Archives of Toxicology (2019) 93:1769–1770
https://doi.org/10.1007/s00204-019-02480-z

LETTER TO THE EDITOR, NEWS AND VIEWS

# Comment on 'Kim, S.-J., Choi, E.-J., Choi, G.-W., Lee, Y.-B., and Cho, H.-Y. (2019). Exploring sex differences in human health risk assessment for PFNA and PFDA using a PBPK model, Arch Toxicol 93:311–330'

**Christoph Hethey[1] · Hans Mielke[1] · Ursula Gundert-Remy[1]**

Received: 17 April 2019 / Accepted: 14 May 2019 / Published online: 29 May 2019


In the absence of human-specific data, animal data have been used to establish a physiology-based pharmacokinetic (PBPK) model and to extrapolate findings from animals to humans. Kim et al. studied perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), two perfluoroalkyl substances, and stated marked sex differences in humans, based on in the kinetics of the two substances in rats.

The publication deserves two major critics: (1) the structural model they have set up is not in conformity with the physiological processes for renal clearance—we show that based on the data reported in their publication; and (2) the allometric extrapolation from rats to humans does not take into consideration marked interspecies differences in the activity of kidney transporters, which preclude this extrapolation step.

To point (1), when developing a PBPK model, the processes for absorption, distribution and excretion have to be taken into consideration. With respect to modelling urinary excretion, Kim et al. exclusively account for glomerular filtration and tubular reabsorption of PFNA and PFDA.

However, in female PFNA treated rats, the renal plasma clearance (CLren = 0.0265 L/day/kg) of the unbound fraction in plasma (fu) exceeds the glomerular filtration rate (GFR) or equivalently CLren > GFR × fu. We calculated CLren based on the reported values for dose, fraction excreted in urine and area under the plasma concentration time curve.

Hence, the PBPK model for PFNA needs to account for the process for tubular secretion, at least for the female rats, which the authors of the commented article did not.

Point (2) is the extrapolation of the transporter activity by simple allometric scaling. It is well known that kidney transporters may have pronounced species-specific expression and that some transporters are sex specific in rats, but not in other species, including man (Sabolic et al. 2011). For other perfluoroalkyl substances, like perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), sex-specific renal clearance has been reported for rats (Harada et al. 2005), involving OAT2 and OAT3. These anion transporters are not sex specific in humans (Sabolic et al. 2011). Hence, sex-specific differences in renal clearance do not directly translate from rats to humans. Indeed, sex had no significant impact on plasma half-life in humans, despite the described sex differences in rats for PFOS, PFOA, and also for perfluorohexanesulfonate (PFHS) (Harada et al. 2005; Olsen et al. 2007).

Insofar, it is scientifically not well supported to propose sex differences for the renal clearance of PFNA and PFDA in humans by simple extrapolation from rat data.

In conclusion, for a meaningful result in PBPK modelling, the underlying physiological processes have to be elucidated before setting up a structural model. Considering known species differences in physiology precludes naïve extrapolation from animals to humans and helps to avoid wrong assumptions in risk assessment.

## Compliance with ethical standards

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



This comment refers to https://doi.org/10.1007/s00204-018-2365-y.

✉ Christoph Hethey
christoph.hethey@bfr.bund.de

[1] German Federal Institute for Risk Assessment (BfR), Berlin, Germany

## References

Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A (2005) Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ Res 99:253–261

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR (2007) Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115:1298–1305

Sabolic I, Breljak D, Ljubojevi M, Brzica H (2011) Are mice, rats, and rabbits good models for physiological, pharmacological and toxicological studies in humans? Period Biol 113:10