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SELENIUM, CADMIUM AND DIAZINON INSECTICIDE IN TISSUES OF RATS AFTER PERORAL EXPOSURE

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ABSTRACT

The concentrations of selenium (Se), cadmium (Cd) and diazinon (DZN) in selected tissues of rats after an oral administration in various combinations were analyzed. Male rats were orally dosed with diazinon (40 mg.L^{-1}), diazinon (40 mg.L^{-1}) +selenium (5 mg.L^{-1}), diazinon (40 mg.L^{-1}) +cadmium (30 mg.L^{-1}), and diazinon (40 mg.L^{-1}) +selenium (5 mg.L^{-1}) +cadmium (30 mg.L^{-1}) in drinking water. After 90 days of per oral administration of compounds, the samples of liver, kidney, muscle tissue (*m. quadriceps femoris*), and adipose tissue were collected. The content of DZN was analyzed using Gas Chromatography – Mass Spectrometry (GC-MS), Cd was analyzed using an Electrothermal Atomic Absorption Spectrometry (ETAAS) and Se using a Hydride Generation Atomic Absorption Spectrometry (HG-AAS) methods. Cadmium significantly increased in liver and kidney after DZN +Cd and DZN +Se +Cd administration. Se significantly increased in liver of DZN +Se, DZN +Se +Cd and DZN +Cd exposed rats, in kidney of DZN +Se and DZN +Se +Cd and DZN +Cd, and in muscle of DZN +Se +Cd group. Highest DZN content was found in the adipose tissue in DZN, DZN +Cd and DZN +Se +Cd but not in combined exposure with Se. Anyway, the differences between the control and experimental groups were not significant. The results indicate that cadmium and selenium accumulate mainly in liver, kidney and selenium also in muscle after p.o. administration but diazinon concentrations increases were not signifcant. The co-administration of diazinon, Se and Cd affects the content of these compounds in the organism and the accumulation rate depends on the combination of administered compounds. Diazinon and cadmium could contribute to the selenium redistribution in the organism after the peroral intake.

Keywords: cadmium; selenium; diazinon; tissue; rat

INTRODUCTION

Diazinon is used in agriculture to control soil and foliage insects and pests on a variety of fruit, vegetable, nut and field crops. Diazinon (DZN) (O,O-diethyl O-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate) is also used on non-lactating cattle in an insecticidal ear tag. Prior to the cancellation of all residential uses by 2004, diazinon was used outdoors on lawns and gardens, indoors for fly control and in pet collars designed to control fleas and ticks. Diazinon was one of the most widely used insecticides for household and agricultural pest control. In 2000, the United States Environmental Protection Agency (U.S. EPA) announced an agreement with the registrants of diazinon to cancel all residential uses of DZN. Indoor uses were canceled in 2002 and outdoor uses in 2004, leaving only agricultural uses for diazinon **(U.S. EPA, 2007)**. Current agricultural uses of DZN are limited to selected crops, and diazinon products (other than cattle ear tags) are regulated as restricted use pesticides **(U.S. EPA, 2006)**. Organophosphate insecticides are able to induce the neurotoxicity and impair the neurobehavioral functions **(Ross et al., 2012; Wang et al., 2014)**. Like other organophosphates, diazinon toxicity is realized through the inhibition of enzyme acetylcholinesterase (AChE) which biological role is the termination of impulse transmissions at cholinergic synapses within the nervous system by rapid hydrolysis of the neurotransmitter, acetylcholine **(Schumacher et al., 1986)**. Inhibition of the activity of AChE by phosphorylation of the serine hydroxyl group of the enzyme results in accumulation of acetylcholine **(Fulton and Key, 2001)**. Symptoms of chronic poisoning are always connected with depression of cholinesterase activity **(Gallo and Lawryk, 1991; Tomlin, 1997; Toman et al., 2013)**. Despite of this general conclusion, reduction in AChE activity does not necessarily mean that the neurotoxic symptoms will also disappear. The manifestations of exposure persist long after ChE levels return to normal **(Rohlman, Anger and Lein, 2011)**.

Diazinon is not a typical cumulative compound in the animal or human organisms but increased levels of this insecticide or its metabolites can be found in fat tissue, liver and hair during relatively short time period **(Túri**

Soós and Végh, 2000; Maravgakis et al., 2011). **Kamel et al. (2007)** stated that symptoms reflecting several neurologic domains, including affect, cognition, autonomic and motor function, and vision, are also associated with pesticide exposure. Neurologic symptoms are associated with cumulative exposure to moderate levels of organophosphate and organochlorine insecticides, regardless of recent exposure or history of poisoning. Due to its liposolubility, organochlorines can be absorbed via skin contact and their accumulation in the human's organism has been related to hepatotoxic and neurologic injuries and reproductive problems, among others **(Cabaj et al., 2010; 2012)**. Co-administration to Cd and DZN led to weakened mechanical properties of the bones. Moreover, Cd in combination with DZN had less expressive effect on bone microstructure in male rats than Cd in a sole dose **(Chovancova et al., 2014)**. Information about organophosphorus insecticide distribution and its metabolites are also important since they have significant consequences for the treatment of contaminated persons **(Paraiba, Castro and Maia, 2009)**.

Selenium (Se) is an essential trace element, and its low status in humans has been linked to increased risk of various diseases, such as cancer and heart disease **(Tinggy, 2008)**. It has important antioxidant role in human and animal organisms. The human selenoproteome consists of 25 selenoproteins **(Kryukov et al., 2003)**. However, selenium can be toxic in large amounts and alters the liver transcriptome and growth decrease in rats **(Raines and Sunde, 2011)**, causes nephrotoxicity in mice **(Nagy et al., 2015)**, negatively affected the macroscopic and microscopic structures femoral bone tissue in rats **(Martiniakova et al., 2013)**. Selenium is characterized by a narrow safety range between deficiency and toxic doses **(Spallholz and Hoffman, 2002; Tapiero, Townsend and Tew, 2003)**. This element together with genetic variations in selenoprotein genes may influence susceptibility to cancer risk **(Gupta et al., 2013)**. Se accumulation was observed after selenate, selenite, SelPlex, selenite and nanoSe administration in mice kidney **(Nagy et al., 2015)**. Organoselenium compounds like SelPlex are associated with greater Se accumulation in both maternal and fetal tissues **(Ma et al., 2014)**. Rats treated via oral administration with 5 μg of selenium showed the highest Se concentration in liver and kidney 24 hours after the Se administration **(Polettini et al., 2015)**.

Cadmium (Cd) is an extremely toxic metal found in polluted industrial and agricultural areas. Exposure to cadmium occurs as a result of atmospheric emission during Cd production and processing, from combustion of fossil energy sources, waste and sludge, phosphate fertilizers and deposition of waste and slag at disposal sites. Higher concentrations of cadmium are found in the kidneys of animals slaughtered for food, in wild mushrooms and in seafood such as mussels and oysters **(Fried et al., 2008)**. In general, about 50% of the total body burden is found in liver and kidney, so that they are considered to be the major site of Cd accumulation. The functional and structural changes in almost all organs were described **(Massanyi et al., 2007; Martiniakova et al., 2011; Lukacinova et al., 2012; Stolakis et al., 2013; Oh et al., 2014; Dkhil et al., 2014; Wallin et al., 2014; Adamkovicova et al., 2016; Rinaldi et al., 2017)**. Cadmium interacts with essential elements such as zinc, copper, iron, and calcium **(Ohta, Ichikawa and Seki, 2002)** and may cause their deficiency. Moreover, some of these essential elements may ameliorate the cadmium toxicity, such as selenium and zinc, the well-known cadmium antagonists **(Kippler et al., 2009; Ugwuja et al., 2015; Liu et al., 2015; Rasic-Milutinovic et al., 2017).**

Scientifical hypothesis

The contamination of the environment and food chain and interactions between the contaminants entering the human body may have a negative impact on the human health and is hard to predict. Therefore, the main goal of this study was to determine the level of pesticide diazinon and elements cadmium and selenium in the organism of rats after the separate and combined administration and if there is any relationships between the compounds accumulation in the animal organism.

MATERIAL AND METHODOLOGY

Experimental design

Fifty males Wistar rats were divided to five groups, diazinon treated group DZN (40 $mg.L^{-1}$), DZN +Se group (diazinon 40 $mg.L^{-1}$ +selenium 5 $mg.L^{-1}$), DZN +Cd group (diazinon 40 $mg.L^{-1}$ +cadmium 30 $mg.L^{-1}$), and DZN +Se +Cd group (diazinon 40 $mg.L^{-1}$) +selenium 5 $mg.L^{-1}$) +cadmium 30 $mg.L^{-1}$), and control, untreated group, each containing 10 males. The males were housed in plastic cages (Tecniplast, Italy) in an environment maintained at 20 – 24°C, 55 ±10% humidity, with access to water and food (feed mixture M3, Machal, Czech Republic) ad libitum. Young, 4 weeks old males were chosen at the beginning of the experiment and continuously dosed with diazinon (Sigma-Aldrich, USA), selenium (Na_2SeO_3, Sigma, USA) and cadmium ($CdCl_2$, Reachem, Slovak Republic) in drinking water for 90 days, reaching the sexual maturity at the end of the experiments.

Tissue diazinon, Se and Cd content analysis

The liver, kidney, adipose tissue and muscle tissue (m. quadriceps femoris) were sampled 90 days after the daily diazinon, Cd and Se peroral intake. The samples were weighed and stored at -20°C and then analyzed. Cadmium was analyzed using the electrothermal atomic absorption spectrometry (ETAAS, Varian SpectrAA 220, The Netherlands). Selenium was determined using the hydride generation atomic absorption spectrometry (HGAAS, Varian SpectrAA 220 with VGA-76 hydride generator, The Netherlands), diazinon was determined using the gas chromatography–mass spectrometry (GC–MS, Varian MS-4000, USA) in certified laboratory (EL, s.r.o. Spišská Nová Ves, Slovak Republic).

Statistical analysis

The values of control and experimental animal analyses were expressed as mean ±SD. The results were analyzed by one-way analysis of variance (ANOVA) followed by Scheffe's test for post hoc comparisons using statistical software Stata 9 (StataCorp LP, TX, USA). Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The results of our experiments summarize Tables 1 – 4. Diazinon content in the selected tissues was almost under the detection limit (<0.005 mg.kg^{-1}). When administered with Se or Cd or Se +Cd, the levels of diazinon were lower in liver and kidney but not in the muscle and adipose tissues than that of the diazinon-exposed group. This could be caused by co-administration with selenium because Se could act as a protective element against the diazinon effects. Selenium in combination with DZN partially or totally alleviated its toxic effects on the liver and kidney. Therefore, selenium could be able to antagonize DZN toxicity **(El-Demerdash and Nasr, 2014)**. Moreover, some authors speculate that adipose tissue could be the target organ to organophosphate pesticides (OPs) toxicity **(Pakzad et al., 2013)**. OPs are known to accumulate in adipose tissue and **Tanvir et al. (2016)** found the highest concentration of OPs chlorpyrifos in the adipose tissue. The similar results were confirmed in our experiments (Table 4).

Treatment of rats with diazinon significantly enhances renal lipid peroxidation which is accompanied by a decrease in the activities of renal antioxidant enzymes

Table 1. Content of diazinon, Cd and Se in the rat liver.

Group	Diazinon (mg.kg^{-1} ±SD)	Selenium (mg.kg^{-1} ±SD)	Cadmium (mg.kg^{-1} ±SD)
Control	<0.005	1.085 ±0.26	0.006 ±0.002
DZN	0.0054 ±0.001	1.099 ±0.10	<0.005
DZN+Se	<0.005	2.946 ±0.48**	<0.005
DZN+Se+Cd	<0.005	3.098 ±0.88**	0.067 ±0.02**
DZN+Cd	<0.005	2.422 ±0.15**	0.072 ±0.03**

***p* <0.01; 0.005 – detection limit.

Table 2. Content of diazinon, Cd and Se in the rat kidney.

Group	Diazinon (mg.kg^{-1} ±SD)	Selenium (mg.kg^{-1} ±SD)	Cadmium (mg.kg^{-1} ±SD)
Control	<0.005	1.527 ±0.24	0.013 ±0.003
DZN	0.014 ±0.003	1.574 ±0.30	0.015 ±0.008
DZN+Se	<0.005	4.023 ±1.06**	0.03 ±0.009
DZN+Se+Cd	<0.005	3.775 ±0.55**	0.647 ±0.174**
DZN+Cd	<0.005	2.424 ±0.15*	1.566 ±0.30**

**p* <0.05; ***p* <0.01; 0.005 – detection limit.

Table 3. Content of diazinon, Cd and Se in the rat muscle.

Group	Diazinon (mg.kg^{-1} ±SD)	Selenium (mg.kg^{-1} ±SD)	Cadmium (mg.kg^{-1} ±SD)
Control	<0.005	0.250 ±0.03	0.006 ±0.001
DZN	0.012 ±0.002	0.207 ±0.04	0.005 ±0.0006
DZN+Se	<0.005	0.214 ±0.12	0.005 ±0.0009
DZN+Se+Cd	0.008 ±0.003	0.884 ±0.48**	<0.005
DZN+Cd	0.007 ±0.001	0.210 ±0.03	<0.005

***p* <0.01; 0.005 – detection limit.

Table 4. Content of diazinon, Cd and Se in the rat adipose tissue.

Group	Diazinon (mg.kg^{-1} ±SD)	Selenium (mg.kg^{-1} ±SD)	Cadmium (mg.kg^{-1} ±SD)
Control	<0.005	0.137 ±0.05	<0.005
DZN	0.032 ±0.01	0.031 ±0.02	<0.005
DZN+Se	<0.005	0.197 ±0.096	0.005 ±0.0006
DZN+Se+Cd	0.038 ±0.01	<0.005	<0.005
DZN+Cd	0.033 ±0.02	<0.005	0.015 ±0.01

0.005 – detection limit.

(catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, glutathione S-transferase) and depletion in the level of glutathione reduced. These changes result in the oxidative stress and renal dysfunction **(Shah and Iqbal, 2010)**. Selenium has the ability to counteract free radicals and protect the structure and function of proteins, DNA and chromosomes against the injury of oxidation **(Reddy, Sailaja and Krishnaiah, 2009)**. There is a difference between the effective dose of selenium in relation to the activity of glutathione peroxidase (GSH-Px) and depends on the animal species. The highest GSH-Px level was observed when the animals were fed 0.5 $mg.kg^{-1}$ dietary Se level in roosters **(Shi et al., 2014)** but at the 4.0 $mg.kg^{-1}$ in goats **(Shi et al., 2010)**. Due to the scavenging of free radicals and increasing the antioxidant status, Se particularly at low doses had a potent antigenotoxic effect against DZN-induced toxicity in rats **(Shokrzadeh et al., 2013)**. However, mechanisms of interaction between DZN and Se are still not clear and further studies are still required.

Excessive exposure to cadmium and selenium causes increase in their contents in the internal organs. Cadmium content in the selected tissues in our experiments was low, mostly near or under the detection limit. Only cadmium content in kidney was higher in all groups than in other tissues. The main cadmium storage organs are kidneys and liver which has been confirmed in many studies **(Toman and Massányi, 1996; Jihen et al., 2008; Kolesarova et al., 2008; Roggeman et al., 2014)**. In fact, the significant increase in Cd content was observed in the liver and kidney after p.o. exposure in DZN +Cd and DZN +Se +Cd group (Table 1 and 2).

Ongjanovic et al. (2008) reported that with increased Cd concentration in the liver and kidneys, Se concentration also rises, although it was not administered additionally. We confirm these findings as selenium content in analyzed tissues was highest in kidney, followed by liver, muscle and adipose tissue. The same trend in Se tissue concentrations was recorded by **Zachara et al. (2001)**. The statistically significant increase in selenium content was found in the kidney and liver when Se was administered with DZN or Cd or DZN+Cd (Table 1 and 2). In muscle tissue, the significantly higher Se content was found only in DZN +Se +Cd group (Table 3). Selenium antagonizes cadmium, especially in acute exposures and was found to have a protective effect by decreasing Cd content in the liver and kidneys **(Chen, Whanger and Weswig, 1975)**. However, it has also been observed that simultaneous administration of cadmium and selenium (200 ppm and 0.1 ppm, respectively) in drinking water for five weeks did not decrease Cd concentration in the liver and kidney and only affected the toxic effects of Cd in these organs **(Jihen et al., 2008)**. Dietary selenium did not significantly affect the concentration of cadmium in tissues in our experiments but there was also diazinon present in the same period and dose which could affect the role of Se in antioxidant capability. Similarly, no decrease in cadmium, zinc, iron or copper in rat liver was found after selenium intake in food **(Meyer, House and Welch, 1982)**. The lipid peroxidation, one of the main manifestations of the oxidative damage, plays an important role in the toxicity of many xenobiotics. Intoxication with cadmium causes a significant increase of lipid peroxidation in liver and kidneys of rats **(Ognjanovic et al., 2008)** which are also the main organs cumulating the cadmium. Therefore, increase in selenium content in these organs (Table 1 and 2) may be connected with the selenium protective role in oxidative stress induced by cadmium and diazinon. This protection includes the capability of Se to alter the distribution of Cd in tissues and induces binding of the Cd-Se complexes to proteins, which are similar to metallothioneins **(Jamba, Nehru and Bansal, 1997; Combs and Gray, 1998; Ognjanovic et al., 2008)**. The significant increase in cadmium content in kidney and liver after its administration in DZN +Cd or DNZ +Se +Cd is a logical consequence but was somewhat limited by selenium addition (Table 1 and 2).

CONCLUSION

The results indicate that cadmium and selenium accumulate mainly in liver, kidney and selenium also in muscle after p.o. administration but diazinon concentrations increases were not signifcant. The co-administration of diazinon, Se and Cd affects the content of these compounds in the organism and the accumulation rate depends on the combination of administered compounds. We propose the role of diazinon and cadmium in redistributon of selenium as these compounds administered simultaneously caused the elevation in the selenium content in liver and kidney.

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