To the Editor:

We enjoyed reading the excellent and stimulating paper of Ørntoft et al., describing the intrahepatic kinetics of a novel 11C-labelled bile acid analogue, 11C-CSar before and after food consumption. They performed linear least squares computerised modelling to obtain $K_1$, defined as the unidirectional clearance of 11C-CSar from sinusoidal blood into hepatocytes, and the rate constants that respectively govern tracer movement from hepatocytes back into blood ($k_2$), from hepatocytes into bile canaliculi ($k_3$) and from liver tissue to extrahepatic bile ($k_5$). Transport from the bile canaliculus to hepatocytes ($k_4$) is assumed not to take place.

Extraction efficiency of tracer from blood to hepatocyte ($E_0$) was almost 100%, so $K_1$ is equal to hepatic perfusion. $K_1$ was almost identical to total hepatic blood flow (derived from indocyanine green clearance) divided by total hepatic volume ($Q$). From its method of measurement, hepatic volume will include hepatic blood volume, which in a seminal paper by the same group was determined to be 25% of total liver volume. In contrast, $K_1$ is obtained from modelling in units of ml/min per hepatocyte volume. Because the sinusoidal endothelium is highly permeable, interstitial volume, which this group estimated to comprise another 15% of total volume, can be added to the blood volume to give a so-called extended blood volume of 40%. $Q$ should, therefore, have been about 40% less than $K_1$, but they were found to be equal.

There are 3 further aspects of the study that we hope Ørntoft et al. would kindly comment on.

Firstly, based on histological measurements, bile duct volume has been set as 3.2 ml/L liver tissue. This value is based on a limited dataset ($n = 5$) and showed substantial inter-subject variability, with the uncertainty on fractional duct volume being around 50%. It is questionable whether or not this is a reasonable term to fix in the model, without some validation of the robustness of the model in response to variation in this value of bile duct volume.

Secondly, a fasting $k_3$ value as high as 0.4 min$^{-1}$ and a $k_2$ value of 0.1 min$^{-1}$ give a $k_3/k_2$ ratio of 40, rising to 223 after fasting. From compartmental analysis, we find in comparison a corresponding ratio for the 99mTc-labelled organic anion hepatobiliary iminodiacetate (99mTc-HIDA) of about unity. A high ratio such as 40 should give a mono-exponential blood clearance curve, but the arterial curves in Fig. 2 of the study of Ørntoft et al., especially fasting, give a strong impression of being bi-exponential (ignoring the 1 min point), as they are with 99mTc-HIDA.

Indeed, estimation by eye of individual values in the upper panel of their Fig. 2 gives a second exponential rate constant of about 0.07 min$^{-1}$, not dissimilar to 99mTc-HIDA.

Finally, $k_5$ should be the same for 11C-CSar and 99mTc-HIDA. With a value as low as 0.07 min$^{-1}$, $k_5$ for 99mTc-HIDA would be expected to lower the rate constant ($x_2$) of the declining phase of the hepatic time-activity curve. Because it is disconnected...
from the blood curve, a low but variable $k_5$ should abolish any correlation between $\alpha_2^b$ and the rate constant ($\alpha_2^b$) of the second exponential of the corresponding blood time-activity curve. Yet $\alpha_2^h$ and $\alpha_2^b$ are not only similar but, more importantly, correlate with each other, in keeping with a 2-compartment model with ‘run-off’ into bile, as previously proposed, in which $k_5$ is high enough to have minimal influence on $\alpha_2^h$. This correlation is not the result of basing $\alpha_2^h$ on a small peripheral ‘parenchymal’ region of interest (ROI) with a small bile volume because, at least in a healthy liver with no intrahepatic bile duct dilatation, small parenchymal and global hepatic ROIs give very similar values of $\alpha_2^h$ (Fig 1). Thus, it is difficult to see how $k_5$ could be so low. If $k_5$ is indeed higher, then bile flow rate will have been underestimated.

**Financial support**
Neither the work reported in this submission, nor the contributors, received any financial support.

**Conflicts of interest**
The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

**Authors’ contributions**
NH analysed data and produced the figure. AMP wrote the submission.

**Supplementary data**
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100357.

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