

Accepted Manuscript

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

Daniel Mueller, Lisa Krämer, Esther Hoffmann, Sebastian Klein, Fozia Noor

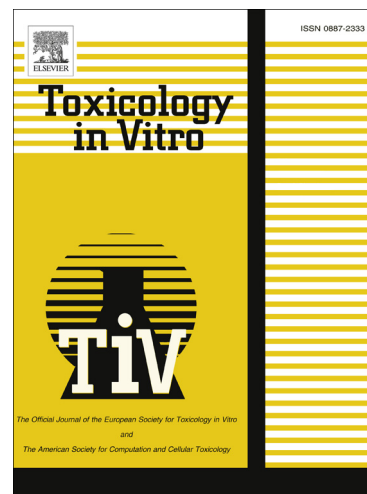
PII: S0887-2333(13)00176-8
DOI: <http://dx.doi.org/10.1016/j.tiv.2013.06.024>
Reference: TIV 3144

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>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



1 **TIV-D-12-00557 R2**

2 **3D organotypic HepaRG cultures as in vitro models for acute and repeated**
3 **dose toxicity studies**

4 Daniel Mueller, Lisa Krämer, Esther Hoffmann, Sebastian Klein, and Fozia Noor*
5 Biochemical Engineering, Campus A1 5, Saarland University, D-66123
6 Saarbruecken, Germany

7 **corresponding author*

8

9 **Abstract**

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

28

Download English Version:

<https://daneshyari.com/en/article/5862007>

Download Persian Version:

<https://daneshyari.com/article/5862007>

[Daneshyari.com](https://daneshyari.com)