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THE EFFECT OF BENZENE ON SERUM HORMONES AND THE ACTIVITY OF SOME ENZYMES IN DIFFERENT TISSUES OF RATS

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The effects of a 100 mg.kg $^{-1}$ dose of benzene, an occupational and environmental toxicant, were investigated on serum, estradiol and testosterone concentrations as well as lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), and pyruvate kinase (PK) activities in the liver and kidney of rats after 2, 4, 8, 16, 32, 64 and 72 hours. Benzene was given intraperitoneally to Rat rattus norvegicus and the control groups were injected with physiological saline. Liver tissue LDH, AST, ALT and kidney tissue LDH, ALP, AST, ALT activities were lower in the benzene treated group when compared to those in the control group ($p<0.05$). A tendency for an increase in the liver tissue ALP activity was observed, which was significant at 8 and 16 hours ($p<0.05$). There were significant increases in ALT in the liver and LDH, AST, and ALT enzyme activities in the kidney tissue at the beginning of the experiment in both groups and these activities were found to be nearly the same. Pyruvate kinase enzyme activities in rats given benzene were slightly increased in kidney tissues but lower in liver tissues. Differences between the groups tended to disappear towards the end of the experimental period. However, serum estradiol concentrations in the serum diverged significantly ($p<0.05$).

Consequently, it was found that benzene administration led to some changes (increases then decreases) in LDH, ALP, ALT, AST, and PK activity and estradiol, testosterone concentrations in different tissues of rats. Possible causes of the increases and decreases in enzyme activities and hormone levels are discussed.

Key words: Benzene, liver, kidney, enzyme, serum hormone

INTRODUCTION

Benzene is an aromatic hydrocarbon often used for industrial purposes. It can cause serious, negative health effects in humans depending upon both the amount and duration of the exposure. It is a clastogenic and carcinogenic agent. It may induce acute myelogenous leukemia in humans and multiple types of tumors

in animals (Yardley *et al*. 1990, Mark and Gary, 2001, Frantz and Chen, 1996). The main toxic effect of benzene is its myeloid effect. However, most of its metabolism occurs in the liver. Observations have shown that benzene has further toxic effects after it is metabolized by the cytochrome p 450 II E1 enzyme system (Dieter *et al*. 1996).

Benzene enters into the environment because of both human and natural activities. Generally it originates from the following sources: exhaust emissions of motor vehicles, gas stations, oil refineries, cigarettes, coal mines, garages, some consumer items (sprays, synthetic rubber, adhesives and other items which contain benzene), the shoe industry, waste products of the timber industry, etc. (Andrews *et al*. 1977, Sammett *et al*. 1979, Anonymous, 1993). Since benzene is able to be conjugated, the elevation of metabolites and metabolite interactions may increase its toxicity (Arfellini *et al.* 1985). Chronic benzene exposure causes lesions to develop in haematopoietic functions, including anemia, leukopenia trombocytopenia, parcytopenia, bone marrow depression, aplastic anemia and non-Hodgkin's lymphoma related to the aforementioned and in some cases benzene causes leukemia and several types of carcinomas (Cronkite *et al*. 1982, Wong and Raabe 2000).

People, who work on sites where benzene concentrations are high, may have physical discomfort and changes in their blood glucose level. In addition, some benzylidyne groups become attached to monosaccharides and disaccharides. Benzene causes energy metabolism dysfunctions in some people and may attach to microsomal proteins and hepatic enzymes (Powley ans Carlson, 1999, Raunio *et al.* 1988). The sub metabolites, which are formed from benzene metabolites, depend on microsomal fractions, proteins and enzymes of the liver and may affect several hepatocyte functions (Brodfuehrer *et al.* 1990). According to Subrahmanyam *et al.* (1990) a high level of phenol metabolites was observed at the fourth hour during their studies of benzene metabolism.

Benzene also affects many enzyme activities in the liver and other tissues, decreasing the activity of glucose 6-phosphatase so that hyperglycemia occurs in the blood (Chierpotta *et al.* 1984, Sukhodub, 1997). However, no changes in catalase and superoxide dismutase activities of serum, liver and kidney tissues were observed but the activity of glutathione S-transferase was increased (Serif et al 1999). Nevertheless, some structural and functional changes occurred in the cytochrome P-450 system under benzene treatment (Sukhodub and Vlademir, 1999).

In the present study the effects of benzene were investigated on lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), and pyruvate kinase (PK) activities in the liver and kidney as well as, on estradiol and testosterone concentration in the serum of rats.

MATERIALS AND METHODS

Male albino rats (*Rat rattus norvegicus*) weighing 250-300 g were used in our experiments (n=84). The animals were housed in 49x35 cm stainless steel wire

mesh cages with a bedding of ground wood chips at 21 °C. They were fed fresh-pelleted food and their water was placed in glass bottles of 500 ml. Four rats from the control group and eight rats from the benzene treated group were used for each trial period. The control group was treated with physiological saline. The animals used in the trial were left without food and water for 24 hours, and then a 100 mg kg^{-1} dose of benzene (99.5%) was injected intraperitoneally using 1 ml sterile injectors. Following the injection, food and water were regularly given to the animals both in the control and benzene treated groups until the trial was completed.

They were killed by cervical dislocation 0,2,4,8,16,32, and 64 hours after the injection. The blood of heart, liver, and kidneys were quickly removed and perfused with 0.15 M KCl. The wet weights of tissues obtained were obtained. Homogenates were prepared after addition of ice-cold 0.15 M KCl (1/3 mass/volume) in a glass homogenizer with a teflon pestle. Four shots vere used livers and three shots for kidneys at 2000 rpm in a T-line laboratory stirrer (model No: 136-2) type homogenizer. Each homogenate was centrifuged in a Dupont Instruments Sorval "RC-5 super speed refrigerated centrifuge" at 48000 g for 30 min. The enzymatic reaction rates were determined with these freshly made preparations. Care was taken to achieve homogenization, centrifuging and all enzymatic studies at 0-4 °C. The activities of LDH, ALP, ALT, and AST were determined using a Hitachi 911 autoanalyser with the aid of Hitachi kits; PK activity was determined spectrophometrically (Bohringer and Mannheim, 1973). Blood obtained from the heart was centrifuged in a Nüve NT 201 centrifuge at 12000 rpm for 15 min. Serum was used for testosterone and estradiol determination according to the Immulite 2000 method (DPC, 2000.) and Chiron Diagnostics Corporation (1996). The estradiol and testosterone assays were competitive immunoassays using a direct, automated chemiluminescence system. Kruskal-Wallis and Mann-Whitney tests were applied to evaluate the differences between the groups which were considered significant at $P<0.05$. All the values in the text are given as mean±SE (Jerrold, 1984). Benzene was from Merck. All the other chemicals were analytical grade.

RESULTS

The effects of benzene on the LDH, ALP, ALT, AST and PK activities in the tissues of the liver and kidney

The effect of benzene on the LDH, ALP, ALT, AST and PK activities in liver and kidney tissues are given in Figure 1-10. The statistical data may be seen in Table 1.

A reduction was observed in the LDH activity of both liver and kidney tissues. The difference in activity within the first hours was found to be statistically significant for each tissue. It was observed that activity increased only in kidney tissue at 16 hours (Figure 2). However, this increase was not significant ($p>0.05$). Kidney tissue LDH activity was found to be nearly the same as that of the control group at the last experimental period but the significant decrease seen in the LDH activity in liver tissues remained ($p<0.05$) (Table 1). This inhibition in the liver tissues was 43.7% at 32 hours but maximal initially (46%).

Figure 1. The effect of benzene on LDH activity in liver tissues

Figure 2. The effect of benzene on LDH activity in kidney tissues

No significant difference between the groups was determined in ALP enzyme activity in the liver tissues until 8 hours when it increased in the benzene treated group (Figure 3). This led to a significant difference between the groups at 8 and 16 hours. The difference at 8 hours was about 34%. Initial ALP activity in the kidney tissues was lower when compared with the control group (Figure 4). The difference became insignificant at 4, 8 and 16 hours but reemerged at the end of the trial. The initial difference about 47% while at 32 and 64 hours it was found to be 20% inhibition.

Figure 3. The effect of benzene on ALP activity in liver tissues

Figure 4. The effect of benzene on ALP activity in kidney tissues

Lower ALT activity was found in the experimental group both liver and kidney tissues. Statistically significant increase was observed only in kidney tissues at 16 hours (Figure 6). Almost the same value as the control group occurred at 64 hours at each tissue. The maximal (25%) difference was observed in liver tissues at the first period in the trial. Activation was seen only kidney tissues at 16 hours (31%).

Figure 5. The effect of benzene on ALT activity in liver tissues

Figure 6. The effect of benzene on ALT activity in kidney tissues

AST activity in the liver tissues was significantly lower than in the control group in the whole trial period except at 16 hours (Figure 7). The inhibition was 37% on average. Although lower AST activity was found in the kidney, it was not significant at 16, 32, and 64 hours ($p>0.05$) (Figure 8).

Figure 7. The effect of benzene on AST activity in liver tissues

Figure 8. The effect of benzene on AST activity in kidney tissues

Mild activation in PK activity was occurred in the kidney tissues of both groups beginning from the first hours (Figure 10), whereas PK activity in the liver tissues of the benzene treated group was lower (Figure 9). The difference was statistically significant at all periods ($P<0.05$) except the last.

Figure 9. The effect of benzene on PK activity in liver tissues

Figure 10. The effect of benzene on PK activity in kidney tissues

The effects of benzene on testosterone and estradiol concentrations in serum

The effect of benzene on testosterone and estradiol activities in serum is given in Figure 11 and 12. The statistical data may be seen in Table 2.

An increase was observed in testosterone concentration in both groups (Figure 11). However, no significant differences were detected between the groups until 16 hours. Estradiol concentrations decreased in the control group but not in the experimental group leading to a statistically significant difference at 32 and 64 hours (Figure 12).

Figure 11. The effect of benzene on serum testosterone concentration

Figure 12. The effect of benzene on serum estradiol concentration

Table 1. The effects of benzene on LDH, ALP, ALT, AST, and PK activities in liver and kidney tissue in relation to time

Enzyme		Time (Hours)	0 Mean ± SE[r]	2 Mean ± SE	4 Mean ± SE	8 Mean ± SE	16 Mean ± SE	32 Mean ± SE	64 Mean ± SE
LIVER	LDH	Control	662±23.2 x	575±19.2 x	622±25.5 x	560±20.3 x	582±33.3 x	530±35.4 x	540±27.6 x
		Benzene	404±16.5 y	379±19.5 y	350±18.4 y	485±23.5 x	374±27.5 y	348±25.1 y	331±29.4 y
	ALP	Control	1.00±0.05 x	0.83±0.06 x	0.86±0.13 x	0.75±0.08 x	1.00±0.07 x	1.00±0.05 x	0.89±0.08 x
		Benzene	0.75±0.14 x	0.97±0.15 x	0.75±0.14 x	1.14±0.21 y	1.28±0.20 y	1.25±0.19 x	1.10±0.23 x
	ALT	Control	92±12.2 x	108±23.2 x	96±25.3 x	102±30.2 x	80.4±22.2 x	82.7±19.2 x	69±18.2 x
		Benzene	69±15.2 y	91±14.5 x	90.2±22.1 x	87.5±20.5 x	75±14.2 x	62.5±13.6 y	68±16.5 x
	AST	Control	310±22.2 x	311±20.6 x	305±29.2 x	263±20.7 x	244±24.1 x	256±28.0 x	216±25.3 x
		Benzene	212±11.2 y	225±12.6 y	186±10.6 y	160±15.2 y	184±18.2 x	149±19.2 y	146±16.5 y
	PK	Control	2.75±0.56 x	2.80±0.87 x	3.20±0.91 x	3.30±0.42 x	3.28±0.89 x	3.25±0.76 x	3.22±0.73 x
		Benzene	1.86±0.63 y	1.92±0.93 y	2.13±0.95 y	2.26±0.32 y	2.35±0.42 y	2.38±0.22 y	2.95±0.19 x
KIDNEY	LDH	Control	6566±165 x	8450±192 x	12300±210 x	7479±156 x	7000±183 x	9300±177 x	7966±192 x
		Benzene	3550±105 y	9540±175 x	11280±258 x	5413±106 y	7938±155 x	6279±147 y	7557±162 x
	ALP	Control	966±35.5 x	875±30.2 x	1050±63.2 x	966±75.2 x	766±52.1 x	1000±69.2 x	933±82.4 x
		Benzene	514±24.9 y	550±25.6 y	1040±29.4 x	916±20.1 x	637±29.8 x	800±26.8 y	742±20.9 y
	ALT	Control	450±19.3 x	520±20.3 x	533±18.5 x	475±13.2 x	633±20.9 x	588±18.2 x	433±15.7 x
		Benzene	227±13.2 y	420±23.5 y	500±21.5 x	338±18.5 y	925±19.5 y	428±26.5 y	367±28.5 x
	AST	Control	2975±125 x	3425±160 x	3400±158 x	3150±125 x	3313±120 x	3900±106 x	3333±127 x
		Benzene	2083±102 y	2571±103 y	2125±115 y	2480±112 y	3280±124 x	3280±152 x	3243±160 x
	PK	Control	2.00±0.29 x	1.98±0.50 x	2.04±0.32 x	2.18±0.25 x	2.21±0.40 x	2.05±0.38 x	2.09±0.36 x
		Benzene	2.02±0.21 x	2,09±0.12 x	2,11±0.23 x	2.39±0.26 x	2.35±0.34 x	2.25±0.35 x	2,20±0.41 x

* Data shown with the same symbols in the vertical column are not different from each other at 0.05 statistical level (x.y)
[r] All data in the table showed enzyme activities (U/L x 10^2), PK data (U/mg protein)
SE: Standard Error

Table 2. The effects of benzene on serum testosterone and estradiol in relation to time

Hormone	Time (Hours)	0 Mean ± SE[r]	2 Mean ±SE	4 Mean ±SE	8 Mean ±SE	16 Mean ±SE	32 Mean ±SE	64 Mean ±SE
Estradiol	Control	37.0±8.50 x	26.7±10.2 x	29.3±7.25 x	25.4±6.32 x	31.2_7.59 x	23.0±10.3 x	24.6±10.8 x
	Benzene	35.4±11.0 x	30.1±12.2 x	31.7±9.68 x	26.3±5.29 x	39.1±8.24 x	33.0±9.36 y	39.0±10.2 y
Testosterone	Control	113.0±20.1 x	114.0±22.2 x	115.5±19.3 x	152.1±25.4 x	134.0±29.1x	161.0±29.5 x	186.0±28.5 x
	Benzene	116.0±16.9 x	128.0±20.6 x	126.0±18.5 x	170.0±23.9 x	177.1±24.2y	164.2±27.1 x	212.0±30.8 x

* Data shown with the same symbols in the vertical column are not different from each other at 0.05 statistical levels (x.y)
[r] Testosterone (ng/dl) and estradiol (pg/ml)
SE: Standard Error

DISCUSSION

The present study showed that benzene affected some enzymes activities in rat liver and kidney. In general, LDH, ALP, ALT, and AST activities in the kidney and LDH, ALT, AST, and PK activities in the liver were inhibited whereas PK activity in the kidney and ALP activity in the liver were enhanced. Enzyme activities may show differences depending on the tissues examined. In a study carried out after subcutaneous administration, it was shown that the activity of catalase (C) and superoxide dismutase (SOD) activities of serum, liver and kidney tissues did not change in rabbits and rats treated with 880 mg/kg/day (Serif *et al.* 1999). In the same study, glutathione S-transferase activity increased in the hepatic cytosol of rabbits. C activities were highest in the kidney, followed by the liver and serum of both rabbits and rats. SOD activities were highest in the liver, followed by the kidney and serum (Serif *et al.* 1999). In another study, glucose-6-phosphatase and glucose dehydrogenase activities indicated that 3-month-old rats microsomal vesicles were more stable against benzene injury than those of 24-month-old rats (Sukhodub and Vlademir, 1999). Benzene decreased the activity of glucose 6-phosphatase and hyperglycemia occurred in the blood (Chierpotta *et al.* 1984, Sukhodub, 1997). Thus, benzene decreases the effects of glucose 6-phosphatase (Manenti *et al.* 1987).

A reduction was observed in the LDH activity of both liver and kidney tissues. As a result of this, lactate may accumulate in the surroundings. It has been pointed out that the remarkable increase of lactic acid in tissues depends on the effect of benzene (Misra *et al.* 1991; Lu *et al.* 1995). These discussions seem to support our findings.

Benzene may directly affect organelles at the cellular level in various tissues, which will indirectly influence enzyme activities. Thus, it was shown that some properties of membrane phospholipids were changed (Engelke *et al*. 1993). Observations of the effects of inhaled benzene on murine testis showed that benzene did not affect the weight of the testis but the cells of the testis were highly deformed and this caused some morphologic changes in some sperm cells (Spano *et al.* 1989).

The main hepatic metabolites of benzene are phenol, catechol and hydroquinone. Microsomal metabolism of benzene plays a critical role in benzene toxicity (Synder and Hedli, 1996). The above mentioned and other intermediate products reach target tissues by the hepatic portal vein and cause much of direct or indirect damage. Such damage occurs either by attachment to molecules such as DNA, protein, carbohydrates and their smaller components or oxidative metabolism or by different types of enzymatic activity. The reason for the low or high enzyme activities in our experimental group may be that benzene affected the metabolism through some metabolites such as phenol and benzene oxide. Cytochrome p 450 II E1 enzymes in the liver metabolize benzene to phenol and other various metabolites. Further metabolites, which arise from the benzene metabolites, depend on microsomal fractions, proteins and enzymes of the liver and may affect several hepatocyte functions (Brodfuehrer *et al.* 1990). Thus, a high level of

phenol metabolites was observed after 4 hours during studies of benzene metabolism (Subrahmanyam *et al.* 1990).

The main reason for later fluctuations in enzyme activities of the studied tissues is that benzene or its metabolites can become attached to DNA or RNA and cause some changes in replication, transcription and translation processes. Thus, Lattanzi *et al.* (1991) showed that benzene and its sub metabolites become attached to both DNA and RNA in mice and rats in vivo and in vitro. Benzene inhibited protein synthesis by inactivating some proteins and damaging DNA molecules, and this supports our suggestion. A previous study has demonstrated the formation of DNA-protein cross-links, a potentially cytotoxic and genotoxic lesion induced by many leukemogenic agents, in bone marrow cells of mice given benzene. However, the reactive benzene metabolites involved in DNA-protein cross-links have not been characterized. Schoenfeld and Witz (2000) examined DNA-protein cross-link formation in HL60 cells treated with trans,trans-muconaldehyde, a hematotoxic ring-opened metabolite of benzene, trans,trans-muconaldehyde metabolites and structurally related compounds. Moreover, benzene metabolites inhibit topoisomerase II enzymes in living organisms, which defines the interaction of benzene at the replication level (Frantz and Chen, 1996).

In our study, the increases and decreases in the enzymes and hormones were generally statistically insignificant at 64 hours after benzene treatment when compared with the control group (except for LDH and AST in the liver and ALP in the kidney and serum estradiol). Benzene is removed from the body in the urine 77% and faeces 15% after the 72 hours, (Adams *et al.* 1996). At the same time blood glucose reached a normal level (Peters *et al.* 1997). Thus, benzene leaves the body after a certain time. At 64 hours, the variation in enzyme activities decreased. However, LDH, AST activities in the liver and ALP activity in the kidney remained lower in the experimental group, while estradiol concentration in the serum was higher $p<0.05$. This may have been due to small amounts of benzene remaining in the body being metabolised further. Benzene has caused leukemia during these further metabolic interactions (Finkelstein, 2000). However, the recovery in the enzyme levels of the tissues indicates that benzene and its metabolites cause temporary effects. It was shown that 2,3,5-tris (glutathione-S-yl) hydroquinone, a putative metabolite of benzene, induces apoptosis in human promyelocytic leukemia (HL-60) cells (Bratton *et al.* 2000). Large amounts of benzene are a great danger and risk to life.

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REFERENCES

1. *Adams PE, Feil VJ, Paulson GD,* 1996, Metabolism of ^{14}C-sulphadimethoxane in swine. *Xenobiotica* (England), 26, (9): 921-33.
2. *Andrews LS, Lee EW, Witner CM, Kocsis JJ, Synder R,* 1977, Effects of toluene on the metabolism, disposition and hematopoietic toxicity of (^{3}H)-benzene. *Biochem Pharmacol*, 26, 293-300.
3. *Anonymous*, 1993, World Health Org. Environmental Health Crýteria 150 Benzene. Genova.
4. *Arfellini G, Grilli S, Colacci A, Mazzullo M, Prodi G,* 1985, In vivo and in vitro binding of benzene to nucleic acids and proteins of various rat and mouse organs. *Cancer Lett*, 28, (2): 159-68.
5. *Bratton SB, Lau SS, Monks TJ*, 2000, The putative benzene metabolite 2,3,5-tris (glutathion-S-yl) hydroquinone depletes glutathione, stimulates sphingomyelin turnover, and induces apoptosis in HL-60 cells. *Chemical Research in Toxicology*, 13, (7): 550-556.
6. *Bohringer, Mannheim*, 1973, Biochemical information, pyruvate kinase 155.
7. *Brodfuehrer JI, Chapman DE, Wilke TJ, Powis G*, 1990, Comparative studies of the in vitro metabolism and covalent binding of ^{14}C-benzene. *Drug. Metab. Dispos* (U.S.), 18, (1): 20-7.
8. *Chierpotta E, Poli G, Albano E, Gravela E, Dianzani MV,* 1984. Studies on fatty liver with isolated hepatocytes III cumene hydroperoxide-induced change of several cell functions. *Exp Mol Pathol* (US), 41, (2): 191-201.
9. *Chiron/Diagnostics Corporation*, 1996, Automated Chemiluminescence System. (ACS:180) 333 Coney Street East Walpole MA 02032 USA.
10. *Cronkite EP, Inowe T, Carlsten AL, Miller ME, Bullis JI, Drew RT*, 1982, Effect of benzene inhalation on murine pluripotent stem cells. *J. Toxicol Environ Health,* 9, (3): 411-21.
11. *Diagnostic Products Corporation (DPC)*, 2000, 5700 West 96th Street Los Angeles, CA 90045-5597 Total Testosterone Estradiol.
12. *Dieter SO, Achim RS, Leslic S, Robert B, Brian SI, Magnus BK*, 1996, Phase II metabolism of benzene. *Environ Health Pers*, 104: 6.
13. *Engelke M, Bergmann U, Diehl HA*, 1993, Fluidity of the microsomal membrane and cytochrome P-450 reduction kinetics of pig liver microsomes as a consequence of organic solvent impact. *Xenobiotica*, 23, 71-8.
14. *Finkelstein MM*, 2000, Leukemia after exposure to benzene: temporal trends and implications for standards. *Am J Industr Med,* 38, (19): 1-7.
15. *Frantz CE, Chen H*, 1996, Inhibition of human topoizomerase II in vitro by bioactive benzene metabolites. *Environ. Health Pers Suppl*, 104, (6): 1319-24.
16. *Jerrold HZ*, 1984, Biostatistical Analysis. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. 138-78.
17. *Lattanzi G, Bartoli S, Bomora B, Colacci A, Grilli S, Niero A, Mazzullo M*, 1991, In vivo and in vitro interaction of 1,2-dichlorobenzene with nucleic acids and proteins of mice and rats. *Tumori* (Italy), 76, (4): 339-44.
18. *Lu J, Jiang C, Kaeck M, Ganther H, Ip C, Thompson HT*, 1995, Cellular and metabolic effects of triphenylselonium chloride in a mammary cell culture model. *Carcinogen* (England), 16 (3), 513-7.
19. *Manenti G, Dragani TA, Della GP*, 1987, Effects of phenobarbital and 1,4-Bis[2-(3,5-dichloropyridyloxy)] benzene on differentiated functions in mouse liver. *Chem Biol Interact,, (Netherlands), 64, (1-2): 83-92.*
20. *Mark PW, Gary PC,* 2001, Hepatic and pulmonary microsomal benzene metabolism in CYP2E1 knockout mice. *Toxicol*, 169: 187-94.
21. *Misra V, Kumar V, Pandey SD, Viswanathan PN,* 1991, Biochemical alterations in fish fingerling exposed to sublethal concentration of linear alkyl benzene sulphonate. *Arch Environ Contam Toxicol*, (US), 21, (4): 514-7.
22. *Peters MM, Jones TW, Monks TJ, Lau SS*, 1997, Cytotoxicity and cell-proliferation induced by the nephrocarcinogen hydroquinone and its nephrotoxic metabolite 2,3,5-(Tris-glutathion-S-Yl) hydroquinone. *Carcinogen* (England), 18 (12), 2393-4.
23. *Powley MW, Carlson GP,* 1999, Species comparison of hepatic and pulmonary metabolism of benzene. *Toxicol*, 139, (3): 207-17.

24. *Raunio H, Kojo A, Juvonen R, Honkakoski P, Jarvinen P, Lang MA, Vahakangas K, Gelboin HV, Park SS, Pelkonen O*, 1988, Mouse hepatic cytochrome P-450 isozyme induction by 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene, pyrazole, and phenobarbital. *Biochem. Pharmacol*, (England), 37, (21): 4141-7.
25. *Sammett D, Lee EW, Kocsis JJ, Synder R*, 1979, Partial hepatectomy reduced both the metabolism and toxicity of benzene. *J Toxicol Environ Health*, 5: 785-92.
26. *Schoenfeld HA, Witz G,* 2000, Structure-activity relationships in the induction of DNA-protein cross-links by hematotoxic ring-opened benzene metabolites and related compounds in HL60 cells. *Toxicol. Lett.* 116, (1-2): 79-88.
27. *Serif A, Alper G, Murat Ö, Abdullah O, Kurtulus Y, Türker K, Emel A*, 1999, The effect of benzene on serum, hepatic and renal glutathione S-transferase, superoxide dismutase, catalase of rat and rabbit. *Biochemical Archives*, 15, 239-46.
28. *Spano M, Pacchierotti F, Ucelli R, Amendola R, Bartoleschi C*, 1989, Cytotoxic effects of benzene on mouse germ cells determined by flow cytometry. *J. Toxicol. Environ. Health*, (US), 26, (3): 361-72.
29. *Subrahmanyam VV, Doane PS, Steinmentz KL, Ross D, Smith MT*, 1990, Phenol-induced stimulation of hydroquinone bioactivation in mouse bone marrow in vivo: possible implications in benzene myelotoxicity. *Toxicol* (Netherlands), 62, (1): 107-16.
30. *Sukhodub AL*, 1997, Activity of microsomal liver enzyms and blood glucose level in normal and benzene-treated rats of various ages, Ukr Biokhim Zh (Ukraine), 69, (3): 119-21.
31. *Sukhodub AL, Vlademir IP*, 1999, Age-dependent changes in rat liver microsomal membrane structure and functions under benzene treatment. *Mech Ageing Develop*, 106, 273-82.
32. *Synder R, Hedli CC*, 1996, An overview of benzene metabolism. *Environ Health Perspect*, 104, 1165-71.
33. *Wong O, Raabe GK*, 2000, Non-Hodgkin's lymphoma and exposure to benzene in a multinational cohort of more than 308.000 petroleum workers, 1937-1996. *J Occupational and Env. Med.* 42, (5): 554-68.
34. Y*ardley JA, Anderson D, Lovel DP, Jenkinson PC,* 1990, Analyses of chromosomal aberration in workers exposed to low-level benzene. *Br J Ind Med*. 47: 48-51.

UTICAJ BENZENA NA NIVO HORMONA U SERUMU I AKTIVNOST NEKIH ENZIMA U RAZLIČITIM TKIVIMA PACOVA

DERE E, GYBOROVA i AYDIN H

SADRŽAJ

U ovom radu su izneti rezultati ispitivanja uticaja benzena kao jednog od ambijentalnih zagađivača na nivo estradiola i testosterona u serumu kao i na aktivnost laktat dehidrogenaze (LDH), alkalne fosfataze (ALP), alanin amino transferaze (ALT), aspartat amino transferaze (AST) i piruvat kinaze (PK) u jetri i bubrezima pacova. Benzen je intraperitonealno aplikovan pacovima u dozi od 100 mg/kg a ispitivanja su vršena u intervalima od 2, 4, 8, 16, 64 i 72 sata. U tkivu jetre tretiranih pacova registrovana je smanjena aktivnost enzima LDH, AST i ALT a u tkivu bubrega osim ovih, još i enzima ALP. U tkivu jetre 8. i 16 sata po aplikaciji registrovano je povećanje aktivnosti ALP. Aktivnost PK je bila nešto niža u jetri a veća u bubrezima. U serumu oglednih životinja registrovano je povećanje koncentracije estradiola ali ne i testosterona.