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Research article

ASSESSING RISKS OF FUNCTIONAL DISORDERS OF HEPATOBILIARY SYSTEM IN WORKERS EMPLOYED AT BUTYL RUBBER PRODUCTION ALLOWING FOR ANALYSIS OF THE *OGG1* GENE POLYMORPHIC VARIANT rs1052133

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Contemporary petrochemical productions maintain strict control over contents of adverse chemicals in workplace air. Despite that, the chemical factor remains one of the major harmful occupational factors and can produce adverse effects on workers' health by increasing, among other things, risks of general somatic diseases. Given that, prevention of chronic non-communicable diseases in workers employed at chemical productions remains a vital challenge for occupational medicine. A way to tackle it is to timely detect risk groups relying on, among other things, analysis of workers' genetic peculiarities.

This article presents a study with 140 volunteers participating in it; they had basic occupations required at contemporary butyl rubber production. It was conducted within a periodical medical examination that involved using up-to-date hygienic, clinical-laboratory and genetic methods. The study included hygienic assessment of the chemical factor at the analyzed production, examination of hematologic and biochemical blood indicators, identification of workers' genetic status as per the rs1052133 polymorphic variant of the OGG1 gene and the severity of DNA breaks.

The study revealed adverse effects produced by the chemical factors on health of workers with basic occupations based on deviations in biochemical blood indicators obtained by tests that included indicator enzyme identification, and DNA damage. Following the study results, a risk group was created as per the state of the hepatobiliary system. To preserve workers' health, it is necessary to implement certain preventive measures that include providing safe working conditions as regards the chemical factor, timely detection of risk groups and rehabilitation activities.

Keywords: *health, workers, blood, liver, polymorphic variant, OGG1 gene, DNA breaks, preventive medicine.*

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Many chemicals that are used in production can disrupt such biological processes in a cell as synthesis and modification of biomolecules, cell breathing, metabolic transformations and cellular signal transmission [1–4]. Xenobiotics entering the human body often induce formation of reactive oxygen species that stimulate lipid peroxidation primarily by impairing morphofunctional properties of cells with active metabolism, hepatocytes being among them [5–8]. Toxic effects produced by chemicals even in low concentrations induce cytotoxic and cholestatic lesions in the liver [8–19].

Oxidation of biomolecules in the liver stimulates a growing number of neutrophils in blood, which, together with other non-parenchyma liver cells, are significant sources of pro-oxidant chemical compounds able to damage DNA in other cells [8, 20]. At present, there are data available in research literature on changes in DNA molecules in leucocytes in the form of breaks, chromosome aberrations, a growing share of altered bases, micronuclei and sister-chromatid changes in workers exposed to toxicants including those employed at petrochemical productions [21–23].

Lower reparation activity due to occurring polymorphisms in a specialized group of genes is a risk factor [24, 25]. The human *OGG1* gene (chromosome 3, short arm p25.3, 9749944-9788246 b.p., plus-chain) codes 8-oxoguanin-DNA-glycosylase (the molecular mass is 38782 Da, 345 amino acids). This protein participates in reparation of double-stranded DNA molecules by cutting residual 8-oxoguanine from the DNA nucleotide chain and reducing 7,8-dihydro-8-oxoguanine and 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine [26][1]. Products of the *OGG1* gene participate in pathogenesis of many diseases, including hepatobiliary ones such as bile duct cancer, non-alcoholic fatty liver disease (NAFLD), cirrhosis, gallbladder cancer, and hepatocellular carcinoma[2].

In case the allele C is replaced with the allele G in rs1052133 polymorphism of the *OGG1* gene, we can observe changes in the protein sequence 326 as the amino-acid residue serine is replaced with the residue cysteine and this might be associated with developing hepatocellular carcinoma [27]. Patients with chronic hepatitis C and hepatocellular carcinoma much more frequently had GG genotype (Cys/Cys) and the allele G in the *OGG1* gene against the reference group together with 8-oxoguanin detected in urine [28]. An assumed reduction in reparation activity can be primarily associated with dimerization of the homozygote recessive variant (GG) of the OGG1 enzyme and its resistance to stimulation by the APE1 protein (AP-endonuclease 1) that also participates in reparation [29]. According to some other data, the occurrence of the dominant homozygote genotype CC is associated with developing lung cancer and head and neck cancer in smokers; this is probably due to a highly active OGG1 enzyme in this genotype [30].

Over the last years, DNA-comet assay has become a significant instrument for examining human health. A project called hCOMET was started by the European Comet Assay Validation Group and supported by the European Cooperation in Science and Technology in 2016. Within its implementation, it was suggested to develop

[1] O15527. OGG1_HUMAN. *UniProt: freely accessible resource of protein sequence and functional information*. Available at: https://www.uniprot.org/uniprot/O15527 (June 20, 2022).

[2] OGG1. *MalaCards: human disease database*. Available at: https://www.malacards.org/search/results?query=ogg1 (July 12, 2022).

the ComNet international database (since 2011) with information on investigations of human DNA-comets obtained from 1999 to 2019 [31].

It is quite relevant to examine molecular-genetic lesions and their reparation in workers exposed to harmful chemicals at their workplaces. Research in the area makes it possible to identify significant DNA damage at the earliest stages in development of a toxic process.

In this study, our aim was to examine a relationship between rs1052133 polymorphism of the *OGG1* gene and the state of the hepatobiliary system in workers employed at butyl rubber production.

Materials and methods. The study involved voluntary participation by 107 male workers who had a profound medical examination. They were employed at an enterprise that manufactured butyl rubber. Their age varied between 21 and 66 years. The reference group was made up of 33 engineers and technicians who were not exposed to chemical factors at their workplaces; they were of the same age as the test group. Each participating worker gave his voluntary informed consent to it.

Workers who were not exposed to chemicals at their workplaces and were included into the reference group did not differ from the workers in the test group as per their average age and work records ($p > 0.05$). Both groups did not have any statistically significant differences as per age and work records when compared with Student's t-test for independent samplings ($p > 0.05$). The test group of 107 workers included those with the following occupations: 31.78 % were operators; 34.58 %, repairmen responsible for technological equipment (TE repairmen for short); 33.64 %, repairmen responsible for control and automatic equipment (C&AE repairmen for short).

Sanitary-hygienic examinations were accomplished by using conventional procedures in accordance with the existing regulations. Clinical tests of biochemical blood indicators were performed by using standardized and unified laboratory diagnostic procedures on Humalyzer-900 Plus auto-analyzer[3]. Total blood count, including hemoglobin concentration, was performed with DREW-3 hematology analyzer (Drew Scientific, USA). Erythrocyte sedimentation rate (ESR) was identified as per Panchenkov method.

Leucocytes were extracted from workers' blood by extraction in ficoll gradient (1.077 g/cm^3, PanEko, Russia). Leucocyte micro-slides were prepared from 100 μl of a freshly extracted cellular suspense in 1 % low-melting agarose. The micro-slides were submerged into a cooled lytic salt solution (pH = 10) and kept there for 1.5–2 hours (+2 – +8 °C). Then, they were incubated for 20–25 minutes in a cooled alkaline buffer solution for further electrophoresis (pH > 13) of single cell DNA (the procedure was performed under 0.9–1 W/cm). As soon as electrophoresis completed, the microslides were fixed in ethanol, and then dried, dyed with ethidium bromide and their photos were made with Zeiss Axio Imager.D2 microscope (magnification 100x) and AxioCam MRc5 digital camera. Not less than 150 'comets' were photographed in each sample. Relative DNA contents in 'comet' tails (%) were identified with ImageJ 1.48 software (Wayne Rasband).

We used DNA in blood leucocytes extracted with Extract DNA Blood kit (Evro-

[3] Kishkun A.A. Rukovodstvo po laboratornym metodam diagnostiki [The guide on laboratory diagnostic procedures]. Moscow, GEOTAR-Media, 2007, 798 p. (in Russian).

gen, Russian Federation) to analyze rs1052133 polymorphism of the *OGG1* gene. A pair of primers (forward and reverse) and a pair of fluorescent probes that were different as per one nucleotide were created to identify G and C alleles of rs1052133 single nucleotide polymorphism in DNA sequence of the *OGG1* reparation gene.

Amplification and detection were accomplished with the Rotor-Gene Q real-time cycler (Qiagen). Optimal reaction conditions providing high fluorescence of an accumulated product were selected specifically to amplify a section in each gene and detect probe fluorescence. The resulting curves of fluorescence accumulation were analyzed with Rotor-Gene 6000 Series Software.

The research data were statistically analyzed with SPSS Statistics 25.0 software package.

Results and discussion. Butyl rubber is a most significant product manufactured with petrochemical synthesis. It is used in varied branches. Production technology for butyl rubber manufacture involves use of chemicals with general toxic, irritating and hepatotropic effects.

Workers employed at butyl rubber production are exposed to multiple adverse occupational factors, chemicals being the leading one. The chemical factor occurs due to chemicals in workplace air that produce general toxic, irritating, narcotic and hepatotropic effects. These chemicals enter workers' bodies from workplace air through inhalation and skin contacts. Major chemicals occurring in workplace air at butyl rubber production include olefins (butadiene, ethylene, isobutylene, etc.) and alkanes (methane, propane, butane, and pentane), methyl chloride, and aromatic hydrocarbons (benzene and toluene).

Working conditions of operators at butyl rubber production were ranked as hazardous, overall hazard category 3.2, as per average shift concentrations of harmful chemicals, in particular, single maximum concentrations of methyl chloride and aromatic hydrocarbons. Workplace air was polluted most intensely when some gas-involving hazardous works were performed (technological sampling, cleaning and maintaining the equipment). Chemical analysis of workplace air at workplaces of TE repairmen established that, as a rule, levels of saturated hydrocarbon did not exceed MPC during routine repairs. Levels of unsaturated hydrocarbons reached 2 MPC (35–39 % of the analyzed samples) and levels of methyl chloride were up to 3 MPC (80 % of the analyzed samples). When machinery overhaul was performed and cases of devices and pipelines were opened, levels of methyl chloride reached their peak in workplace air at TE repairmen's workplaces, up to 4 MPC. Therefore, the chemical factor was reasonably estimated at these workplaces as corresponding to hazard categories 3.2–3.3. Workplace air at C&AE repairmen's workplaces did not contain any chemicals in concentrations exceeding MPC and this made it possible to rank their working conditions as permissible ones (class 2) as per the chemical factor.

Harmful chemicals in workplace air determined the significance of hematological and biochemical blood indicators that should be analyzed in workers exposed to them. Table 1 provides the results.

Obviously, the results obtained by analyzing hematological and biochemical indicators clearly indicated there were apparent negative changes in liver indicator enzymes in TE repairmen and operators in comparison with the reference group (Table 1). The most apparent change was an increase in alanine aminotransferase activity, which was by 1.5 times higher in TE repairmen and operators than in the reference group ($p < 0.05$). We did not identify any statistically significant

Table 1

Hematological and biochemical blood indicators in workers employed at petrochemical production

Indicator	Operators	TE repairmen	C&AE repairmen	Reference group
Leucocytes, $\times 10^9$/l	7.41 ± 2.36	7.47 ± 1.43*	6.47 ± 1.34	6.46 ± 1.22
Erythrocytes, $\times 10^{12}$/l	5.03 ± 0.34	5.18 ± 0.52	5.12 ± 0.45	4.98 ± 0.39
Hemoglobin, g/l	138.79 ± 8.83	144.43 ± 7.41	140.28 ± 3.82	141.48 ± 5.67
Thrombocytes, $\times 10^9$/l	227.38 ± 36.19	225.70 ± 39.10	212.33 ± 32.93	218.36 ± 33.17
ESR, mm/hours	6.94 ± 3.83	7.30 ± 2.71	6.06 ± 1.12	6.67 ± 1.43
AST, U/l	25.24 ± 3.26	25.84 ± 3.11*	22.78 ± 1.76	23.85 ± 2.96
ALT, U/l	28.88 ± 4.26*	29.68 ± 3.33*	18.94 ± 2.53	19.76 ± 2.50
De Ritis ratio	0.89 ± 0.16*	0.88 ± 0.14*	1.21 ± 0.08	1.21 ± 0.07
γGTP, U/l	25.49 ± 1.50	26.08 ± 1.57*	24.70 ± 1.61	24.53 ± 1.59
AP, U/l	89.65 ± 5.49*	90.86 ± 3.03*	73.33 ± 3.35	72.21 ± 4.57
Cholesterol, mmol/l	4.86 ± 0.63*	5.22 ± 0.44*	4.35 ± 0.63	4.06 ± 0.40
Glucose, mmol/l	4.89 ± 0.35	5.02 ± 0.65	5.06 ± 0.34	4.91 ± 0.40
Total bilirubin, μmol/l	11.24 ± 5.32	11.62 ± 6.05	11.03 ± 3.32	10.81 ± 3.81

Note: * means statistically significant difference from the reference group ($p < 0.05$). Abbreviations: ESR is erythrocyte sedimentation rate, AST is aspartate aminotransferase, ALT is alanine aminotransferase, γGTP is γ- glutamyl transpeptidase, AP is alkaline phosphatase.

differences between hematological and biochemical indicators of C&AE repairmen and workers from the reference group ($p > 0.05$). Besides, we detected a statistically significant increase in average DNA levels in a 'comet' tail that was by 1.1–1.4 times higher in all the occupational groups of workers exposed to hepatotropic chemicals than in the reference group; this indicates clearly that these workers face increased chemicals burdens (Table 2). Median DNA levels in a 'comet' tail were by 1.2–1.4 times higher in TE repairmen and operators against the reference group ($p < 0.05$). In addition, average occurrence of 'comets' with lesions detected in more than 5 % of DNA was by 2.2 times higher in TE repairmen than the same indicator in the reference group ($p < 0.05$).

We used results obtained by amplifying the *OGG1* gene section to calculate odds ratios for impaired reparation in case a specific genotype of the rs1052133 polymorphism was identified in workers with the basic analyzed occupations. We established that the recessive G allele in the rs1052133 polymorphic variant was a risk factor for operators (OR = 4.464; 95 % CI: 1.564–12.744), TE repairmen (OR = 5.134; 95 % CI: 1.820–14.481) and C&AE repairmen (OR = 3.906; 95 % CI: 1.391–10.969) against the reference group (Table 3).

Risks of weaker DNA reparation might be associated, first of all, with dimerization of the homozygote recessive variant (GG) of the *OGG1* enzyme as it was described in literature [29].

Table 2

DNA breaks in leucocytes in peripheral blood of workers employed at petrochemical production

Group	Average DNA levels in 'comet' tails ± standard deviations, %	Median DNA levels in 'comet' tails (interquartile interval 25–75), %	Average occurrence of 'comets' with lesions detected in more than 5 % of DNA in a tail ± standard error of mean, %
TE repairmen	4.43 ± 1.31*	3.69 (2.92–3.98)*	27.30 ± 3.80*
Operators	4.09 ± 0.73*	3.45 (3.10–3.86)*	15.59 ± 3.43
C&AE repairmen	3.45 ± 0.80*	2.85 (2.46–3.25)	14.96 ± 2.08
Reference	3.28 ± 0.50	2.73 (2.38–2.94)	12.36 ± 5.16

Note: * means statistically significant difference from the reference group as per Kruskal – Wallis test ($p < 0.05$).

Table 3

Risks of impacts exerted by the G allele of the rs1052133 polymorphic variant of the *OGG1* gene on DNA reparation in workers exposed to hepatotropic chemicals

Occupation	Odds ratio	95 % CI
TE repairmen	5.134	1.820–14.481
Operators	4.464	1.564–12.744
C&AE repairmen	3.906	1.391–10.969

Therefore, in case the allele G occurs in the rs1052133 polymorphism of the *OGG1* gene, workers who have negative changes in activity of indicator enzymes and DNA lesions can be considered a risk group and should be provided with medical screening in dynamics.

Conclusions:

1. The chemical factor occurs at the analyzed workplaces due to harmful chemicals with predominantly general toxic and hepatotropic effects. Working conditions estimated as per this factor are ranked as hazardous, hazard category 3.2, at operators' workplaces and as hazardous, hazard category 3.3, at TE repairmen's workplaces.

2. Health disorders were identified in operators and TE repairmen including a significant increase in activity of such indicator enzymes as aspartate and alanine aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase against the reference group. These disorders indicate developing impairments of the hepatobiliary system under exposure to harmful chemicals.

3. We examined DNA extracted from leucocytes in workers' peripheral blood and identified increased levels of DNA breaks and damage; this can be applied as a biomarker of negative effects produced by harmful chemicals at petrochemical production.

4. We performed genetic examinations with their focus on the rs1052133 polymorphism of the *OGG1* gene; as a result, workers who have the recessive allele G in their genotype are considered a risk group as regards the hepatobiliary system (OR = 4.474; 95 % CI: 1.848–10.835).

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