 | 0.468 |
| **C.A.** | 15 | 1.5±1.081 | 11 | 1.1±0.875 | 1.007 | 0.328 |
| **E. mitosis** | 8 | 0.8±1.032 | 7 | 0.7±0.674 | 0.28 | 0.782 |
| **Del.** | 9 | 0.9±0.994 | 6 | 0.6±0.699 | 0.856 | 0.401 |
| **Frag.** | 7 | 0.7±1.059 | 5 | 0.5±0.707 | 0.543 | 0.593 |
| **EtoE** | 4 | 0.4±0.699 | 5 | 0.5±0.707 | 0.213 | 0.837 |

*Se= selenium; vit. E= vitamin E; Cr(VI)= hexavalent chromium; C.A.= centromeric attenuation; E. mitosis= end mitosis; Del.= deletion; Frag.= fragments; E to E= end to end chromosome fusion; n= number; S.D.= standard deviation; *= significant (P≤ 0.05); **= highly significant (P≤ 0.01).*

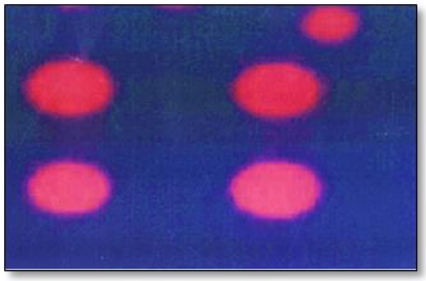

**Photo (1): Fluorescent microscope photomicrograph of hepatocytes of control groups, Se or vit. E treated groups showing no migration of DNA out of the nucleus into the tail of the comet.**

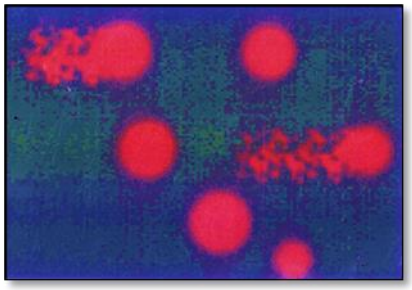

**Photo (2): Fluorescent microscope photomicrograph of hepatocytes of Cr(VI)toxic groups showing migration of DNA out of the nuclus into the tail of the comet as compared to the control group.**

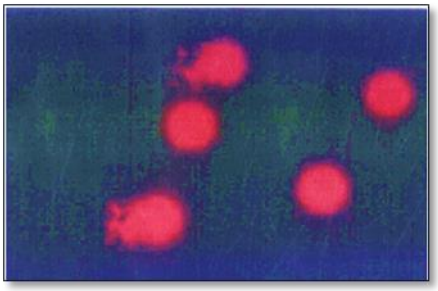

**Photo (3): Fluorescent microscope photomicrograph of hepatocytes of Cr(VI)+Se and Cr(VI)+Vit. E groups showing reduction in the migration of DNA out of the nucleus into the tail of the comet as compared to the Cr(VI)toxic groups.**

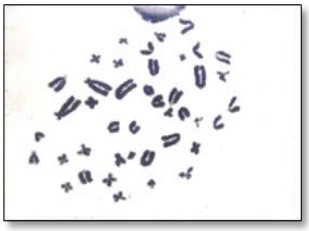

**Photo (4): Metaphase spread from bone marrow of rat showing normal chromosomes (Giemsa stain.x100).**

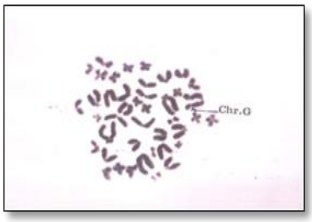


**Photo (5): Metaphase spread from bone marrow of exposed rats to Cr(VI) showing gap chromosomal aberration (Giemsa stain.x100)**

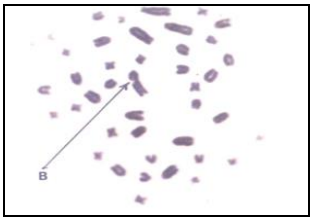


**Photo (6): Metaphase spread from bone marrow of exposed rats to Cr(VI) showing break chromosomal aberration (Giemsa stain.x100).**

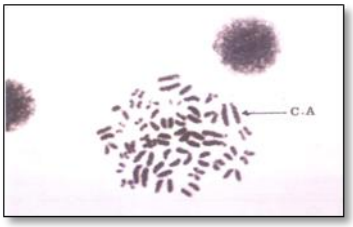


**Photo (7): Metaphase spread from bone marrow of exposed rats to Cr(VI) show centromeric attenuation chromosomal aberration (Giemsa stain.x100)**

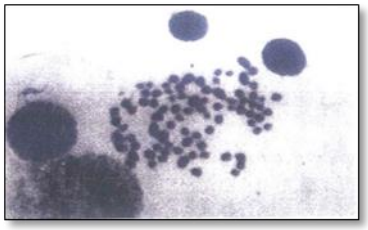

**Photo (8): Metaphase spread from bone marrow of exposed rats to Cr(VI) showing endomitosis chromosomal aberration (Giemsa stain.x100).**

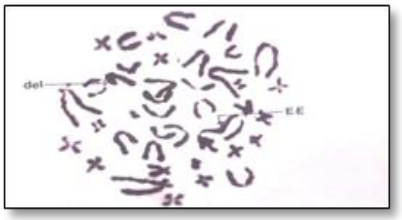


**Photo (9): Metaphase spread from bone marrow of exposed rats to Cr(VI) showing deletion and end to end chromosomal aberration (Giemsa stain.x100).**

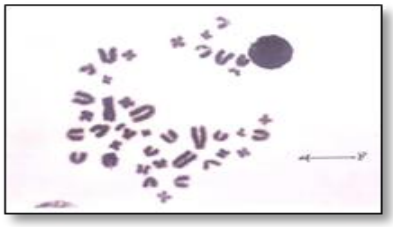

**Photo (10): Metaphase spread from bone marrow of exposed rats to Cr(VI) showing fragment chromosomal aberration (Giemsa stain.x100)**

## Discussion

Acute C r(VI) toxicity resulted in significant increase in the levels of serum AST, ALT, ALP and total bilirubin as compared to the control group. These findings agreed with those of *Hashish and Elgaml (2016)* and can be explained by *Giannini et al., (2005)* who reported that the hepatotoxicity of chromium resulted in increase of the hepatic enzymes activity (AST and ALT) as they are located in the liver cell cytoplasm and after cellular damage, they are released in the blood stream. Also, *(Soudani et al., 2013)* stated that the chromium leads to disturbance in biosynthesis of hepatic enzymes due dysfunction and alteration in the permeability of the hepatic membrane.

In the present study, co-administration of selenium (Se) or vitamin E (vit. E) with Cr(VI) to rats resulted in significant decrease in serum levels of AST, ALT, ALP and total bilirubin as compared to acute Cr(VI) toxic group. These results were in agreement with those of (*Balakrishnan et al., 2013a)*.

The results of the present work revealed significant decrease in the total protein level in the serum in acute Cr(VI) toxic group as compared to the control group .These results were in agreement with those of (*Hashish and Elgaml, 2016).Yousef et al., (2008)* revealed that to the reduction in protein synthesis or increase proteolytic activity or degradation that caused by Cr(VI) toxicity . In addition, *Shati (2014)* stated that the protein and glycogen content are decreased in response to $K_2Cr_2O_7$ administration may be due to the harmful effect of its active metabolite.

In this study, co-administration of Se or vit. E with Cr(VI) showed significant increase in the total protein level in the serum as compared to acute Cr(VI) toxic group.This finding almost agreed with those of *Balakrishnan et al., (2013a and b*).

The results of present study revealed significant increase in urea concentration and creatinine level in the serum as compared to the control group and this was in accordance with those of *Salamaa et al., (2016)* and supported by *Patlolla et al., (2009)* who said that the peroxidative damage by Cr(VI) causes reduction in kidney function, which was reflected by significant increase in serum levels of blood urea nitrogen (BUN) and creatinine suggesting nephrotoxicity.

In present study, co-administration of Se or vit. E with Cr(VI) to rats, produced significant decrease in urea concentration and creatinine level in the serum as compared to acute Cr(VI) toxic group. These results were in agreement with *Balakrishnan et al., (2013a* and *b*).

Acute Cr(VI) toxic group revealed a significant increase in the level of liver malondialdehyde (MDA) as compared to the control group .Similar finding was reported by *Goodarzi et al., (2016)*and *Hegazy et al., (2016)* while *Cengiz et al., (2016)* observed that the level of MDA had not changed in $K_2Cr_2O_7$ treated rats as compared to the control group.

The increase in the level of MDA due to Cr(VI) toxicity can be explained by *Patlolla et al., (2009)* who reported that Cr(VI) can induce free radical production leading to peroxidation with increase the peroxidation markers as MDA and decrease the antioxidant markers as SOD and reduced glutathione.

Similar to *Mehany et al., (2013)* co-administration of Se or vit. E with Cr(VI) in this study produced significant decrease of liver MDA level as compared to acute Cr(VI) toxic group.

In the present study, there were significant increase in superoxide dismutase (SOD) activity and significant decrease in the serum level of reduced glutathione (GSH) and catalase activity in acute Cr(VI) toxic group as compared to the control group similar to *Goodarzi et al., (2016)*.However, *Cengiz et al., (2016)* observed that SOD, catalase and reduced GSH levels had not changed in $K_2Cr_2O_7$ treated rats .

The findings of the current work were explained by *Amin et al., (2011)* who reported that the increase in antioxidant enzymes activities suggests a response toward increased reactive oxygen species (ROS) generation. The mechanism by which Cr(VI) increased the ROS was explained by *Zhang et al., (2011)* who stated that the Cr(VI) generates free radicals, which in turn activate $O_2$ and produce ROS as hydroxyl radicals and hydrogen peroxide and so lead to DNA damage.

In the present study, co-administration of Se or vit. E with Cr(VI) produced significant decrease in SOD activity and significant increase in the serum level of reduced GSH and catalase activity as compared to acute Cr(VI) toxic group. This was in agreement with *Mehany et al., (2013 )*and could be explained by *Flora et al., (2002)* who stated that selenium play important metabolic role in mammalian cell due to its function in the active site of many antioxidant enzymes as glutathione peroxidase and glutathione reductase.

In the current study, there was significant increase in DNA damage as indicated by increase in comet tail length in acute Cr(VI) toxic group as compared to the control group which improved by treatment of rats with Se or vit. E. *Patlolla et al., (2009)* stated that comet tail length is an important parameter in evaluating the DNA damage (comet assay). This finding almost agreed with those of *Cengiz et al., (2016)*and explained by *Stohs et al., (2001)*who reported that Cr(VI) is involved in generating reactive oxygen species (ROS) leading to generation of oxidative stress, which is responsible for many toxic effects in the cell including lipid peroxidation, DNA damage and protein modification. *Also, O'Brien et al., (2003)* stated that the mechanism by which Cr (VI) induce genotoxicity may be due to the intracellular reduction of Cr(VI) into Cr(III) with production of chromium metabolite radicals that lead to different forms of DNA damage as breaking of the strand.

In agreement with *Raju et al., (2012)* the present study revealed significant increase in all forms of chromosomal aberrations in the bone marrow cells of adult male albino rats in acute Cr(VI) toxic group as compared to the control group that improved by treatment with Se or vit. E.

## Conclusion

Concerning the results of the present study; it could be concluded that chromium compounds are very toxic and administration of selenium or vit E could play role against them.

## Recommendation

So it is recommended to do regular medical examination of workers exposed to hexavalent chromium for early detection of any health problem and afford dietary supplementation with vitamin E and selenium.

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## الملخص العربى

# تقييم التسمم الكبدي والكلوي والوراثي (الحمض النووى) الناجم عن التسمم الحاد بالكروم سداسي التكافؤ و الدور الوقائي المحتمل لكل من السيلينيوم و فيتامين ه

مديحه عبد الفتاح محمد حسن و وسام عبد السلام عبد الوهاب و ريحاب محمد محمد مجاهد١ و أميرة عبد الرءوف محمد ٢

تعتبر المعادن الثقيلة من الملوثات البيئية الرئيسية. ونتيجة للاستخدام الواسع لها في التطبيقات الصناعية والزراعية والمنزلية، فقد زاد تعرض الإنسان لها. ويعتبر عنصر الكروم واحد من هذه المعادن، وقد اعتبرته (وكالة المواد السامة وتسجيل الأمراض) أحد المعادن الثمانية فى قائمة المواد السامة.معظم الكروم في البيئة له نوعين من التكافؤ:الكروم ثلاثي التكافؤ والكروم سداسي التكافؤ.

و تستخدم هذه المركبات في الكثير من الصناعات بما في ذلك الطلاء بالكهرباء، ودباغة الجلود، ومحطات الطاقة النووية والصناعات النسيجية والحفاظ على الخشب،وصناعة الأصباغ،وحماية المعادن الأخرى من التآكل،واللحام، وإنتاج الأسمنت، وإنتاج الفولاذ المقاوم للصدأ.

تعتبرمركبات الكروم سداسي التكافؤ شديدة السمية للإنسان والحيوان والكائنات المائية. لأنها تسبب تسمم لأعضاء متعددة، مثل تلف الكلى والكبد والسمية الجينية، والعصبية، والسمية الوراثية، والمناعية، والسمية لمكونات الدم، والحساسية، والربو، والتهاب الشعب الهوائية المزمن،وسرطان الجهاز التنفسي والهضمي، والسمية الإنجابية والتطويرية.

و يتم اختزال الكروم سداسي التكافؤ في داخل الخلايا، إلى الكروم ثلاثي التكافؤ بواسطة مجموعة متنوعة من الأنزيمات والمختزلات الكيميائية. ويرتبط هذا الاختزال بإنتاج شوارد حرة [free radicals] تسبب تلف الخلايا وتوليد أنواع الأكسجين الفعالة[reactive oxygen species(ROS)] .والإفراط في إنتاج أنواع الأكسجين الفعالة يحفز الأكسدةمما يؤدى الى تأثيرات سامة علي الخلايا كما إنها تسبب العديد من الأمراض مثل السرطان وأمراض القلب والأوعية الدموية والاضطرابات العصبية، واضطرابات الكلى، واضطرابات الكبد، والالتهابات وغيرها.

يعد فيتامين ه من مضادات الأكسدة القابلة للذوبان في الدهون، ويمنع تلف الأغشية أو البروتينات بواسطة التخلص من أنواع الأكسجين الفعالة، والتخفيف من الإجهاد التأكسدي [oxidative stress]واستعادة مستوى مضادات الأكسدة بما في ذلك الجلوتاثيون المختزل، والكاتاليز [Catalase] وفوق أكسيد الديسميوتيز[(SOD) superoxide dismutase] .

كما أن السيلينيوم من المغذيات الدقيقة الأساسية وله نشاط مضاد للأكسدة. فإنه يواجه الشوارد الحرة كما انه يحمي هيكل ووظيفة البروتينات والحمض النووي والكروموسومات ضد الأكسدة.

**الهدف من هذه الدراسة:**

كان الهدف من هذه الدراسة هو تقييم السمية الكبدية، والكلوية، والسمية الوراثية الناجمة عن التسمم الحاد لعنصر الكروم سداسي التكافؤ. وأيضا تقييم ومقارنة الدور الوقائي المحتمل لكل من فيتامين ه و السيلينيوم ضد هذا التسمم.

**طريقة البحث**

أجريت هذه الدراسةعلى٦٠ من ذكور الفئران البيضاء. وقد تم تقسيمهم إلى ست مجموعات (١-٦)، (١٠ فئران لكل منها)، وكان تقسيم المجاميع علي النحو الأتي:

مجموعة ضابطة سالبة: وقد تلقت الفئران التغذية الطبيعية والماء المقطر.

مجموعة السيلينيوم الضابطة. :(0.5 mg/kg IP for 5 consecutive days)

مجموعة فيتامين ه الضابطة.(125 mg/kg orally for 14 days)

مجموعة الكروم سداسي التكافؤ.(10 mg/kg single dose IP)

مجموعة الكروم سداسي التكافؤ والسيلينيوم.

مجموعة الكروم سداسي التكافؤ وفيتامين ه.

بعد أربع وعشرين ساعة من إعطاء الجرعة الأخيرة في كل المجموعات،تم أخذ عينات الدم من الموق الإنسي من عيون الفئران لفحص كل من وظائف الكبد، ومستوى البروتين الكلي، ووظائف الكلى، ومضادات الأكسدة.

تم تخدير جميع الفئران وذبحها واخذ كل من الكبد، وكلا عظام الفخذ لقياس علامات الإجهاد التأكسدي ولقياس التلف في الحمض النووي وذلك باستخدام مقايسة المذنب [comet assay]. كما تم استخدام النخاع العظمى من عظام الفخذ لتقدير الانحرافات الكروموسومية.

**النتائج**:

تسبب التسمم الحاد للكروم سداسي التكافؤ الى :

ارتفاع ملحوظ في مستوي كل من:

إنزيم أسبرتات امينو ترانسفيريز[(AST) aspartate aminotransferase] وإنزيم ألانين امينو ترانسفيريز(ALT) وكذلك أنزيم الفوسفاتيزالقلوي، والبيليروبين الكلي في مصل الدم وكل من اليوريا والكرياتينين بالمقارنة مع المجموعة الضابطة السلبية ومستوى المالون داى الدهايد [malondialdehyde] في الكبد و زيادة ملحوظة في نشاط فوق أكسيد الديسميوتيز(SOD).

كما أدي التسمم الحاد للكروم سداسي التكافؤ إلي انخفاض في مستوي كل من:

البروتين الكلي في الدم والجلوتاثيون المختزل والكاتاليز [CAT] بالمقارنة مع المجموعة الضابطة السلبية.

كما وجد أن الكروم سداسي التكافؤ أدى إلى ارتفاع التلف في الحمض النووي كما يتضح بالزيادة في طول ذيل المذنب بالمقارنة مع المجموعة الضابطة السلبية.

أسفر التسمم بالكروم سداسي التكافؤ إلى زيادة في جميع أشكال الانحرافات الكروموسومية بالمقارنة مع المجموعة الضابطة السالبة.

وقد أدي ا لعلاج بكل من السيلينيوم أو فيتامين ه إلى تحسين هذه المظاهر نسبيا.

**الخلاصة والتوصيات:**

أن التسمم الحاد لعنصر الكروم سداسي التكافؤ له اثارسامة خطيرة وأن فيتامين ه والسيلينيوم لهما خصائص مضادة للأكسدة، ولهما دورا حيويا في الوقاية من التسمم الذي يسببه عنصر الكروم سداسي التكافؤ.لذا ينصح بالفحص الطبي المنتظم للعمال الذين يتعرضون لعنصر الكروم سداسي التكافؤ للاكتشاف المبكر لأي مشكلة صحية. كما يجب على العمال والسكان الذين يتعرضون لعنصر الكروم سداسي التكافؤ بوجه عام تناول المكملات الغذائية والأطعمة الغنية بفيتامين ه والسيلينيوم ، وذلك للوقاية ولتحسين أعراض هذا التسمم.

١ قسم الطب الشرعي والسموم الإكلينيكية-كلية الطب -جامعة الأزهر (بنات) - مصر.

٢ قسم بيولوجيا الخلية - المركز القومي للبحوث - دقي -مصر