

# Plasticizers in medical devices

- Exposure assessment of infants following cardiac surgery

E. Eckert, F. Münch, J. Müller, C. Höllerer, R. Cesnejvar, T. Göen

**IPASUM**  
Institute and Outpatient Clinic  
of Occupational, Social and Environmental Medicine

Universitätsklinikum  
Erlangen



**FAU**

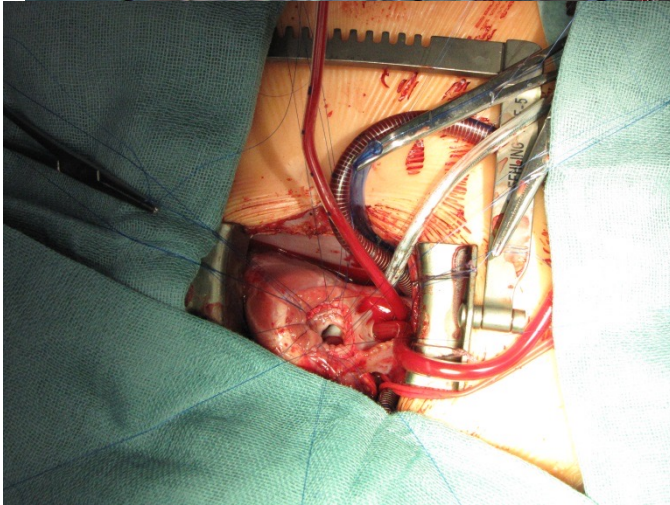
FRIEDRICH-ALEXANDER  
UNIVERSITÄT  
ERLANGEN-NÜRNBERG  
FACULTY OF MEDICINE

- Plastic medical devices are essential equipment in hospitals used for tubings, blood bags, infusion bags, syringes, etc.
- Plasticizer content in plastic material often ranges from **20 to 40 % per weight** → gain of improved flexibility, durability
- Plasticizers are not chemically bound → patient **exposure due to migration** in possible

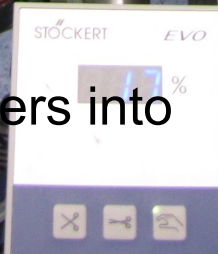
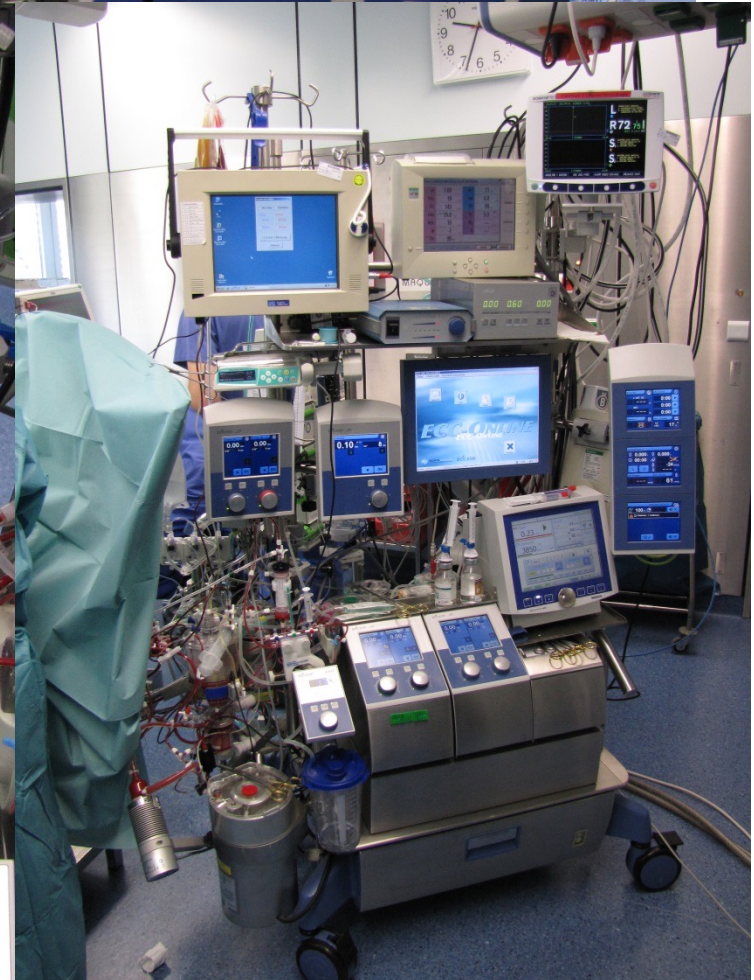


# Plasticizers in medical devices

medical disposables  
during pediatric cardiac surgery using  
cardiopulmonary bypass (CPB)

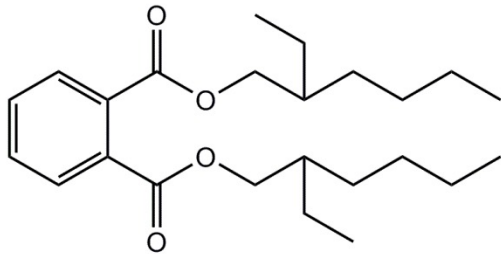


large surface  
elevated migration of plasticizers into  
blood

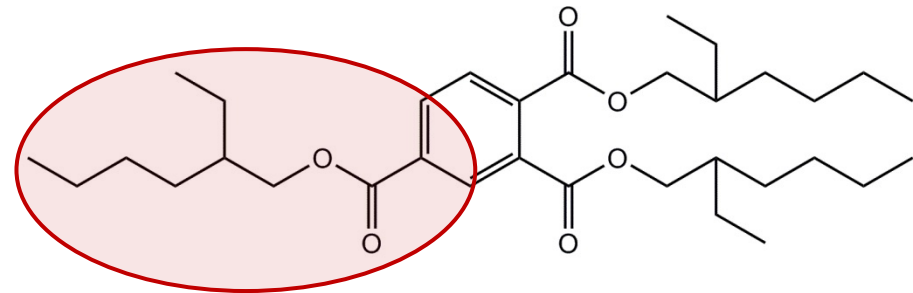


## Comparative evaluation of plasticizer migration rates into blood

- CPB equipped with different tubing sets:
  - (1) DEHP plasticized tubings
  - (2) TEHTM plasticized tubings

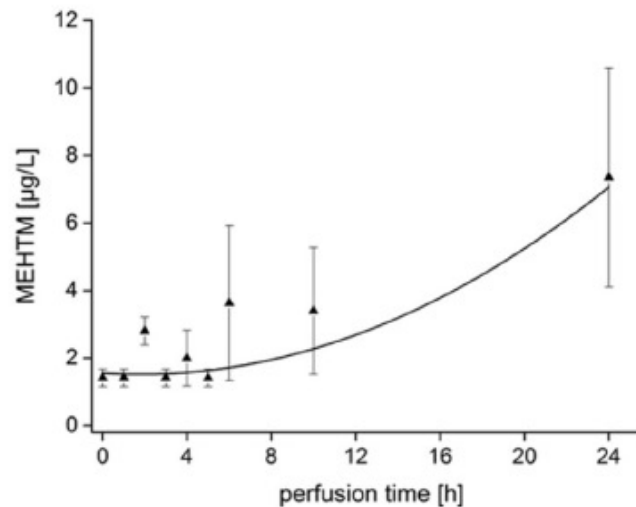
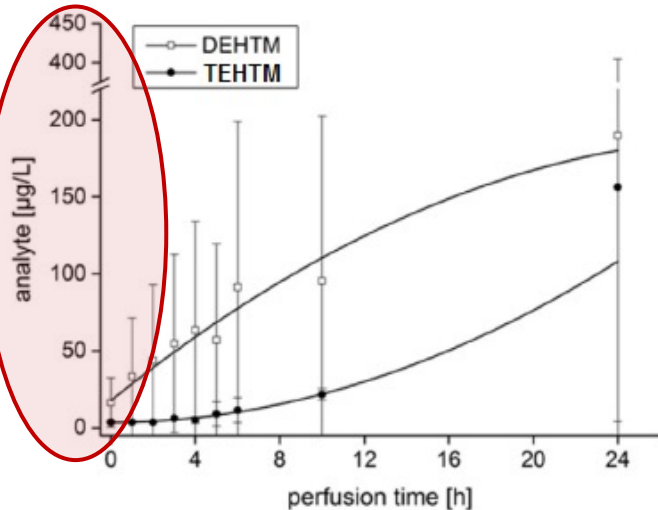
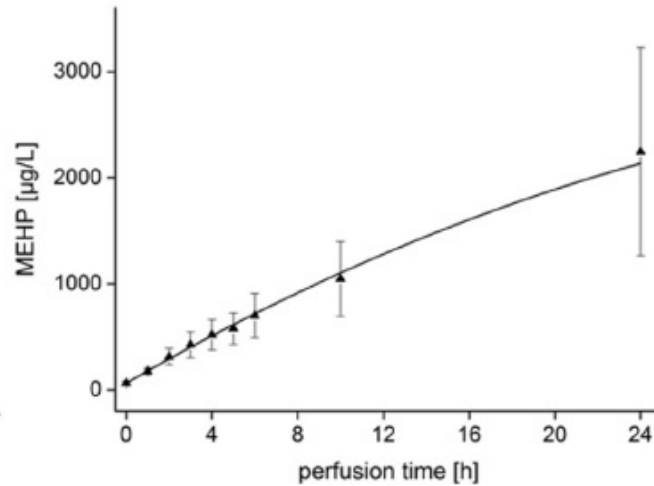
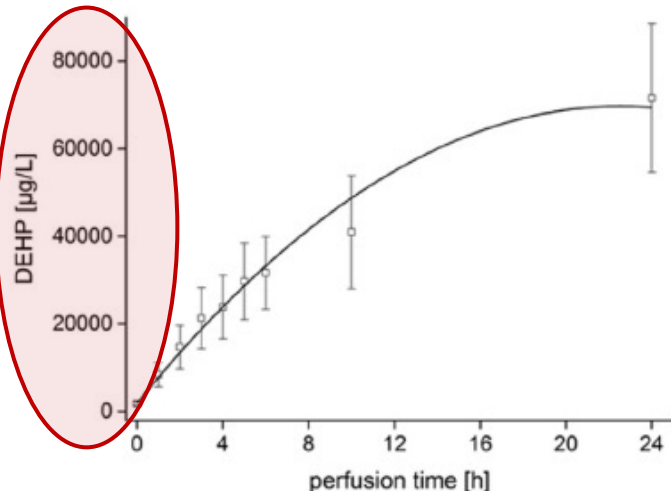


Di-(2-ethylhexyl) phthalate (**DEHP**)



Tri-(2-ethylhexyl) trimellitate (**TEHTM**)

# In-vitro study plasticizer migration



Migration rate of DEHP is **more than 350-fold higher** than of TEHTM

*E. Eckert, F. Münch, T. Göen, A. Purbojo, J. Müller, R. Cesnejvar (2016): Comparative study on the migration of DEHP and TOTM into blood from PVC tubing material of a heart-lung machine. Chemosphere 145, 10-16.*

Migration rate of DEHP **more than 350-fold higher** than of TEHTM

■ Toxicological classification of DEHP:

- possibly carcinogenic to humans (Group 2B, IARC)
- Carinogen category 4 (DFG)
- other critical effects: developmental toxicity, effects on fertility
- TDI: 50 µg/kg body weight (EFSA)



■ Toxicological classification of TEHTM:

- few data available → indicating low acute and chronic toxicity
- TDI: 1130 µg/kg body weight (Danish EPA)

Switch to **exclusive use of TEHTM containing blood tubes** on pediatric cardiology in university hospital Erlangen

## Study design

- In-vitro study: incubation of TEHTM and the DEHTM isomers with porcine liver esterase
- Pilot human study: oral exposure of four volunteers with TEHTM



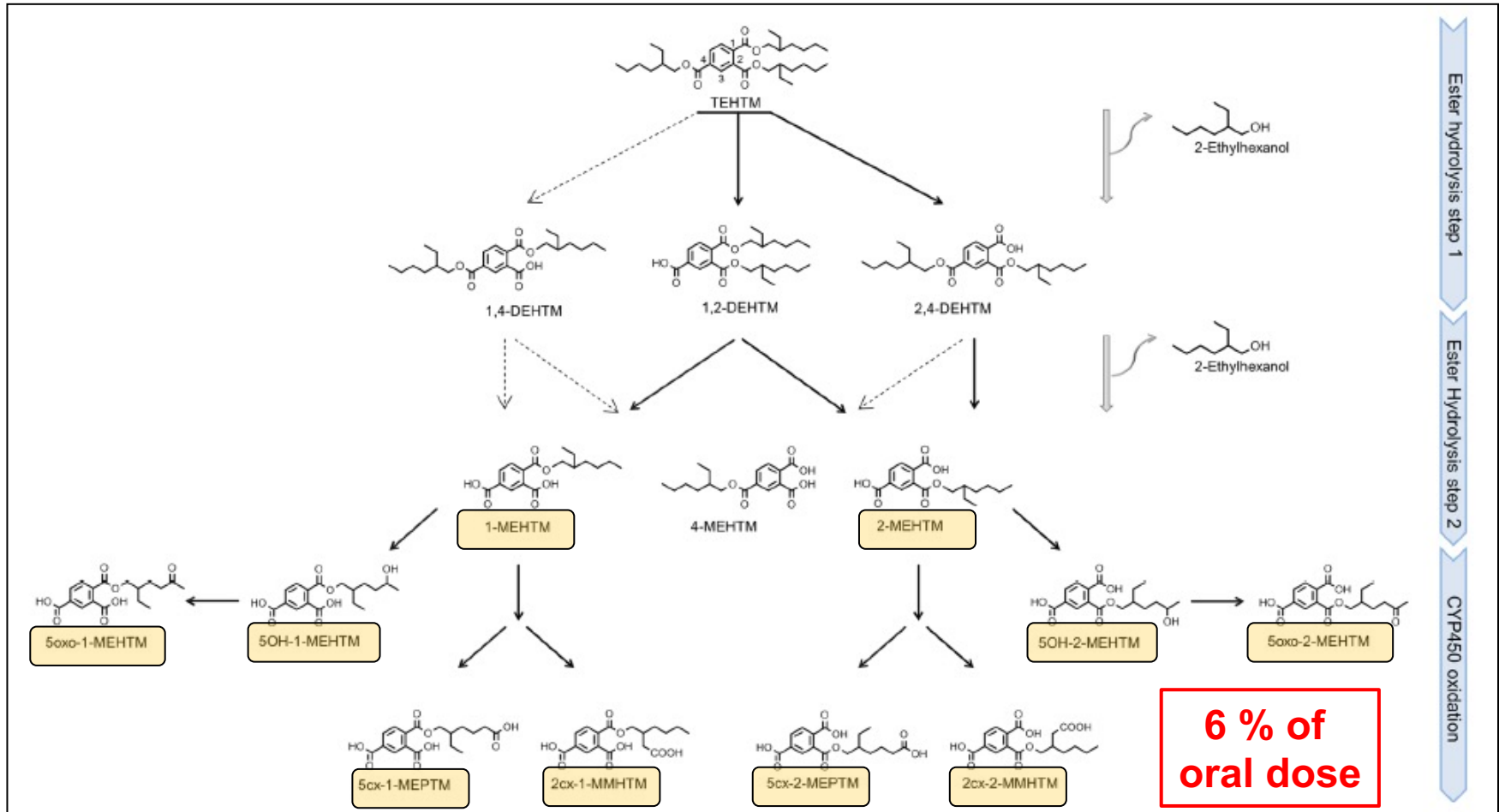
## Results

- Regioselective metabolism of TEHTM
- TEHTM is slowly metabolised with a presumably low resorption rate
- Development of biomonitoring methods for TEHTM in blood and urine

*C. Höllerer, G. Becker, T. Göen, E. Eckert (2018): Regioselective ester cleavage of di-(2-ethylhexyl) trimellitates by porcine liver esterase. Toxicology in Vitro 47, 178-185.*

*C. Höllerer, T. Göen, E. Eckert (2018): Comprehensive monitoring of specific metabolites of TEHTM in urine by column-switching LC-MS/MS. Anal Bioanal Chem 410, 4343-4357.*

# TEHTM metabolism study



C. Höllerer, G. Becker, T. Göen, E. Eckert (2018): Human metabolism and kinetics of TEHTM after oral administration. *Arch Toxicol* 92, 2793-2807.



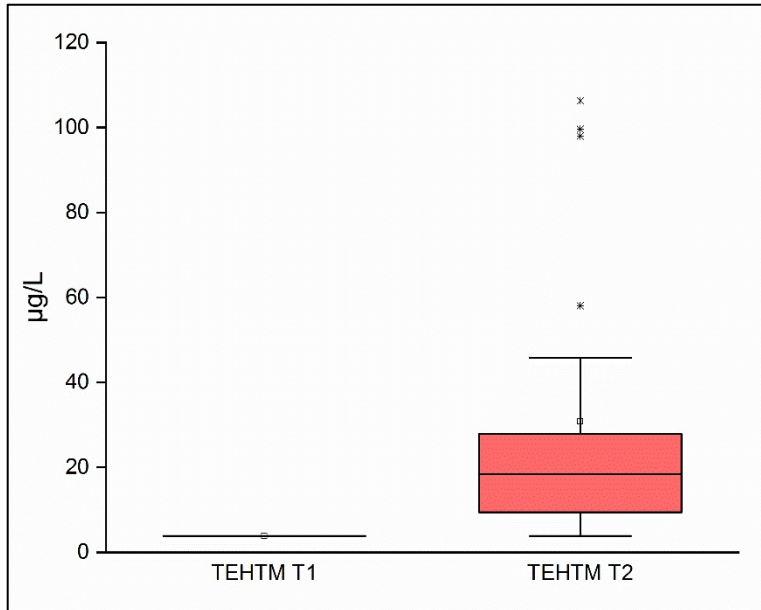
## Study design

- 21 infants aged 4 – 22 months (median age 5 months); 9 female, 12 male; weight 3.3 – 10.5 kg (median 5.5 kg)
- Cardiac surgery using a CPB equipped with TEHTM containing blood tubes, bypass time 38 – 312 min (median 131 min)
- All infant patients (but one) received fresh frozen plasma (median 130 mL) and erythrocyte concentrates (median 190 mL)
- Blood and urine samples taken before (T1) and after surgery (T2)
- Analysis for the plasticizers DEHP and TEHTM in blood and their metabolites in blood and urine

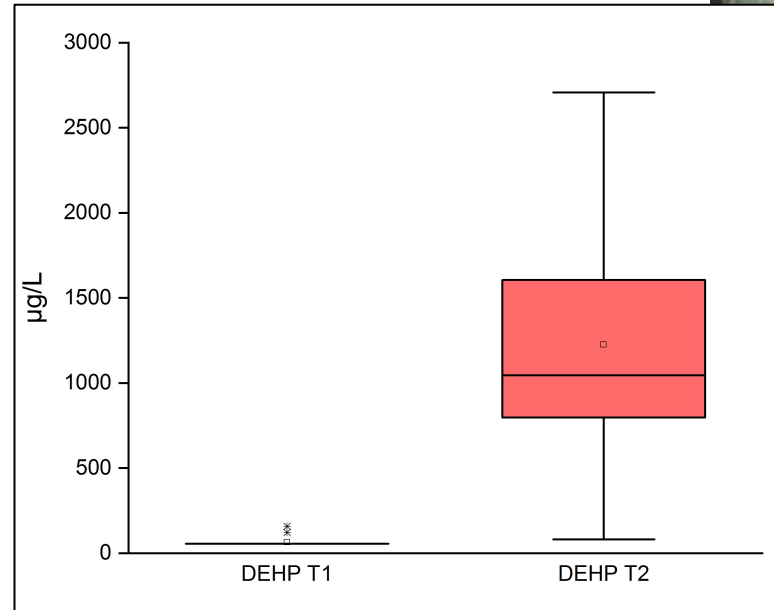


## Results in blood (n = 21)

### (1) TEHTM



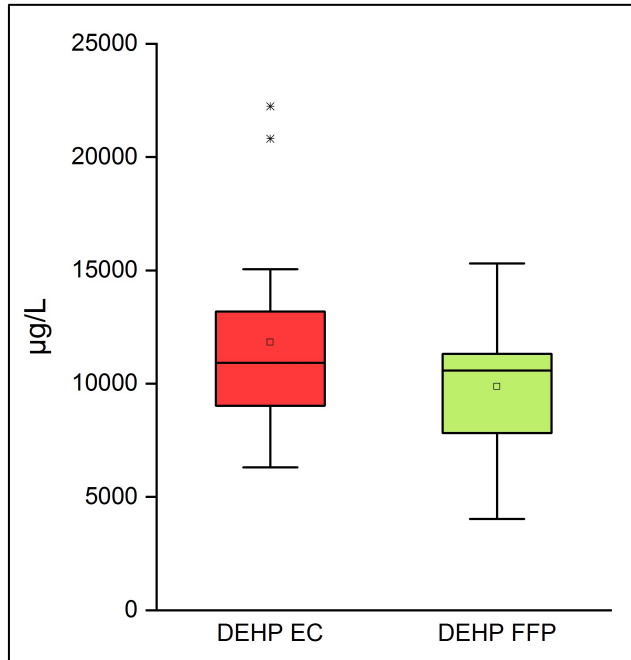
### (2) DEHP



- Moderate TEHTM levels but significantly elevated DEHP levels in blood after surgery

## Plasticizer levels in the given blood products (n = 20)

DEHP levels in EC (erythrocyte concentrates) and FFP (fresh frozen plasma)

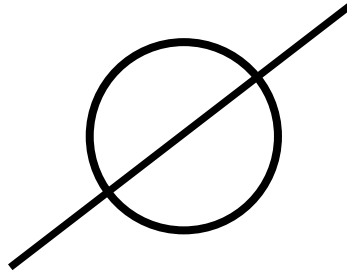


	Given blood products [mL]	Absolute given DEHP amount [µg]	DEHP level [µg/kg body weight]
min	200	1807	329
max	715	7283	1254
<b>median</b>	<b>325</b>	<b>3629</b>	<b>670</b>

**TDI (DEHP) = 50 µg/kg body weight**

## Results in urine (n = 21)

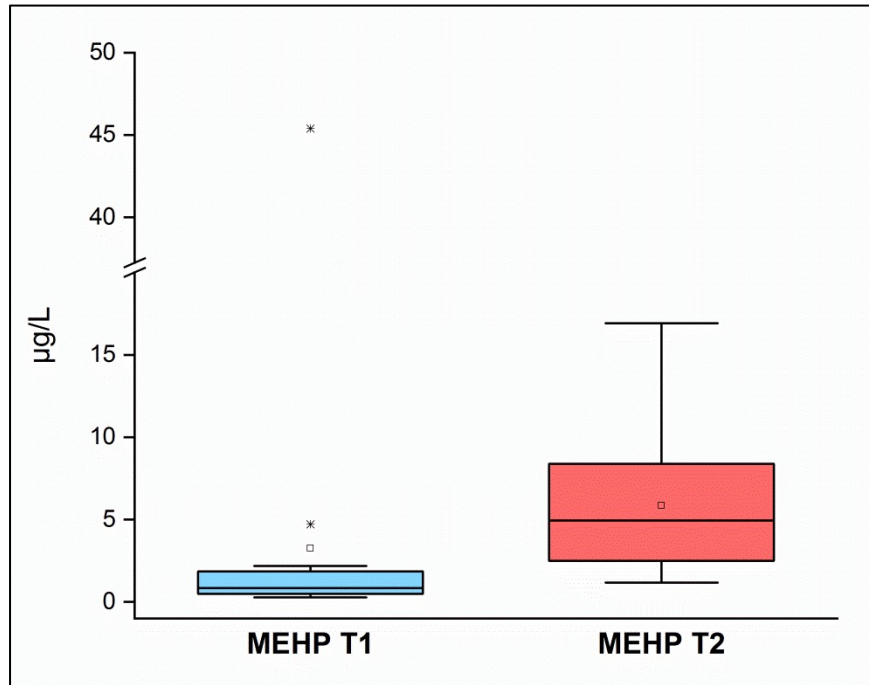
(1) TEHTM metabolites (primary and secondary)



## Results in urine (n = 21)

(2) DEHP metabolites:

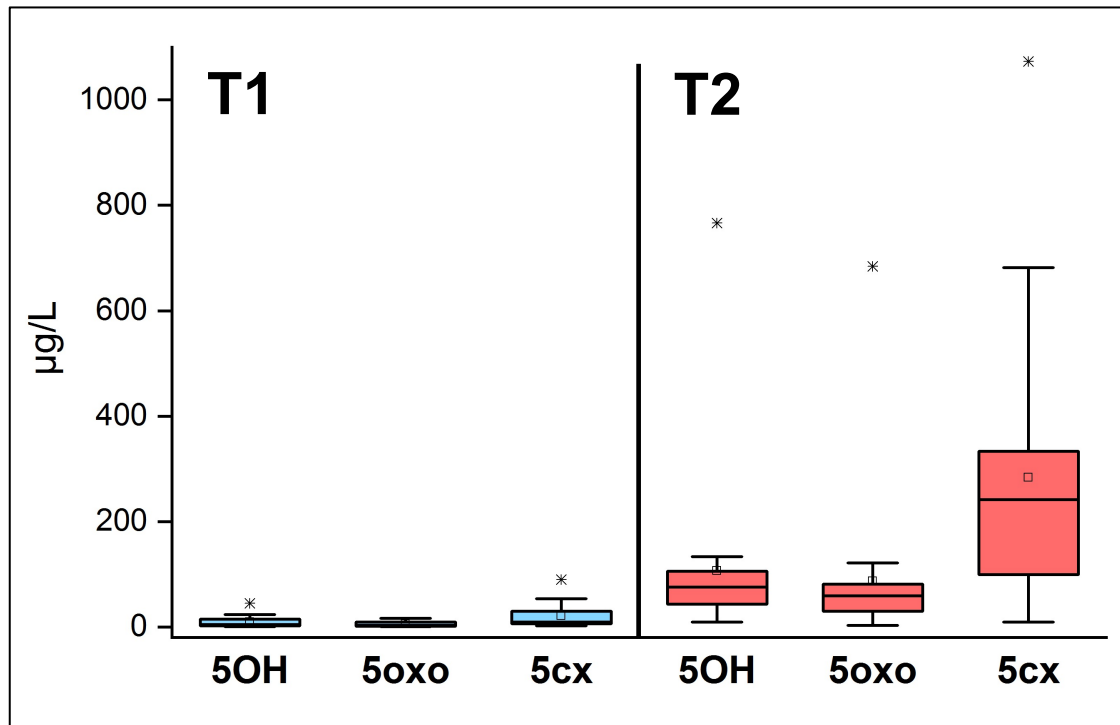
a) Primary metabolite MEHP



## Results in urine (n = 21)

(2) DEHP metabolites:

b) Secondary metabolites 5OH-MEHP, 5oxo-MEHP, 5cx-MEHP



## Conclusion



- Migration rate of plasticizers into blood strongly depends on the type of plasticizer
- The plasticizer TEHTM appears to be a suitable alternative to DEHP due to its low migration rate and presumed low toxicity potential
- Inner burden of infants with DEHP after cardiac surgery is still critically elevated due to DEHP containing stored blood bags
- Use of DEHP in medical devices for treatment of sensitive population groups, like infants, should be restricted