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EDITORIAL

Highlight Report: humanized mice reveal interspecies differences in triclosan hepatotoxicity

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Recently, Yangshun Tang and colleagues from the U.S. Food and Drug Administration in Jefferson contributed an interesting article about the hepatotoxicity of triclosan (Tang et al. 2018). Triclosan is an antimicrobial compound used, e.g., in toothpaste, detergents, soap, and toys. It has been detected in human plasma at concentrations ranging between 0.035 and 1.2 µM (Allmyr et al. 2008; Hovander et al. 2002; Olaniyan et al. 2016) and is also found in breast milk and urine (Adolfsson-Erici et al. 2002; Dayan 2007; Olaniyan et al. 2016; Calafat et al. 2008). At doses of 100 mg/kg/day, triclosan causes hepatotoxicity in mice (Rodricks et al. 2010). It has also been shown that triclosan activates PPARα of mice and humans in vitro (Wu et al. 2014). However, it remained unclear whether activation of PPARα plays a similar role for induction of hepatotoxicity for mouse and human.

To answer this question, Tang and colleagues used PPARα-humanized mice and compared them to the corresponding wild-type animals (Tang et al. 2018). In both wild-type and PPARα-humanized mice, triclosan induced PPARα target genes, such as cytochrome P4504A and acyl-coenzyme A oxidase 1; similarly, elevated expression of peroxisomal genes was observed in mice of both genotypes (Tang et al. 2018). However, an increase in liver weight due to triclosan exposure was observed only in wild-type mice and not in PPARα-humanized mice. In addition, increased expression of proliferation associated genes was obtained only in wild type but not in humanized mice (Tang et al. 2018). This demonstrates that the activation of PPARα has different consequences in humans and in mice, which was also confirmed by analysis of BrdU incorporation.

A better understanding of the mechanisms of hepatotoxicity represents an important research focus in toxicology (Vartak et al. 2016; Weng et al. 2014; Bolt 2017; Ghallab et al. 2016; Hammad et al. 2014; Bystrom et al. 2017; Stöber 2016) and extrapolation of the results of mouse experiments to humans remains a challenge (Leist et al. 2017; Thiel et al. 2015; Jansen et al. 2017). One possibility is the use of primary hepatocyte cultures that allow the comparison of susceptibility of both cell types. However, this type of research is hampered by changes of hepatocyte physiology due to the isolation and cultivation process (Godoy et al. 2013, 2016; Grinberg et al. 2014).

Tang and colleagues are to be congratulated for their elegant approach to study interspecies differences. They give a clear explanation why mice show a hepatocyte proliferation response to triclosan exposure that is not seen in humans.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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