Evaluation of the generic Physiologically Based Pharmacokinetic Model (PBPK) for Organophosphate Flame Retardants (OPFRs) and Neurotoxic Risk Assessment in Children

Deepika Deepika[1], Raju Prasad Sharma[1], Helena García-Cortés[2], Beatriz González-Alzaga[2,3,4], Antonio F. Hérnandez[5,6], Marina Lacasaña[2,3,4,5], Marta Schuhmacher[1], Vikas Kumar[1]*

[1]Environmental Engineering Laboratory, Departament d' Enginyeria Quimica, Universitat Rovira i Virgili, Tarragona, Catalonia, Spain

Introduction

- ✓ The usage of Organophosphate flame retardants (OPFRs) is increasing as plasticizers in consumer products and construction material after ban on brominated flame retardants[1].
- ✓ There are limited literature studies on OPFRs but in-vitro and in-vivo studies suggested their reproductive and neuronal adverse effects, especially on thyroid function and brain[1,2].
- ✓ Currently there are no in-silico models like the physiologically based pharmacokinetic model (PBPK) for OPFRs to evaluate toxicokinetics and understand their accumulation in humans based on limited experimental data.
- ✓ **The objective of this study was to develop a PBPK model for three OPFRs in rats and humans: TDCIPP, TCIPP, and TCEP and conduct a dosimetry IVIVE-based risk assessment for estimating risk in children.**

Methodology

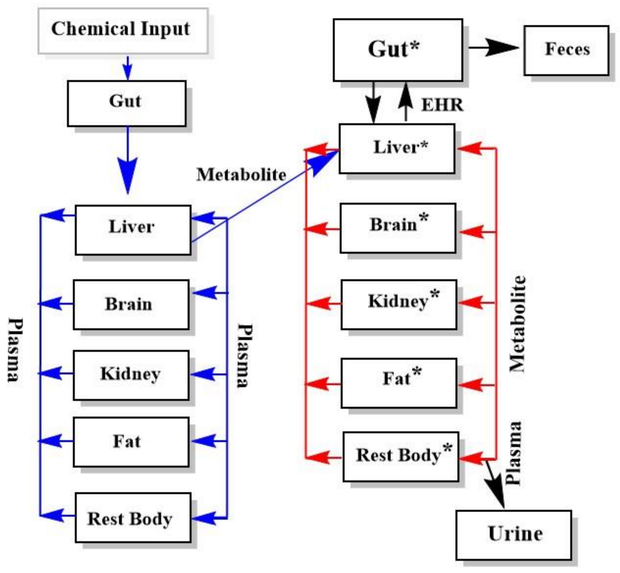

Figure 1: PBPK Model for three OPFRs with seven compartments. Enterohepatic recirculation (EHR) of the metabolite was included in the model. * represents the respective metabolite getting circulated inside the human body.

Equation for perfusion limited model:

$$\frac{dC_i}{dt} = \frac{Q*C_p - \frac{C_i}{Ki:p}}{V_i}$$

Here, C_i refers to the concentration in the particular compartment i (ug/L), Q represent blood flow in that compartment, Cp represents concentration in plasma, Ki:p denotes partition coefficient of that compartment in relation to plasma and Vi is the volume of the compartment.

Rat PBPK Model

- ✓ A seven compartment rat PBPK model was developed for three OPFRs (TDCIPP, TCIPP and TCEP) along with their major metabolites (BDCIPP, BCIPP and BCEP).
- ✓ Few biochemical parameters like absorption rate, elimination rate etc. were optimized using Markov Chain Monte Carlo (MCMC).
- ✓ Partition coefficient ($Ki:p$) was calculated through AUC (eq. 1)

$$Ki:p = \frac{AUC_{Organ\ (0:24hours)}}{AUC_{Plasma\ (0:24hours)}} \quad \text{eq. 1}$$

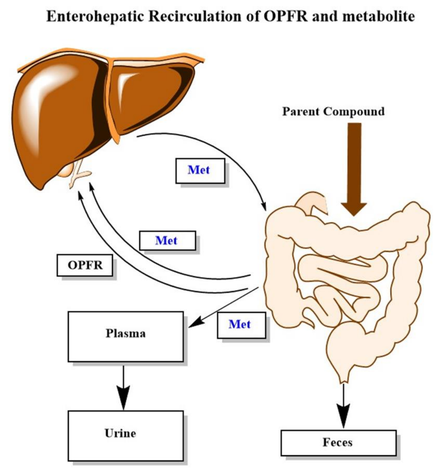

Figure 2: Enterohepatic Recirculation (EHR) between gut and liver for OPFRs. Parent compound is getting transformed into metabolite in liver and then the respective metabolite is getting circulated from liver to gut and gut to liver. Transformation of parent compound to metabolite is very quick in OPFRs.

Human PBPK Model

- ✓ Rat PBPK model was extrapolated to humans (infants).
- ✓ Due to the non-availability of human data, biochemical parameters were considered the same as rats.
- ✓ Daily intake was reconstructed based on urine data from the cohort.

Result

Model evaluation with Rat Data for TDCIPP

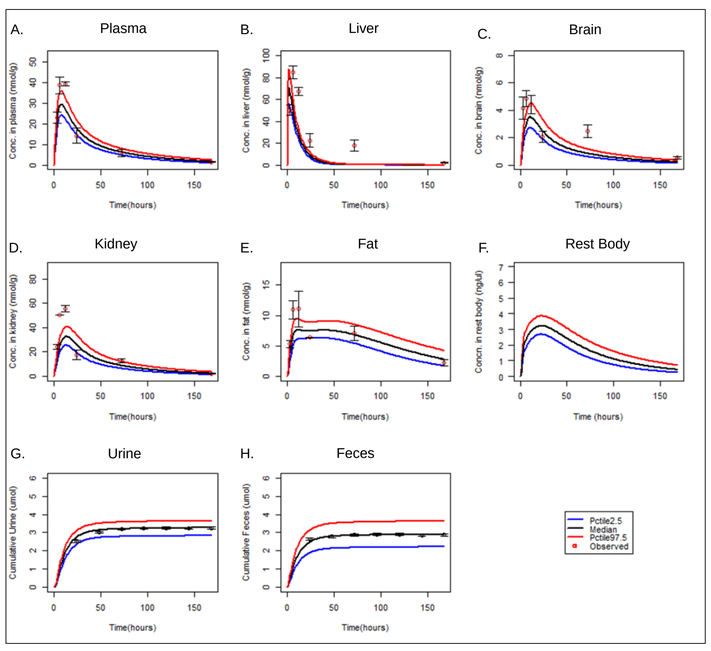

Figure 3 represents the concentration-time profile for TDCIPP in several organs.

- ✓ Simulated data was within two folds of experimental data at 50 µg/Kg BW/day.
- ✓ The model was not able to capture C_{max} for kidneys but the last time points were captured.

Model evaluation with Rat Data for TCIPP and TCEP

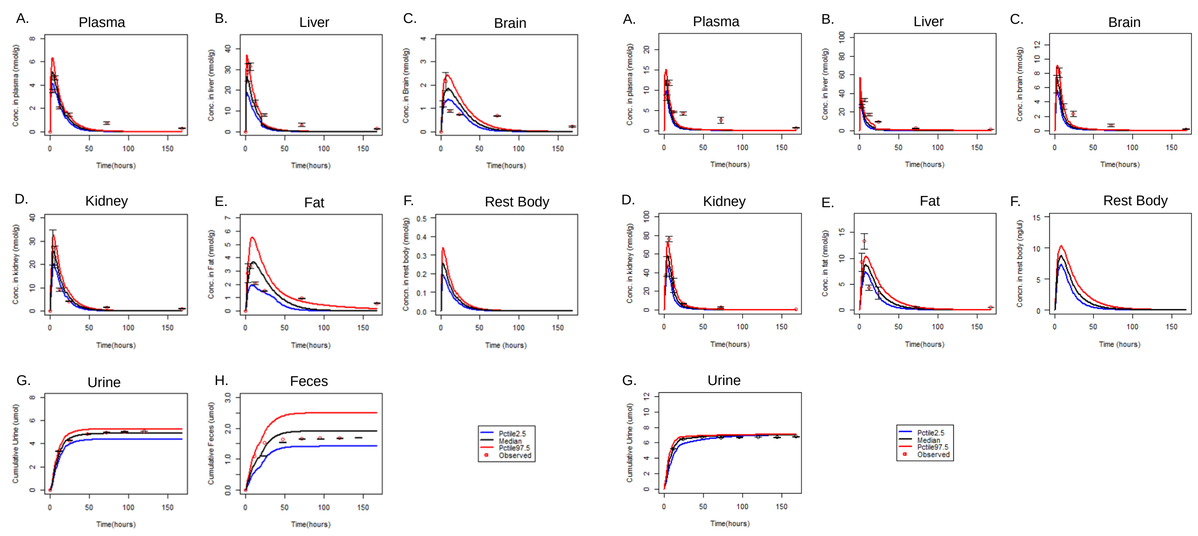

Figure 4 represents the concentration-time plot for TCIPP at the dose of 50 µg/Kg BW/day.

- ✓ A higher amount of compound was being eliminated in urine than in feces.
- ✓ Plasma concentration was lower than TDCIPP at the same dose.

Figure 5 represents the concentration-time plot for TCEP.

- ✓ TCEP gets majorly eliminated in the urine (90%).
- ✓ Elimination from brain and adipose is also fast compared to TDCIPP and TCIPP which is in correlation with log Ko/w.

Application of PBPK for Health Risk Assessment

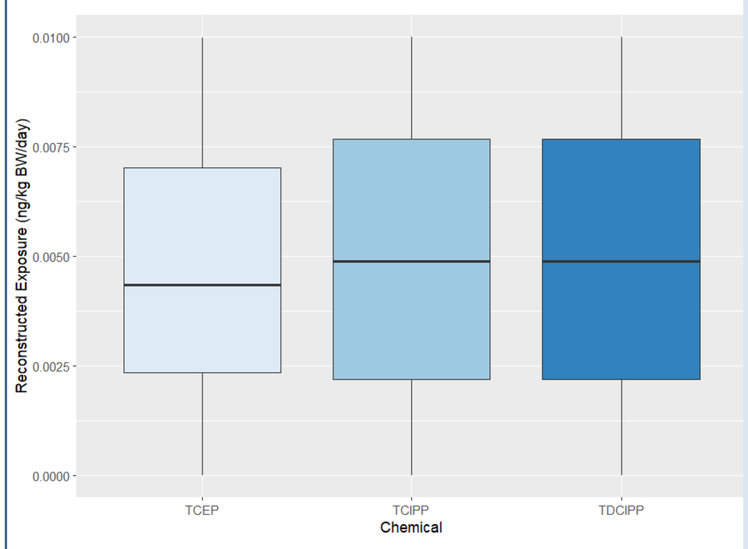

Fig 6: Reconstructed Exposure in children.

- ✓ Exposure was reconstructed by taking urine data from children of the Geneida cohort as input.
- ✓ Reconstructed exposure was the same for TDCIPP and TCIPP.
- ✓ In most of the children, BCIPP and BCEP were below the LOD.
- ✓ Oral RfD was 7000 (TCEP)[4], 10000 (TCIPP)[4], and 15000 ng/Kg BW/day (TDCIPP)[5] as per literature which is higher than reconstructed exposure.
- ✓ The low estimated daily intake for all three chemicals suggesting that children may not be prone to risk upon daily exposure.

Conclusions

- ✓ All three OPFRs showed a longer half-life with the chemical being detected after 168 hours of single administration to rat.
- ✓ OPFR showed higher distribution in kidney and liver while slow elimination in the brain and adipose tissues pointing towards their toxic potential in these organs
- ✓ Reconstructed exposure in children (2 years) was lower for TCEP compared to TDCIPP and TCIPP.
- ✓ In the future, the reconstructed exposure can be associated with the neurotoxic outcome by coupling PBPK with the pharmacodynamic model.

Acknowledgment

This work was supported by Spanish Ministry of Science and Innovation and European Union [EarlyFOOD project, grant number PCIN-2017-012].

References

1. Blum et al., Environ Sci, 10.1021/acs.estlett.9b00582.
2. Du et al., Environ Sci, 10.1007/s11356-019-05669-y.
3. Smirnova et al., altex, 10.14573/altex.1403271.
4. Zhang et al., SOT, 10.1016/j.scitotenv.2019.135995.
5. Li et al., Env. Int., https://doi.org/10.1016/j.envint.2019.03.009.

Abbreviations: TDCIPP: Tris(1,3-dichloropropyl) phosphate, TCIPP: Tris(1,3-dichloropropyl) phosphate, TCEP: Tris(2-chloroethyl) phosphate, IVIVE: In-vitro to in-vivo extrapolation

www.tecnatox.cat

[2]Andalusian School of Public Health, Granada, Spain
[3]Andalusian Health and Environment Observatory, Granada, Spain
[4]Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Granada, Spain
[5]Ciber of Epidemiology and Public Health (CIBERESP), Madrid, Spain
[6]Department of Legal Medicine, Toxicology and Physical Anthropology, University of Granada, Granada, Spain.