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# Single or combined cadmium and aluminum intoxication of mice liver and kidney with possible effect of zinc

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**Abstract** In this study, we planned to test toxic effects of cadmium, aluminum either alone or combined with each other on sensitive organs as kidney and liver. The cadmium alone decreased the animal's body weight. Meanwhile, aluminum did not affect the changes in body weight of cadmium treated animals; adding the zinc significantly reduced the loss of body weight. Serum creatinine and urea were significantly lower in treated group than in control group. Cadmium aluminum or combination of them resulted in a significant increase in serum GPT and GOT activity. Zinc did not prevent the changes caused by aluminum, however, the changes resulted by cadmium intoxication were almost healed or ameliorated by zinc. Treating with Zn alone resulted in drastic effects on kidney tissues more than either cadmium or aluminum. Treating with cadmium or aluminum resulted in infiltration of the liver parenchyma with lymphocytes, fibrosis, micro vesicular steatosis of the hepatocytes for both and appearance of many phagocytic cells, pyknotic cells and vacuolation for cadmium. Combined cadmium and aluminum treatment resulted in less damage than cadmium alone with exception of fatty degeneration. Unexpectedly, zinc induced acute cell vacuolation and steatosis. Cadmium and aluminum combined together did not worsen the situation as expected but was less damaging than cadmium alone, which suggests a possible synergistic effect of combination. Meanwhile, zinc failed to protect kidney from aluminum intoxication, which strengthens the suggestion of two different pathways of cadmium and aluminum intoxication. This finding meant that cadmium is more hepatotoxic than aluminum.



## Introduction

Metallic elements are intrinsic components of the environment. Their presence is considered unique in the sense that it is difficult to remove them completely from the environment. With the increasing use of a wide variety of metals in industry and in our daily life, problems arising from toxic metal pollution

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of the environment have assumed serious dimensions (Mahurpawar, 2015).

Poisoning and toxicity in ecosystem occur frequently through exchange and co-ordination mechanisms. When ingested, they form stable biotoxic compounds, thereby mutilating their structures and hindering bioreactions of their functions (WHO, International Agency for Research on Cancer, 1993).

Toxic effects of aluminum depend on the amount of metal ingested, entry rate, tissue distribution, concentration achieved and excretion rate (Riihimaki et al., 2006; Vasudevaraju et al., 2008; Lemire et al., 2009). Fatty acids common in food may facilitate the paracellular intestinal absorption of aluminum (Aspenstrom-Fagerlund et al., 2009). Mechanisms of aluminum toxicity include inhibition of enzyme activity and protein synthesis, alterations in nucleic acid function and changes in cell membrane permeability.

Cadmium, a naturally occurring metal, can be found in food, water and cigarette smoke. It is a known human carcinogen that appears to act in two ways: it harms DNA directly and disturbs a DNA repair system that helps to prevent cancer. According to the reported studies, Cd and its salts are unable to generate damage themselves and an association is suggested between Cd and free radicals, but the mechanism and pathway for the toxic effects of Cd are not yet well understood (Murugavel and Pari, 2010). The relationship between Cd and oxidative stress is shown by many studies, and compounds with this metal reduce the antioxidant system in animals. Mostly this is due to the decreased levels of glutathione and lipid peroxidation (Zikic et al., 1996).

The human body contains 2–3 g zinc, and nearly 90% is found in muscle and bone (Wastney et al., 1986). Other organs containing estimable concentrations of zinc include prostate, liver, the gastrointestinal tract, kidney, skin, lung, brain, heart and pancreas [Bentley and Grubb, 1991; He et al., 1991 and Llobet et al., 1988). Oral uptake of zinc leads to absorption throughout the small intestine and distribution subsequently occurs via the serum, where it predominately exists bound to several proteins such as albumin, α-microglobulin and transferrin (Scott and Bradwell, 1983).

Zinc is an antioxidative element and it probably mediates the protective action of metallothionein (Bray and Bettger, 1990). Changes in the metabolism of some elements such as zinc can lead to disorders in the antioxidant defense system of liver (Jurczuk et al., 2004; Stohs and Bagchi, 1995).

Chu and Chow (2002), conducted pairwise and triple metal combination testing and demonstrated that these heavy metals displayed synergistic killing effects on *Caenorhabditis elegans* larvae. A drastic increase in mortality rate up to 100% was observed at low metal concentrations. Metals species in the environment almost always exist in mixtures. Yet, few studies have focused on their combined effects on living organisms. There have been scattered reports on synergistic or neutralizing effect of specific heavy metals in biological systems, e.g. copepod *Amphiascus tenuiremis* (Hagopian et al., 1997), nematode *C. elegans* (Power and de Pomerai, 1999) and human keratinocytes (Bae et al., 2001).

However, no systematic testing of synergism among metals has been conducted. Also, there is no consistent explanation for the effect of metal interactions due to their complex relationship in biological systems. Each metal may be involved in a spectrum of metabolic pathway to elicit specific toxic effects. Yet, little is known about the intertwining relationship among these pathways. We therefore made this attempt to investigate the potential interactions of metal toxicants, as found in nature.

Our idea raises the notion that physical/chemical monitoring in most environmental studies may not reflect accurately the toxicity imposed on living system, where the biological impact of a combination of toxicants may require re-examination. In this work, we aimed to study the toxicity of aluminum, cadmium and zinc as single metal on liver and kidney and also the effect of combination of any two of them or even three. We selected kidney and liver as two vital organs since they are sensitive and involved in metal toxicity.

## Materials and methods

### *Animals*

54 males and females of Laboratory mice *Mus musculus* 3–4 weeks old were used. Animals were obtained from the "animal house" of Assiut University, Egypt. For the present study, animals were kept in polycarbonate standard cages at room temperature for about two weeks to reach their optimal conditions of weight and maturity. The humidity was adjusted and the animal house was made sure to be infection free. Each cage contains six animals. The cages were cleaned weekly with a disinfectant to avoid contamination that may affect animals. The food and drinking water were provided *ad libitum*.

### *Animal grouping*

The animals used in this experiment were divided into 9 groups each of which is composed of 6 mice male and female. The first groups did not receive any treatment and served as control 1 (G1), the second group was immunized with sheep red blood cells (SRBCs) according to the protocol of work and served as control group 2 (G2). All the other seven groups also were immunized with SRBCs at the same time and with same quantities and in the same sites of injections as group 2.

The third group (G3) was designed to be fed with aluminum alone. The fourth group (G4) was designed to be fed with cadmium alone. The fifth group (G5) was designed to be fed with combined aluminum and cadmium. The sixth group (G6) was designed to be fed with zinc alone. The seventh group (G7) was designed to be fed with combined aluminum and zinc. The eighth group (G8) was designed to be fed with combined cadmium and zinc. The ninth group (G9) was designed to be fed with aluminum, cadmium and zinc, all combined. All the three elements were introduced in drinking water and their concentrations were adjusted.

The animals were fed intragastrically with 10 mg/kg body weight cadmium (as CdCl2) daily for thirty days and were fed the non-purified diet and water *ad libitum* (Sharma et al., 1991). For aluminum, 1.2 g/kg body weight was used (Sanai et al., 1991), which is a low dose. For zinc, 200 mg/kg body weight was used (Lu et al., 2013). All the chemicals used in this work were of analytical grade.

### *Immunization of animals with SRBCs*

Sheep red blood cells were obtained from innovative research (Catalog No.: IC10-0210), and used for immunization as 2%.