Highlight report: predicting hepatotoxic oral doses of chemicals by in vitro testing and in silico modeling

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Received: 15 July 2019 / Accepted: 18 July 2019 / Published online: 25 July 2019
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Recently, a novel in vitro/in silico strategy has been published which allows the determination of oral doses of test compounds that cause an increased risk of hepatotoxicity (Albrecht et al. 2019). The novelty of this technique is that it is quantitative and allows differentiation of hepatotoxic and harmless dose ranges based on the results of an in vitro test.

A first step of this procedure is to determine the lowest concentration of a test compound that causes an adverse effect in an in vitro test battery ('alert concentration'). This test battery includes cytotoxicity and increased expression of a set of biomarker genes in cultures of cryopreserved human hepatocytes.

Next, this alert concentration is used to extrapolate to the lowest blood concentration ($C_{\max}$) that causes an increased risk of hepatotoxicity in a human population. To allow this in vitro to in vivo extrapolation, the authors established a set of data with compounds, where the $C_{\max}$ in blood is known for a specific oral dose. Moreover, it is known, whether the $C_{\max}$ of a specific compound increases the risk of hepatotoxicity or not. Based on this set of data the authors established the mathematical relationship between alert concentrations (in vitro) and the $C_{\max}$ in blood that causes an increased risk of hepatotoxicity. The alert concentrations in vitro are higher than the lowest $C_{\max}$ in blood that causes an increased risk of hepatotoxicity. Using the equation established by Albrecht et al. (2019) the alert concentration can now be used to calculate a $C_{\max}$ that causes an increased risk of hepatotoxicity in humans.

The third step is to determine the oral doses in repeated exposure scenarios that lead to the corresponding $C_{\max}$ (as determined in the previous step). This is achieved by reverse pharmacokinetic modeling. Depending on the availability

and quality of physico-chemical and pharmacokinetic data this final step may still be associated with a certain degree of uncertainty.

Hepatotoxicity represents an active field of research (Sisung et al. 2019; Grinberg et al. 2014; Stöber 2016) and much effort has been invested to establish adequate in vitro and in silico methods (Grinberg et al. 2014, 2018; Godoy et al. 2016, 2018; Gu et al. 2018; Frey et al. 2014). However, hepatotoxicity in vivo represents a complex process (Ramachandran and Jaeschke 2019; Woolbright and Jaeschke 2018; Hammad et al. 2014, 2017). While hepatocytes often are the primary target (Ghallab et al. 2016, 2019; Leist et al. 2017) initial key events may also occur in cholangiocytes (Jansen et al. 2017; Vartak et al. 2016) or may be mediated by immune cells (Mossanen et al. 2016; Godoy et al. 2013; Reif et al. 2017). Therefore, predicting such complex processes by in vitro in silico methods it is a major challenge. The technique of Albrecht et al. (2019) has now been applied to 36 compounds and allowed surprisingly accurate predictions of hepatotoxic blood concentrations. It will be interesting to learn more about the accuracy of the method when a larger number of compounds will have been studied.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

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