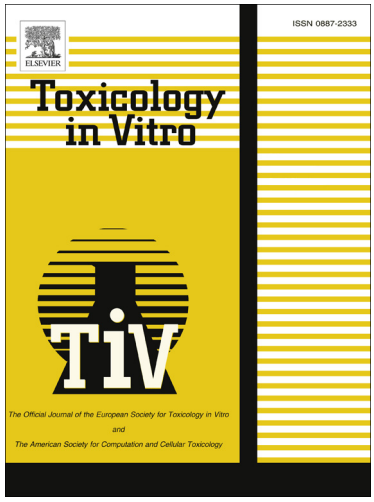

3D organotypic HepaRG cultures as in vitro models for acute and repeated dose toxicity studies

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PII: S0887-2333(13)00176-8
DOI: http://dx.doi.org/10.1016/j.tiv.2013.06.024
Reference: TIV 3144

To appear in: *Toxicology in Vitro*

Received Date: 19 October 2012
Accepted Date: 26 June 2013

Please cite this article as: Mueller, D., Krämer, L., Hoffmann, E., Klein, S., Noor, F., 3D organotypic HepaRG cultures as in vitro models for acute and repeated dose toxicity studies, *Toxicology in Vitro* (2013), doi: http://dx.doi.org/10.1016/j.tiv.2013.06.024

TIV-D-12-00557 R2

3D organotypic HepaRG cultures as in vitro models for acute and repeated dose toxicity studies

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Abstract

Predictive in vitro models alternative to in vivo animal will have a significant impact in toxicology. Conventional 2D models do not reflect the complexity of a 3D organ resulting in discrepancies between experimental in vitro data and in vivo. Using 3D HepaRG organotypic cultures we tested four drugs (aflatoxin B1, amiodarone, valproic acid and chlorpromazine) for toxic effects and compared the results with HepaRG 2D cultures and HepG2 cells. We show that 3D HepaRG cultures are more sensitive than the other tested cultures to aflatoxin B1 which is only toxic upon metabolic activation in the liver. We show that CYP3A4 activity is higher in the 3D HepaRG cultures compared to the 2D HepaRG cultures. Furthermore, we investigated repeated dose toxicity of chlorpromazine and assessed its effects on glucose and lactate metabolism. Sub-toxic concentrations of chlorpromazine induced significant metabolic changes in both 2D and 3D HepaRG cultures upon acute and repeated dose (3 doses) exposure. In summary, our data support the hypothesis that 3D cell culture models better mimic the in vivo tissue and improve cellular functionality. The HepaRG 3D organotypic cultures represent a high throughput system for drug toxicity screening. This system is therefore a promising tool in preclinical testing of human relevance which can allow reducing and/or replacing animal testing for drug adverse effects.