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BIO-INDICATOR'S CHANGES IN COWS DUE TO HIGH LEVELS OF SOME HEAVY METALS IN WELLS WATER OF AL-DAKHLA REGION

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ABSTRACT

Al-Dakhla region wells water contains high levels of some heavy metals including; cadmium (0.15 ppm ±0.006), lead (0.29 ppm ±0.011) and iron (0.86 ppm ±0.019) than that of tap water, **WHO, (2011) and Egyptian standards** 1589/ **(2005)** limits of drinking water. Such high levels of these heavy metals induced adverse deleterious effects in cows including increased serum concentration of lead (Pb), cadmium (Cd) and potassium (K), malondialdehyde (MDA), urea, creatinine, activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyle aminotransferase (γGT) enzymes with decreasing of superoxide dismutase (SOD) enzyme activity, reduced glutathione (GSH), total protein, albumin, albumin/globulin ratio (A/G%), iron (Fe) zinc (Zn), calcium (Ca), phosphorus (P), magnesium (Mg) and sodium (Na) concentrations.

Keywords:

Al-Dakhla Region, Groundwater, Heavy metals, Bio-indicator's changes, Cows.

INTRODUCTION

The diverse deleterious health effect upon exposure to toxic heavy metals in the environment is a matter of serious concern and a global issue **(Patra *et al.,* 2011)**. The term pollution refers to the occurrence of an unwanted change in the environment caused by the introduction of harmful substances or production of harmful conditions. Many chemical toxins such as heavy metals are released into the atmosphere by many natural processes and human activities (i.e. anthropogenic). All heavy metals are toxic at certain levels of intake **(Milam *et al.,* 2017)**. There are various sources of heavy metals include soil erosion, natural weathering of the earth's crust, mining, industrial effluents, urban runoff, sewage discharge, combustion of fossil fuels, insecticides and herbicides **(Yang *et al.,* 2012).**

Owing to their accessibility, shallow groundwater is an essential source of drinking water in rural areas and usually used without authorities control. So, this type of water resource is one of the most vulnerable to pollution, especially in regions with extensive agricultural activity **(Soldatova *et al.,* 2018).**

Pollution of groundwater sources by leachate from landfills have recognized for a long time **(Alloway and Ayres, 1997).** The practice of landfill system as a method of waste disposal in many developing countries is usually far from the standard recommendations **(Adewole, 2009).** Open dump is the most available option for solid waste disposal, even in the capital cities. However, sanitary landfill is rare and unpopular, except among a few institutions and affluent people because of the financial and institutional constraints in some developing countries especially, where local governments are weak or underfinanced and with rapid population growth **(Elaigwu *et al.,* 2007)**. Moreover, the lined (protected) landfills have been inadequate in the prevention of groundwater contamination **(Lee and Lee, 2005)**.

The seepage of chemical constituents in the leachate formed as a consequence of continuous disposal of municipal and industrial wastes at the landfill constitutes a serious threat to the environment and human health **(Abu-Rukah and Al-Kofahi, 2001)**. The uncontrolled disposal of lead acid batteries and spent petroleum products probably cause the relative high levels of Pb, and Fe found in groundwater **(Oyeku and Eludoyin, 2010)**.

Heavy metals is a general collective term applied to the group of transition metals, some metalloids, lanthanides and actinides (over 50 elements) with atomic density greater than 4 or 5 g/cm^3 (i.e 5 times greater than water) or with an atomic weight larger than 50 **(Beşkaya *et al.,* 2008 and Zou *et al.,* 2015)**. Among them, 17 are considered very toxic and relatively accessible. Lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) are generally considered as human poisons even at trace level **(Nishijo *et al.*, 2017 and Obrist *et al.*, 2018)**.

Environmental pollution with heavy metals is a serious threat because of their toxicity, bioaccumulation (not biodegradable) and biomagnifications in the food chain **(Kükrer *et al.,* 2014)**. It is necessary to study the concentrations of toxic heavy metals in order to assess the levels of exposure and maintain an ongoing knowledge on their levels in environment, meat and other animal products for both food safety and human health due to the toxic nature of some of these heavy metals at a relatively low concentrations **(Milam *et al.,* 2017)**.

Cattle may be regarded as a species indicator for long period's assessment of environmental pollutions **(Rogowska *et al.,* 2009)**. Exposure to heavy metals can be due to inhalation of such

pollutants transported by dust through the air, or by consumption of contaminated drinking water and food **(Pizzino *et al.,* 2014)**.

Chronic poisoning resulting from intake of smaller quantities through various routes leads to their accumulation in tissues, bones, hair and blood and is manifested by loss of appetite and body weight, anemia, reproductive disorders and immune-suppression **(Milhaud and Mehennaoui,1988).** The effects of heavy metal pollutants on trace mineral profile are an additional risk to the animals as minerals are essential for normal growth, production and reproduction **(Doyle and Younger, 1984)**.

Lead and cadmium are the most two abundant toxic metals in the environment have no detectable beneficial biological roles and are most implicated in human and animal poisoning **(Rajaganapathy *et al.,* 2011)**. These two elements often co-exist in the environment in the polluted regions **(Phillips *et al.,* 2003)**. Both natural and anthropogenic sources including combustion of coal and mineral oil, smelters, mining and alloy processing units and paint industries are responsible for human and animal exposure **(Patra *et al.,* 2011)**. Anthropogenic sources add 3-10 times more cadmium to the atmosphere than natural sources **(Irwin *et al.,* 2003)**.

Lead and cadmium are cumulative poisons and there is no homeostatic mechanism to keep these metals at safe levels **(Xu *et al.,* 2004)**. Lead and cadmium-induced tissue damages are mainly attributed to oxidative stress **(Patra *et al.,* 2001)**. Cattle exposed to both Pb and Cd had poor skin conditions including rough hair coat, and a few were cachectic and had hyperesthesia **(Swarup *et al.,* 2007)**.

Cadmium is present in various materials as anticorrosive coating pigments (specially red and yellow), stabilizers, polyvinyl chloride (PVC) products, galvanization materials, battery components (nickel-cadmium), eliminated gas from motor vehicles, phosphate fertilizers, pesticides, plastics and glass **(Roman *et al.,* 2002)**. Cadmium is accumulated in environment (soil, water and air) by industrial pollution **(Stanevičinė *et al.,* 2008)**, leading to contamination of soil and pasture and consequently poisoning of animals by ingestion and/or inhalation **(Swarup *et al.,* 2007).**

Cadmium is considered one of the most toxic elements in the environment, with a wide range of organ toxicity and long elimination half-life **(Patrick, 2003)**. Cadmium is the seventh most toxic heavy metal according to ATSDR ranking **(ATSDR, 2017).**

Cadmium toxicity is associated with pulmonary, renal, hepatic, skeletal, reproductive and cardiovascular dysfunctions **(Zhai *et al.,* 2015)**.

When cadmium is ingested, it is absorbed by intestinal cells and transported by blood to liver where it induces synthesis of metallothione protein that evolved in detoxification of heavy metals. Hepatocytes cadmium-metallothione complex is released into blood stream and filtered by kidney glomeruli, where it degrades by lyzosome enzymes of kidney tubular cells. However, metallothionein action is limited and when animals ingest excessive doses of Cd, it accumulates in organism causing acute, subacute, or chronic poisoning **(Dukić-Ćosić *et al.,* 2008; Stanevičinė *et al.,* 2008; Newairy *et al.,* 2007 and Roman *et al.,* 2002)**.

Cadmium increases reactive oxygen species (ROS) concentration by inhibiting activity of superperoxide dismutase, catalase and glutathione peroxidase enzymes of antioxidant system **(Djuić-Ćosić *et al.,* 2008)**.

Cadmium alters levels of other divalent elements that are essential to various biological functions **(EFSA; 2009)**. The potential of cadmium to inhibit iron absorption from the intestinal epithelium through a competitive binding to protein sites was suggested as a possible mechanism of their negative correlation. However, the mechanism of competition of cadmium with iron is not clear. Reduction of iron uptake could be the result of toxic effects of cadmium on cell membrane of absorptive cells or on energy metabolisms **(Patra *et al.,* 2006)**.

Forage, feed and water, are contaminated with Cd of industrial processing and intensive agricultural practices, resulting in Cd exposure for ruminants. Clinical signs of Cd toxicity that developed over a period of 16 to 64 days in calves include an unthrifty appearance, rough coat hair, dry scaly skin, dehydration, loss of hair from legs, thighs, ventral chest and brisket, mouth lesions, edematous, shrunken scaly scrotum, sore and enlarged joints, impaired sight, extreme emaciation and some atrophy of hind limb muscles **(Lane *et al.,* 2015)**.

Lead is a ubiquitous pollutant in the ecosystem. On a global scale the combustion of alkyl lead additives in motor fuels accounts for the major part of all lead emissions into the atmosphere, thus influencing all compartments of the environment**.** Primary or secondary lead smelters may create local pollution problems. Iron and steel production, copper smelting and coal combustion must be regarded as additional sources of lead emissions into the atmosphere **(WHO, 2001).** Thus, lead (Pb) is accumulated in environment by industrial pollution **(Swarup *et al.,* 2007)** and becomes highly toxic to animals and humans **(Patra *et al.,* 2007)**. Therefore, sources of lead exposure include mainly industrial processes, air, food, drinking water and domestic

sources as gasoline, storage batteries, folk remedies, spices and house paint **(Ettinger *et al.*, 2019).**

Lead exposure induces neurological and haematological dysfunctions, renal and hepatic damage, as well as reproductive disorders in human **(Zhai *et al.*, 2015).**

Lead is shown to alter antioxidant activities by inhibiting functional SH groups in several enzymes such as δ-aminolevulinic acid dehydrase (ALAD), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glucose-6-phosphate dehydrogenase (G6PD) **(Chiba *et al*., 1996)**.

Higher blood lead burden enhanced iron bioaccumulation and mobilization into liver **(Liu, 2003)**.

Lead is considered as the most common form of poisoning in farm animals because of natural curiosity, licking habits, and lack of oral discrimination **(Radostits *et al.*, 2007)**. Clinical symptoms of chronic lead poisoning in Cattle include opaque hair, thickening of phalange epiphyses, moderate anemia **(Miranda *et al.*, 2006)**, severe depression, paresis of hypoglossal nerve, incoordination, ataxia, muscle twitching **(Radostits *et al.*, 2002)**, convulsion, coma, respiratory failure and death **(Gilbert *et al*., 2005).**

Domestic animals are an important source of food for humans and so provide a direct source of pollutant transfer to humans. It is estimated that 80 - 90% of all heavy metals enter the human body with food. So, it is necessary to monitor their concentrations in the environment, animals and food of plant and animal origin **(López *et al.*, 2004)**. Lead poisoned animals are considered a risk to public health due to accumulation of this metal in meat and milk when animals have blood concentration ≥ 0.20 µg of Pb/mL **(Miranda *et al.*, 2005 and Swarup *et al*., 2005)**.

Iron is the most crucial element for growth and survival of almost all living organisms **(Valko *et al.*, 2005)**. The source of iron in surface water is anthropogenic and is related to mining activities. Exposure to elevated levels of iron occurs through drinking water **(Grazuleviciene *et al.*, 2009)**.

Iron is a transition metal involved in various biological redox processes due to its inter-conversion between ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions **(Phippen *et al.*, 2008)**. Iron is one of the vital components of cytochromes and catalase enzymes, as well as oxygen transporting proteins; hemoglobin and myoglobin **(Vuori, 1995)**.

Iron toxicity has been reported to involve oxidative stress, lipid peroxidation, DNA damage and changes in calcium and sulfhydryls homeostasis **(Hansen *et al.,* 2006).** Iron toxicity occurs in four stages. The fourth stage occurs within 2-6 weeks of iron overdose. This stage is marked by the formation of gastrointestinal ulcerations and development of strictures **(Jaishankar *et al.,* 2014)**. Iron toxicity and heightened oxidative stress may cause depressed immune function, increased mastitis and metritis, greater incidence of retained placental membranes as well as diarrhea, sub-normal feed intake, decreased growth, and impaired milk yield **(Beede, 2006)**.

Zinc is an essential trace element in the nutrition of man and animals. Zinc is found virtually in food and potable water in the form of salts or organic compounds **(WHO, 2011)**. Zinc serves as a cofactor in RNA polymerase and reverse transcriptase and in zinc-finger proteins that are adducts to DNA **(Oberleas and Harland 2008).** It serves as a co-factor for dehydrogenating and carbonic anhydrase enzymes Zinc is considered to be relatively non-toxic, especially if taken orally. However, excess amount can cause system dysfunctions that result in impairment of growth and reproduction. Zinc has been reported to cause the same signs of illness as does lead, and can easily be mistakenly diagnosed as lead poisoning. The clinical signs of zinc toxicity have been reported as vomiting, diarrhea, bloody urine, icterus, liver failure, kidney failure and anemia. It can be tolerated at higher doses (homeostatic) because its concentration in the blood is well regulated by thyrocalcitonin and parathormone hormones **(Pandey *et al.,* 2016)**. Zinc poisoning has been described in cattle. In several different species, high doses from 2 to 8 mg/kg, of orally ingested Zn generally resulted in gastrointestinal distress with nausea, vomiting, abdominal cramps, and diarrhea **(ATSDR 2005).**

Zinc is released into the environment from both natural and anthropogenic sources. However, anthropogenic emissions are greater than those from natural sources. Zn smelters, Zn containing plant protection chemicals, phosphate fertilizers, industrial and mining waste often reaches groundwater. An important source of environmental pollution by Zn is the combustion of coal and petroleum and petroleum products. Incineration of solid municipal waste may be responsible for about 75% of airborne Zn in urban areas. Waste waters also generally contain significant amounts of zinc **(Kalisińska**, **2019)**

The present work was planned to assess water characters and level of some heavy metals (Cadmium, Lead, Iron and Zinc) in groundwater in El- Dakhla region. In additions to, explaining the effects of these heavy metals on cows by evaluating their oxidative stress effects

through measuring of malondialdehyde (MDA) as indicator of lipid peroxidation, reduced glutathione (GSH) and the antioxidant enzyme; superoxide dismutase (SOD), liver function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyle aminotransferase (γGT) activities, total protein, albumine, globuline concentrations and A/G ratio, kidney function including urea and creatinine concentrations and the levels of these heavy metals and other minerals concentrations including calcium, magnesium, phosphorus, sodium and potassium.

MATERIAL AND METHODS

Water samples and analysis:

Thirty water samples were collected in clean and sterile glass bottles from six wells in AL-Dakhla region and another ten tap water samples from the most adjacent area (with the same climatic conditions) were taken as reference. Each water sample was subjected to chemical analysis for the pH, total hardness, total dissolved solids (TDS), sulphate, chloride, calcium and magnesium according to **American Public Health Association (APHA), (1998)** and for lead, cadmium, iron and zinc estimation after wet digestion according to method recommended by **Graig and Wayne, (1984)** by atomic absorption spectrophotometer using Unicam 969 AA spectrometer according to instrument operation manual procedures.

Blood Samples:

Twenty blood samples (ten of each group) were collected from jugular vein of affected cows (crossbred type) that were drinking wells water **(Affected Cows)** and from other apparently healthy cows; that were drinking tap water **(Control Cows)** from the two water areas respectively. Serum was then separated by centrifugation of blood at 3000 rpm for 20 minutes and kept at - 40 ˚C until used for biochemical, minerals and heavy metals analysis.

Biochemical analysis:

Serum was used for determination of malondialdehyde (MDA) concentration according to **Albro *et al.,* (1986),** reduced glutathione (GSH) content according to **Chanarin, (1989)**, superoxide dismutase activity after **Masayasu and Hiroshi, (1979)**.

Serum samples were also subjected to determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT) activities according to **Reitman and Frankel, (1957)** and γ-glutamyltransferase(γ GT) activity according to **Persijn and Vander Slik, (1976)**, Total

protein (TP) as described by **Cannon *et al.*, (1974)**, albumin assay after **Doumas *et al.*, (1971)**. Serum globulin level and albumin/globulin ratio (A/G ratio) were calculated mathematically according to **Coles (1986)**.

Serum creatinine concentration was measured by the method adopted by **Bowers and Wong, (1980)**. Serum urea level was estimated according to **Fawcett and Scott, (1960).**

Serum calcium and magnesium concentrations were determined according to **Glinder and King, (1972)**. Inorganic phosphorus concentration was determined according to **Daly and Ertingshausen (1972).** Sodium concentration was measured according to **Henry *et al.*, (1974)**. Potassium concentration was measured as described by **Hillman *et al.*, (1967).**

Determination of heavy metals:

The cow's serum samples were wet digested according to method recommended by **Graig and Wayne (1984)** to estimate lead, cadmium, iron, and zinc concentrations as water samples.

All reagents used were of analytical grade and standard solutions of lead cadmium iron and zinc were obtained from Merck, Darmstadat, Germany.

Statistical analysis:

Data were presented as mean ± standard deviation (SD) or standard error (SE) and the significance of difference between means was estimated using student t-test by the computer program **SPSS 14, (2006)**.

RESULTS

Clinical signs:

Cows drinking ground water of Al-Dakhla region exhibited thriftiness, loss of appetite, dehydration, pale mucous membranes, general exhaustion and decreased growth (emaciation). Hair discoloration was also observed in some cows.

Chemical properties of water:

Table (1) shows the pH value, levels of total hardness, total dissolved solids (TDS), sulphate, chloride, calcium, magnesium, lead, cadmium, iron, and zinc in tap and Al-Dakhla wells water samples. The results revealed that levels of lead, cadmium and iron in Al-Dakhla wells water were higher than the provisional guideline values of **WHO, (2011)** and the Egyptian standards 1589/2005 **(ES, 2005)** for drinking water.

Oxidative and Antioxidant Markers:

Table **(2)** demonstrated that, the concentration of malondialdehyde (MDA) was significantly increased in serum, of wells water cows **(Affected Cows)** comparing with tap water cows **(Control Cows)**, while reduced glutathione (GSH) concentration and superoxide dismutase (SOD) activity were significantly decreased in affected cows against control animals.

Liver and kidney functions parameters:

Table **(2)** revealed that liver enzymes activities (ALT, AST and γGT) were significantly higher in affected cows of Al-Dakhla region than that of control cows while, total protein, albumin concentrations and A/G Ratio in the affected cows were significantly lower than Control animals. Both serum creatinine and urea concentrations (kidney function markers) in the affected cows were significantly elevated in comparison with control cows.

Heavy metals and Minerals concentrations:

Table **(3)** showed that cadmium, lead, and potassium concentrations in the serum of affected cows of Al-Dakhla region were significantly increased against the values of control cows. Contrarily, iron, zinc, calcium, phosphorus, magnesium and sodium concentrations in the serum of affected cows were significantly decreased in comparison with control.

DISCUSSION

The contamination chain of heavy metals always follows cyclic order in the environment as industry, atmosphere, soil, water, foods and human. It is clear that chronic exposure to heavy metals and metalloids at low levels causes adverse effects. Heavy metals have been proved to be toxic to environmental and human health **(Bhat *et al.*, 2019)**. Environmental pollution with heavy metals in Egypt derives from rapid industrial growth, advances in agriculture fertilizers and urban human activities. Pollution by the metal and its by-products dispersion during production, recycling and disposal impaired health of the population **(Mahmoud and Abdel-Mohsein, 2015)**.

Table (1): Chemical properties of tap water and Al-Dakhla wells water.

Water type / Parameter	Tap Water* (n=10)	Ground Water* (Min–Max, n=30)	WHO limits[#]	ES Limits[##]
pH	7.02 ± 0.44	7.76 ± 0.051 (7.7–7.8)	6.5-8.5	-
Total Hardness (mg/L)	210.63 ± 9.27	260.72 ± 16.1 (233.0 - 287.0)	Up to 500	-
TDS (mg/L)	699.5 ± 33.87	956.67 ± 75.28 (850.0 - 1050.0)	Up to1000.0	≤ 1000.0
Chloride (mg/L)	157.0 ± 15.67	171.73 ± 26.17 (125.0 - 200.0)		≤ 250.0
Sulphate (mg/L)	32.9 ± 1.97	46.6 ± 2.06 (42.0 - 50.0)	500.0	≤ 250.0
Calcium (mg/L)	64.4 ± 3.27	79.67 ± 6.33 (70.0 - 90.0)	-	-
Magnesium (mg/L)	14.18 ± 2.04	17.59 ± 0.46 (17.0 – 18.0)	-	-
Cadmium (mg/L)	ND	0.15 ± 0.036 (0.1 - 0.23)	0.003 (<0.005)[a]	≤ 0.003
Lead (mg/L)	0.015 ± 0.002	0.29 ± 0.058 (0.18 - 0.42)	0.01	≤ 0.01
Iron (mg/L)	0.052 ± 0.003	0.86 ± 0.10 (0.73 - 1.20)	0.3	≤ 0.3
Zinc (mg/L)	0.002 ± 0.0001	0.013 ± 0.008 (0.001- 0.031)	0.05 (0.003-2.0)[b]	≤ 3.0

***: Each value represents mean ± SD; -: No health-based guideline is proposed.**

[#]: WHO, (2011); [##]: ES, (2005); a: ATSDR, (2012); b: ATSDR, (2005).

Table (2): Serum malondialdehyde (MDA), antioxidants and metabolic parameters in tap water cows **(Control Cows)** and wells water cows **(Affected Cows).**

Parameter \ Group	Control Cows	Affected Cows
	11.21 ± 0.33	**20.44 ± 0.72***
GSH (µM/L)	**15.4 ± 0.3**	**10.98 ± 0.74***
SOD(U/L)	**39.8 ± 1.85**	**28.0 ± 0.84***
ALT (U/L)	**33.8 ±2.01**	**84.8 ±2.22***
AST(U/L)	**41.0 ±2.77**	**96.6 ±3.01***
γGT(U/L)	**12.6 ±1.08**	**36.4 ±3.83***
Total Protein (g/dL)	**7.68 ±0.16**	**6.84 ±0.12***
Albumin(g/dL)	**3.76 ±0.08**	**2.74 ±0.09***
Globulin (g/dL)	**3.92 ±0.14**	**4.10 ±0.19**
A/G Ratio	**0.96 ±0.05**	**0.68 ±0.06***
Urea (mg/dL)	**28.8 ±1.83**	**57.6 ±1.81***
Creatinine (mg/ dL)	**0.95 ±0.08**	**2.44 ±0.24***

Each value represents mean ± SE (n = 10).
***: Significant difference against Control by t-student test at p ≤ 0.05.**

Table (3): Serum heavy metals and minerals concentrations in control and affected cows.

Parameter \ Group	Control Cows	Affected Cows
Cadmium (mg/L)	**0.016 ±0.002**	**0.29 ±0.012***
Lead (mg/L)	**0.142 ±0.012**	**0.332 ±0.016***
Iron (mg/L)	**1.58 ±0.078**	**1.10 ±0.035 ***
Zinc (mg/L)	**0.24 ±0.019**	**0.14 ±0.023***
Calcium (g/dL)	**11.08 ±0.25**	**8.06 ±0.31***
Phosphorus (g/dL)	**5.46 ±0.19**	**4.6 ±0.19***
Magnesium (g/dL)	**2.94 ±0.12**	**1.73 ±0.18***
Sodium (mEq/dL)	**141.00 ±1.18**	**129.80 ±2.63***
Potassium (mEq/dL)	**4.48 ±0.12**	**5.14 ±0.07***

Each value represents mean ± SE (n = 10).
***: Significant difference against Control by t-student test at p ≤ 0.05.**

Water is essential to sustain life, and a satisfactory (adequate, safe and accessible) supply must be available to all. Improving access to safe drinking-water can result in tangible benefits to health. Every effort should be made to achieve drinking-water that is as safe as practicable **(WHO, 2011)**.

Water is one of the prime necessities of life. We can hardly live for a few days without water. Still more than one billion people all over the world do not have ready access to an adequate and safe water supply and more than 800 million of those unsaved live in rural areas **(Kumar and Puri, 2012)**. **Zhang and Li, (2009)** reported that 75% of the rural population uses ground water for drinking.

As showed in **(**Table 1); cadmium, lead and iron levels in wells water in Al-Dakhla region were higher than that of tap water , the Provisional guideline values of **WHO, (2011) and Egyptian standards** 1589/2005 **(ES, 2005)** for drinking water. These results are nearly agreed with that of **Mahmoud, (2015)** who found that Cd, Pb, and Fe concentrations in shallow wells water were 0.05, 0.18 and 2.18 ppm respectively in Al-Dakhla region Lead, cadmium, zinc are potential toxic metals and classified as numbers 2, 7 and 75 respectively in the priority list of the most hazardous substances in the environment by the Agency for Toxic Substances and Diseases Registry **(ATSDR**, **2017)**. **Klee and Graedel, (2004)** assumed that 90% of Fe, 84% of Pb, 47% 0f Zn and 17% of Cd amounts that present in the natural environment were mobilized as the result of human activity (anthropogenic mobilization).

Lead is the 2nd most dangerous environmental poison according to Agency for Toxic Substances and Diseases Registry Priority Substance List **(ATSDR, 2013)**. No lowest safe concentration exists for lead, which contributes to 0.6% of the global burden of disease **(WHO, 2009)**. **The International Agency for Research on Cancer; IARC, (2016)** has classified inorganic lead compounds to Group 2A: Probably carcinogenic to humans and lead to Group 2B: Possibly carcinogenic to humans. World Health Organization had concluded that concentrations of lead in water intended for drinking should not exceed 10 µg/ L **(WHO 2011)**. Drinking water is major source of environmental exposure to Pb **(Kim *et al.,* 2014)**.

Cadmium is an environmental contaminant unique among metals because of its diverse toxic effects, extremely prolonged biological half-life, low rate of excretion from the body and predominant storage in soft tissue **(Beňová *et al.,* 2007)**. Its biological half-life is estimated to range from 6 to 38 years in the kidney and 4 to 19 years in the liver **(ATSDR, 2011)**.

The International Agency for Research on Cancer has classified Cd as a human carcinogen (group I), for prostate and kidney cancer, on the basis of sufficient evidence in both humans and experimental animals **(IARC, 1993)**. The coexposure to lead and cadmium has synergistic cytotoxicity **(Phillips *et al.,* 2003)**. Cadmium is more toxic than lead and causes renal and hepatic damage in exposed animals **(Humphreys, 1991)**.

Zinc may enter waters from a variety of sources, including mine drainage, industrial and municipal wastes, urban runoff, and soil erosion particles containing Zn **(US EPA 1980)**. Zinc is present in water in the form of hydrated cations and soluble salts, mainly carbonates and sulfates, as well as compounds with organic colloids **(Kabata-Pendias and Szteke 2012)**. Despite its high mobility, Zn reaches groundwater in relatively low quantities. It has been established that an acceptable Zn level in groundwater is 50µg/L **(VROM, 2012)**.

The mean Zn concentrations in drinking water range from 0.01 to 0.1 mg/L **(ATSDR, 2005)**. Drinking water containing zinc at levels above 3 mg/l may not be acceptable to consumers **(WHO, 2011)**.

In fresh water iron concentration is very low (5 µg/L), whereas in groundwater the concentration of dissolved iron is very high (20 mg/L) **(US EPA, 1993)**. Iron in drinking water is the most frequent and important anti-quality element for dairy cattle. Excess total iron intake can be a problem especially when drinking water contains high iron concentration.

Iron concentration in drinking water greater than 0.3 ppm is considered a health risk and affects performance of dairy cattle. High iron level in drinking water may reduce the palatability and amount of water intake **(Beede, 2006)**.

The problems associated with chemical constituents of drinking water arise primarily from their ability to cause adverse health effects after prolonged periods of exposure, particularly the contaminants that have cumulative toxic properties, such as heavy metals **(WHO, 1996)**.

Toxicological studies have shown that, the impact of heavy metals contaminants can be evaluated by measuring biochemical parameters in the affected animals that respond specifically to the degree and type of contamination **(Barhoumi *et al.,* 2012)**. Currently, the use of living or died organisms in biotesting, bioindication, and biomonitoring is an established method of determining inorganic and organic contaminants and pollutions **(Markert, 2013)**. Cattle are the species which are poisoned more frequently **(Miranda *et al.,* 2006)**. Therefore,

cattle may be regarded as a species indicator for the assessment of environmental pollutions **(Kruslin *et al.,* 1999 and Kołacz *et al.,* 1996)**.

Al-Dakhla wells water heavy metals induced oxidative changes in cows:

The concentration of malondialdehyde (MDA) was significantly increased in serumn of affected cows comparing with control cows, while reduced glutathione (GSH) concentration and superoxide dismutase (SOD) activity were significantly decreased in affected cows against control animals as shown in **(**Table 2). The obtained results were found to be consistent with that recorded by **Offor *et al.,* (2017)** who recorded that administration of lead acetate solution 60 mg/kg daily for 28 days in rats showed significant increases in MDA concentration and decreases superoxide dismutase, glutathione peroxidase activities and total glutathione concentration. Also, levels of GSH concentration, SOD, catalase (CAT) and glutathione peroxidase (GPx) activities, were significantly decreased in lead acetate treated rats (0.5 g/100 ml in drinking water for 2 months) as compared to control group **(Azoz and Raafat, 2012)**.These results are similar to that recorded by **Kumar *et al.,* (2013), Ibrahim *et al.* (2012), Sujatha *et al*., (2011) and Veena *et al.,* (2011)**.

Furthermore, administration of cadmium chloride with concentration of 50 mg Cd/dm^3 in drinking water for 12 weeks induced significant increase in MDA and H_2O_2 concentration accompanied with significant decrease in Mn-SOD activity and GSH concentration in the hepatic mitochondria in rats **(Jurczuk *et al.,* 2006)**. Moreover**,** rats administrated $CdCl_2$ (5 mg/kg BW) orally every other day for 30 days exhibited a significant increase in plasma, liver and brain lipid peroxidation **(El-Demerdash *et al.,* 2004)**.

Oxidative stress represents an imbalance between the production of free radicals and the biological system's ability to detoxify the reactive intermediates or to repair the resulting damage. Lipid peroxidation is biomarker of oxidative stress and is one of the most investigated consequences of ROS on lipid membranes. Increased malondialdehyde concentration indicates increased lipid peroxidation due to oxidative stress developed by heavy metals **(Flora, 2011)**. Oxidative stress represents the basic mechanism of Cd and Pb toxicity **(Liu *et al*., 2009)**.

Lead toxicity is insidious hazard with potential of causing irreversible health effects. Exposure to lead produces various deleterious effects on hematopoietic, renal, reproductive and central nervous systems, mainly through induction of oxidative stress **(Alisha *et al.,* 2018)**.

Under the influence of lead, onset of oxidative stress occurs by two different pathways; either through the generation of ROS, like hydroperoxides ($HO_2^{\bullet}$), singlet oxygen and hydrogen

peroxide (H_2O_2), and or, the depletion of antioxidant reserve of glutathione **(Flora *et al.,* 2012)**. Lead inactivates glutathione by binding to its sulfhydryl groups **Sujatha *et al.,* (2011)**. Also lead inactivates δ-amino levulinic acid dehydratase (ALAD) **(Sudha and Kavimani, 2011)**, glutathione peroxidase (GPx) glutathione reductase (GR), and glutathione-S-transferase (GST) enzymes and further depletes the glutathione level **(Gad *et al.,* 2011 and Ahamed and Siddiqui, 2007)**. Furthermore, the elevated δ-amino levulinic acid (ALA) level due to inhibition of ALAD generates hydrogen peroxide and superoxide radical and also interact with oxyhemoglobin, resulting in the generation of hydroxyl radicals **(Patrick, 2006)**. Additionally, lead can also replace zinc**(Flora *et al.,* (2007)** and copper **Sujatha *et al.,* (2011)** ions that serve as important co-factors for superoxide dismutase (SOD) and catalase (CAT) enzymes and inactivates them.

Cadmium shows a high affinity for thiol groups of glutathione (GSH), leading to depletion of the GSH pool **(Lopez *et al.,* 2006)**, which results in a disturbance of the redox balance and leading to an oxidative stress **(Yu *et al.,* 2008)**. Cadmium indirectly produces ROS **(Valko *et al.,* 2004)**. Cadmium is capable of eliciting a variety of ROS ($O^{2\cdot}$, H_2O_2, and $^{\cdot}OH$), which could be the main mechanism of its cellular toxicity **(Sharma *et al.;* 2014)**. Mitochondria are a major cellular site of ROS production, but the quantity produced under normal and stress conditions is unknown. The physiological activity of the respiratory chain (complexes I to V) present in the inner mitochondrial membrane produces ROS at complex I (NADH/ubiquinone oxidoreductase) and complex III (Ubiquinol/cytochrome oxidoreductase) **(Gao *et al*., 2008).**

Cadmium induces ROS generation at the level of complex III leading to accumulation of unstable semi ubiquinones, prone to transfer one electron to molecular oxygen and thereby forming superoxide radicals. The production and accumulation of ROS inhibit the electron transfer chain in mitochondria **(Wang *et al.,* (2004)**. Cadmium can induce oxidative stress via the inhibition of the gene expression of cytosolic Cu/Zn-SOD antioxidant enzyme **(Thijssen *et al.,* 2007)**.

Excessive uptake of iron or disturbances in its regulation can be toxic which is related to its ability to catalyze ROS formation, the deleterious effects of iron include DNA damage, lipid peroxidation (LPO), and oxidation of proteins **(Valko *et al.,* 2005)**.

Al-Dakhla wells water adverse effects on cow 's liver and kidney functions:

It is evidenced from data recorded in **(**Table 2) that, liver enzymes activities including, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (γGT) were significantly higher in affected cows of Al-Dakhla region than that of control cows while, total protein, albumin concentrations and albumin/globulin (A/G) ratio in the affected cows were significantly lower than control animals. Both serum creatinine and urea concentrations (kidney function markers) in the affected cows were significantly elevated in comparison with control.

Several authors reported similar results in different species of animals. **Abd El-Hameed *et al.,* (2008)** revealed an increase in AST, ALT and γGT activities in pregnant female Baladi goats dosed 4.5 and 6.0 mg /kg b.w. lead acetate daily from beginning of pregnancy till abortion which occurs at the 14th week of pregnancy, as well as, in levels of urea and creatinine, with a decrease in total protein, albumin and globulin concentrations. Rats given lead acetate solution 60 mg/kg daily for 28 days showed significant increases in serum AST and ALT activities and urea concentration, and decreases in total proteins, albumins concentrations **(Offor *et al.,* 2017)**. **Azoz and Raafat, (2012)**, demonstrated a significant increases in serum AST, ALT and γGT activities and decreased total protein concentration in rats offered lead acetate at a dose of 0.5 g/100 ml in drinking water for 2 months in accordance with **Azab, (2014); Diefy *et al.,* (2014), Taha *et al*., (2013); Ibrahim *et al.,* (2012) and Allouche*, et al.,* (2011)**.

Mice administrated $CdCl_2$ (10 mg/kg body) per gavage, daily for thirty days revealed a significant increase in serum AST and ALT activities and urea concentration **(Ibraheem *et al.,* 2016).** A significant elevation of serum enzymes AST and ALT activities, urea and creatinine concentrations with significant decrease in total protein abumine, globulin and A/G ratio were showed in Guinea pigs exposed to either lead acetate (5.5 mg Lead/kg b.w), or Cd Cl_2 (2.5mg Cd/Kg b.w) orally three times a week for 9 weeks **(Hassan *et al.,* 2012)**. Administration of $CdCl_2$ (5 mg/kg BW) orally every other day for 30 days caused a significant increase in AST, ALT activities, urea and creatinine levels. However plasma total protein, albumin concentrations were significantly decreased in rats **(El-Demerdash *et al.,* 2004). Kjalf *et al.,* (2001)** stated that, the effect of $CdCl_2$ was represented by significant elevation of serum creatinine and urea concentrations in rats. **Karmakar *et al.,* (2000)** revealed that subchronic Cd administration in mice resulted in time- dependent elevation in AST and ALT activities after 7, 14 and 21 days of exposure.

Liver plays a key role in trace element regulation, bioaccumulation, and detoxification **(Neuschwander-Tetri, 2007).** In additions, the liver is one of the most extensively used biological materials in ecotoxicological studies for quantifying trends in medium- to long-term contaminant exposure **(Kitowski *et al.,* 2017).** The concentration of cadmium increases 3,000 fold as it binds to the cystein-rich protein (Metallothionein) which forms the cystein-metallothionein complex. This cystein metallothionein complex causes the hepatotoxicity in liver and it circulates to the kidney were it causes nephro-toxicity after its accumulation in renal tissue **(Sabolic *et al.,* 2010)**.Cadmium long exposure with low concentration leads its deposition in kidneys, nephropathy and fragile bones **(Richter *et al.,* 2017)**.

Suradkar *et al.,* (2009) reported that increased AST and ALT might be due to increased cell membrane permeability or cell membrane damage of hepatocytes caused by lead acetate. Increase in γGT is an indication of hepatotoxicity and oxidative damage in the hepatocytes **(Tatjana *et al.,* 2003)**. Elevation of AST and ALT activities may be attributed to the toxic effect of lead on liver cells in cows and bulls **(Mona *et al.,* 2001)**. The levels of total protein, albumin, globulin and A/G ratio were significantly decreased in cows from farms adjacent to the heavily traffic roads **(Ibtisam, 1998)**.

The decreasing of serum total protein values may be attributed to a decrease in hepatic DNA and RNA or due to decreased utilization of free amino acids for protein synthesis induced by lead intoxication **(Moussa and Bashandy 2008 and Shalan *et al.,* 2005)**. Additionally, Cadmium toxicity causes structural distortion of proteins due to Cd binding to sulfhydryl groups **(Valko *et al.,* 2005)**.

Effects of Al-Dakhla wells water on serum minerals profile in cows:

Assessment of the toxic and trace metal concentrations in livestock in the polluted environment is essentially required for assessing the effects of pollutants on domestic animals **(Lopez *et al.,* 2000)**. Farm animals (especially ruminants) are very useful indicators of environmental pollution **(Korénekov*á* *et al.,* 2002)**. In ruminants blood lead level (BLL) up to 0.25 µg/mL is considered safe, but above 0.35 µg/ mL is toxic **(Radostits *et al.,* 2007)**.

The obtained results in **(**Table 3) showed that, cadmium, lead, and Potassium concentrations in the serum of affected cows of Al-Dakhla region were significantly increased against the values of control cows. Contrarily, iron, zinc, calcium, phosphorus, magnesium and sodium

concentrations in the serum of affected cows were significantly decreased in comparison with control.

Lead concentrations in the serum and tissues (liver, Kidney, muscle, spleen) were significantly higher in lead acetate exposed rats (0.5 g/100 ml in drinking water for 2 months) than control **(Azoz and Raafat, 2012)**. These results are in accordance with **Fahim *et al*., (2009)** in rats and **Durgut *et al.,* (2008)** in rabbits.

Guinea pigs exposed to either lead acetate (5.5 mg lead/kg b.w), or Cd Cl_2 (2.5mg Cd/Kg b.w) orally three times a week for 9 weeks revealed an increase in Pb and Cd levels in serum with time compared with control **(Hassan *et al*., 2012)**. Also, **Trottier *et al.,* (2002)** found that cadmium blood concentration of guinea pigs exposed to $CdCl_2$ by inhalation increased by 127 and 223% than control after 1^{St} and 5^{Th} day of exposure, respectively.

Kjalf *et al.,* (2001) stated that, the effect of $CdCl_2$ was represented by significant decrease in serum sodium concentration in rats.

Patra and Swarup, (2004) recorded that administration of lead significantly decreased zinc concentration in cardiac tissue of calves. Moreover, marked decrease in plasma zinc level and prominent hypocalcaemia accompanied by increase in potassium were observed by **Abd El-Hameed *et al.,* (2008)** in goats subjected to oral administration of 4.5 and 6.0 mg lead acetate /kg b. wt daily from beginning of pregnancy till abortion which occurs at the 14^{th} week of pregnancy. Rats exposed to lead acetate in drinking water (2 g/L) for 60 days showed a decrease in blood Fe, Zn and Ca contents **(Hassan *et al*., 2019)**. Also, there was a significant decrease in zinc concentration in liver and kidney and iron in liver of rats exposed to lead acetate; (1000 ppm) through drinking water for a period of 4 weeks when compared to their respective controls **(Kumar *et al.,* 2013)**. Furthermore, **Azoz and Raafat, (2012)** recorded that rats exposed to lead acetate at concentration of 0.5 g/100ml drinking water for 2 months showed a significant drop in the serum concentration of iron, zinc and calcium as compared to control group.

The underlying basic mechanisms of Cd and Pb toxicity may be due to the interactions between Cd/Pb and essential metals **(Ahamed and Siddiqui, 2007 and Vesey, 2010).**

There is no known safe blood lead concentration **(WHO, 2016).** Ionic mechanism of lead toxicity is mainly due to its ability to substitute other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations like Na^{+} (though bivalent cations are more readily substituted), affecting various fundamental biological processes of the body **(Lidsky and Schneider, 2003 and Flora**

***et al.,* 2008)**. Iron, zinc and calcium deficiency have been associated with higher absorption of lead **(Wang *et al.,* 2012)**.

Lead induced inhibition of ferrochelatase; the enzyme catalyzes the insertion of iron into protoporphyrin IX with a consequence increase in the concentration of zinc proporphyrin (ZPP) which is excreted from the body in the urine. This may cause a decrease of the zinc and iron concentration **(US EPA, 2009; Jin *et al.,* 2008 and Ahmed and Siddiqui, 2007)**. Also, **Hande and Nuran, (2000)** found that, lead reduced the absorption of iron from gastrointestinal tract and inhibited the heme biosynthesis. Moreover, **Anuradha, (2007)** said that lead inhibited transferrin (TF) endocytosis and iron transport across the cell membrane of reticulocytes. Transferrin is the major iron- transport protein in serum and other biological fluids capable of transporting various metals.

Hypocalcaemia reflects perturbation of calcium metabolism. Lead interferes with calcium in several metabolic pathways leading to decrease in calcium level. The most widely accepted reason of hypocalcaemia due to lead toxicity is the interference of lead with the final metabolism of vitamin D to the active metabolite, calcitriol (1, 25-DHCC); a hormone required for adequate calcium absorption **(Anetor *et al.,* 2005 and Ronis *et al.,* 2001)**. Cadmium appears to perturb calcium metabolism **(Gardarin *et al.*, 2010)**. Cadmium is primarily toxic to kidney, especially to proximal tubular cells **(Nkansah and Ansah, 2014)**. Cadmium causes reductions in both intestinal zinc absorption and hepatic zinc reserves in cattle due to its competition for the cation-binding sites of metallothionein **(Orisakwe *et al.,* 2017)**.

Cadmium interacts with calcium and iron and disturbs zinc metabolism **(Flora *et al.,* 2008)**. Cadmium interaction with zinc and magnesium is a relevant mechanism of cadmium toxicity. Cadmium competes with zinc for the same binding sites and/or ligands in biological systems, interferes with Mg absorption in the gastrointestinal tract and affects its homeostasis. **(Matović *et al.,* 2011)**. The skeletal damage is a critical effect of cadmium exposure along with disturbances in the calcium metabolism which results in renal stone formation and hypercalciuria **(Bhat *et al.,* 2019)**. The recorded hyponatriumia and hyperkalemia may be attributed to the renal disturbance which revealed by the marked increase of both urea and creatinine levels as showed in **(**Table 2).

CONCLUSION

Al-Dakhla ground water contained high levels of cadmium, lead and iron with subsequent adverse deleterious effects on the antioxidant status, liver, kidney functions and the general performance of cows. To prevent health risks, government and relevant regulatory agencies should adopt more stringent measures to reduce and monitor heavy metal contamination of Al-Dakhla ground water and livestock, so it is advisable to treat such water for heavy metals to be valid for both human and animal consumption. We may also advise by supplying animals of Al- Dakhla region with antioxidant agents in ration and chelating agents in water.

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تغير المؤشرات الحيويه فى الأبقار نتيجه ارتفاع مستوى بعض العناصر الثقيله فى مياه الأبار بمنطقة الداخله.

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الملخص العربي

أجريت هذه الدراســه لإلقاء الضــوء على بعض التغيرات البيوكيميائيه وبعض مضــادات الأكســده فى الأبقار نتيجه ارتفاع مســتوى بعض العناصــر الثقيله فى مياه الأبار بمنطقة الداخله بالوادى الجديد. لتحقيق هذا الغرض تم تجميع عدد 30 عينة مياه من عدد 6 آبارمن منطقة الداخله و تجميع عدد 10 عينة مياه شــرب من شــبكة المياه العموميه من منطقة مجاوره للمقارنه كما تم تجميع عينات دم أبقار تشــرب من مياه الآباربمنطقة الداخله(أبقار مصــابه) وعينات دم أخرى لأبقارسـليمه ظاهريا تشرب من شبكة المياه العموميه (مجموعه ضابطه).

أظهرت نتائج التحليل الكيميائى لعينات مياه الآبار إرتفاع مستوى تركيز عناصـرالكادميوم و الرصـاص والحديد بالمقارنه لعينات مياه الشرب ومواصفات منظمة الصحه العالميه لسنة 2011 والمواصفه القياسيه المصريه رقم 1589 لسنة 2005 لمياه الشرب.

أظهرت نتائج تحليل دم الأبقارالمصابه زياده معنويه فى تركيز المالونالدهيد وتركيز الكرياتينين و اليوريا و نشاط انزيمات الألانين أمينو ترانســفيريز و الأســبرتات أمينو ترانســفيريز والجاما جلوتامي ترانســفيريز و تركيز عناصــرالكادميوم و الرصاص والبوتاسيوم و نقص معنوى فى نشاط إنزيم السوبر أوكسيد ديسميوتاز و تركيز الجلوتاثيون المختزل والبروتين الكلى والألبيومين و والنسبه بين الألبيومين والجلوبيولين وتركيز عناصرالحديد والزنك والكالسيوم والفسفور والماغنيسيوم بالمقارنه بالأبقار السليمه.