THE HEPATOTOXIC POTENTIAL OF A MIXTURE OF TOLUENE, STYRENE AND ETHANOL: *IN SILICO* TOXICOGENOMIC DATA-MINING

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Organic solvents are still widely used in various industries and considered the most common chemicals associated with liver injury in workers. For research into the relationships between these chemicals and genes, interactions among chemicals, molecular pathways and biological processes, a significant place in toxicity testing has been taken by *in silico* methodologies. This study aims to provide evidence for the involvement of a selected mixture of organic solvents (toluene, styrene, ethanol) in liver disease development and show the potential of *in silico* toxicogenomic data-mining in determining possible mechanisms of mixture toxicity. The Comparative Toxicogenomics Database (CTD), GeneMania and ToppGene Suite were used for data-mining. The results showed that there were 17 genes connected with liver injury common for all the tested solvents. Co-expression (61.73%) was the most prominent interaction between the genes, while physical interactions were present at 14.56%, co-localization at 12.54% and interactions predicted by the server at 6.62%. Gene ontology analysis revealed biological processes affected by the investigated mixture (reactive oxygen species metabolic and biosynthetic process, response to oxidative stress, and response to organic cyclic compound). Oxidative stress response, antioxidant and oxidoreductase activity, vitamin B12 metabolism were noted as the key molecular pathways contributing to liver disease development. Our results emphasize the role of oxidative stress as one of the mechanisms of organic solvents' mixture toxicity and provide new insights into molecular mechanisms involved in hepatotoxicity.

HEPATOTOKSIČNI POTENCIJAL SMEŠE TOLUENA, STIRENA I ETANOLA: *IN SILICO* TOKSIKOGENOMIČKA ANALIZA

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Organski rastvarači se još uvek široko koriste u raznim industrijama i smatraju se najčešćim hemikalijama povezanim sa oštećenjem jetre kod radnika. Za istraživanje odnosa između ovih hemikalija i gena, interakcija među hemikalijama, molekularnih puteva i bioloških procesa, značajno mjesto pripada i *in silico* metodologijama. Cilj ove studije je da pruži dokaze za povezanost odabrane smeše organskih rastvarača (toluen, stiren, etanol) u razvoju bolesti jetre, i da pokaže potencijal *in silico* toksikogenomičke analize podataka u određivanju mogućih mehanizama toksičnosti smeše. Za prikupljanje podataka korišteni su *Comparative Toxicogenomics Database* (CTD), *GeneMania* i *ToppGene Suite*. Rezultati ove analize su pokazali da postoji 17 gena povezanih s oštećenjem jetre zajedničkih za sva tri navedena rastvarača. Koekspresija (61,73%) bila je najistaknutija interakcija između gena, dok su fizičke interakcije bile prisutne sa 14,56%, kolokalizacije sa 12,54%, a interakcije predviđene od strane servera sa 6,62%. Analiza ontologije gena izdvojila je biološke procese na koje utiče ispitivana smeša (metabolički i biosintetski proces reaktivnih kiseonikovih vrsta, odgovor na oksidativni stres i odgovor na organska ciklična jedinjenja). Odgovor na oksidativni stres, aktivnost antioksidanata i oksidoreduktaze, i metabolizam vitamina B12 su navedeni kao ključni molekularni putevi koji dobrinose razvoju bolesti jetre. Rezultati ovog rada naglašavaju ulogu oksidativnog stresa kao jednog od mehanizama toksičnosti smeše organskih rastvarača i daju novi uvid u molekularne mehanizme uključene u hepatotoksičnost.