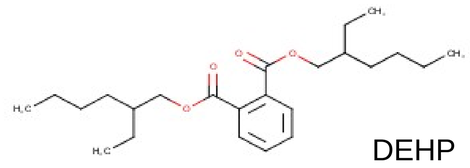
A review of phthalate pharmacokinetics in human and rat: what factors drive phthalate distribution and partitioning?

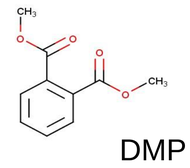
Elena Domínguez-Romero[1]* and Martin Scheringer[1]

[1]Research Centre for Toxic Compounds in the Environment (RECETOX), Masaryk University, Faculty of Science, Kamenice 753/5, 62500 Brno, Czech Republic. E-mail: elena.dominguez-romero@recetox.muni.cz

Introduction



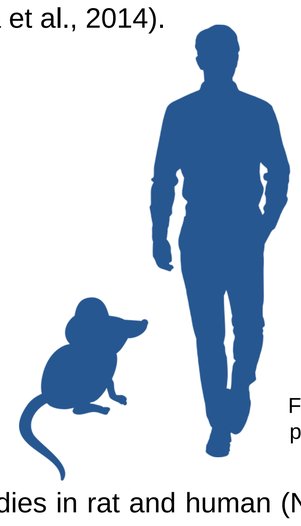
DEHP



DMP

Figures from ECHA

- **Phthalates** are a class of compounds that have been extensively used as plasticizers in different applications.
- Several phthalates have been recognized as substances of very high concern (**SVHCs**) in the EU, because of their toxicity for reproduction. However, high amounts of other phthalates and related plasticizers are still produced and imported in the European Economic Area.
- In China and the US, recent studies show **increasing concentrations of several phthalates in the air and in human urine**, respectively (Chen et al., 2012; Zota et al., 2014).
- The understanding of phthalate absorption, distribution, metabolism and elimination ('pharmacokinetics') in the organism is still limited.
- Specifically, **phthalate partitioning among tissues is insufficiently understood**. Reported partition coefficient (PC) values for phthalates show a high variability.



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Objectives

- To **analyze the steady-state partitioning of phthalates** and **compare different estimation methods** (algorithms, *in vivo*, *in vitro*).
- To review available data on absorption, distribution, metabolism and elimination of different phthalates and related plasticizers in human and rat.

Material and methods

Literature search and data compilation Based on the Web of Science. **Data from 133 publications** were compiled and analyzed, including: experimental studies in rat and human (N=85), PBPK models in rat and human (N=4) and development of algorithms for PC estimation (N=5).

PC estimation

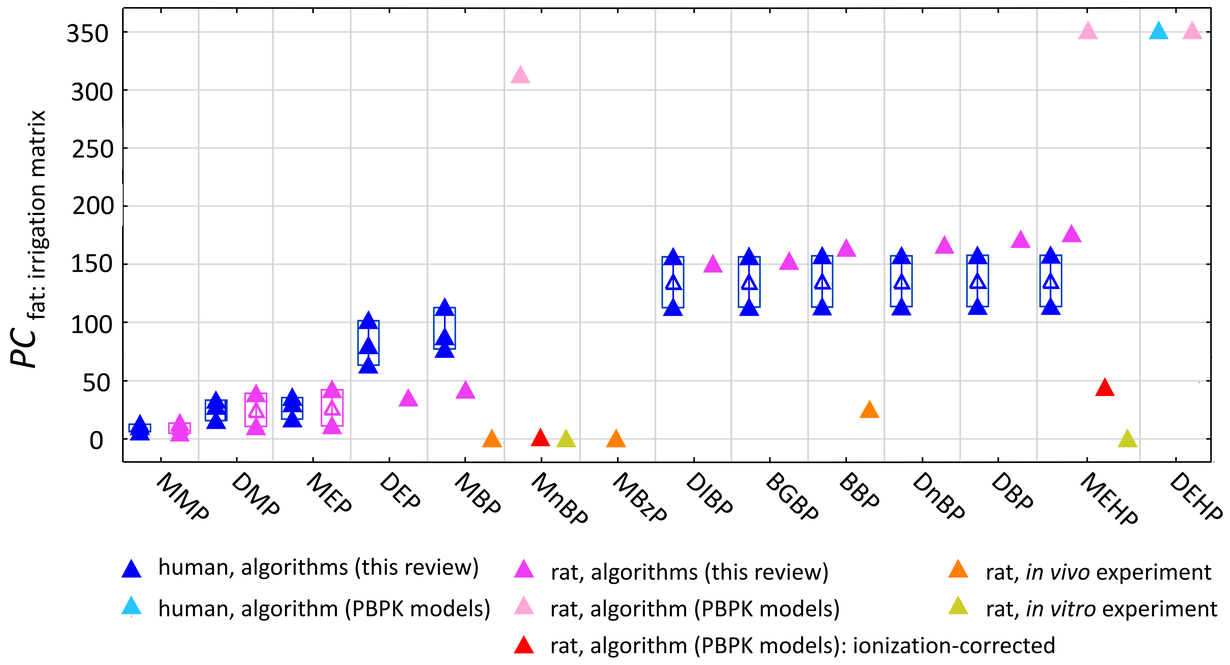
- **Experimental**: ***In-vivo*** data after extended exposure, followed by sampling within a few hours (2 h) of last dosing.
  In-vitro data at steady state, application of the "Vial equilibration method" (Murphy et al., 1995; Keys et al., 1999)

$$PC_{tissue:\,blood} = \frac{C_{phthalate\_tissue}}{C_{phthalate\_blood}}$$

- **Algorithms:** **5 algorithms** (Poulin and Krishnan, 1995a, 1995b; Fiserova-Bergerova and Diaz, 1986; Balaz and Lukacova, 1999; DeJongh et al., 1997)
  Calculations based on **hydrophobicity (Kow)** and **tissue composition**
  11 phthalates with log Kow between 1.1 (MMP) and 4.7 (MEHP), i.e. comprised within the **applicability domain of hydrophobicity** of the algorithms

Results and discussion

PC values



Number of *PC* values (N) = 52 in fat; 50 in liver, 10 to 42 in other tissues. Few experimental *PC* values at steady state were found.

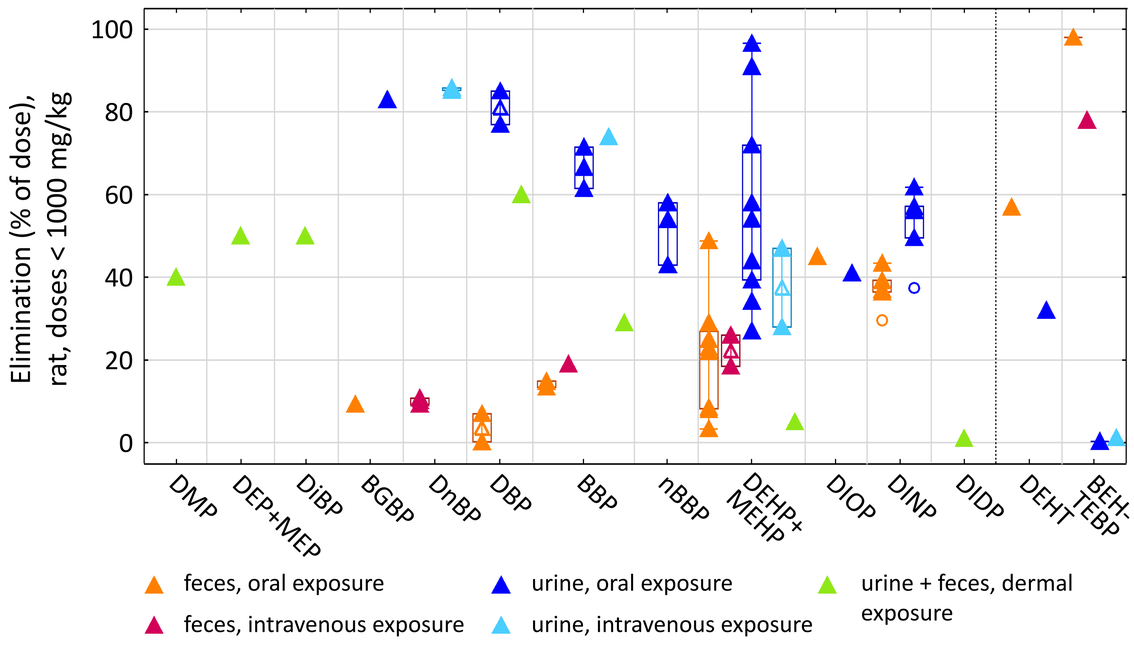
Measured (experimental) and algorithmically estimated *PC* values show strong and systematic differences. **Different factors determined the *PC* values** in each estimation method and explained the variability in PC values:

Algorithmic *PC* values >> **Experimental *PC* values**

- Hydrophobicity
- **Hydrophobicity**
- **Ionization**
- **Metabolism**
- **Binding to plasma proteins**

More data needed

Elimination in urine and feces



Number of compiled values (N) = 82. Cumulative elimination (% dose) in urine and feces for 24–72 h (oral, intravenous), or for 5–7 d (dermal)

Factor of influence	Total elimination in urine + feces	Elimination in urine	Elimination in feces
↑ Hydrophobicity	↓ (D)	↓ (O and IV)	↑ (O and IV)
Exposure route	O and IV > D	-	-

Exposure routes: oral (O), intravenous (IV), dermal (D)

Conclusions

- **Four main processes drive phthalate distribution, i.e. binding, ionization, passive partitioning, and metabolism in tissues.**
- We recommend the ***in vitro "vial equilibration"* method** by Murphy et al. (1995) to estimate phthalate *PC* values (or rather "distribution factors"), if possible for parent phthalates and their metabolites. More *in vitro* measurements of phthalate **binding** are also needed.
- The **exposure route** has an influence on some pharmacokinetic steps, for example in elimination. More data after inhalation or dermal exposure would be useful.
- The **hydrophobicity** has an influence on phthalate distribution, elimination, and globally on all phthalate pharmacokinetic steps. More pharmacokinetic data for less hydrophobic dimethyl phthalate (DMP) and diethyl phthalate (DEP), as well as for very hydrophobic diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and similar phthalates are needed.

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