Regulation of human hepatic drug transporters by environmental chemicals

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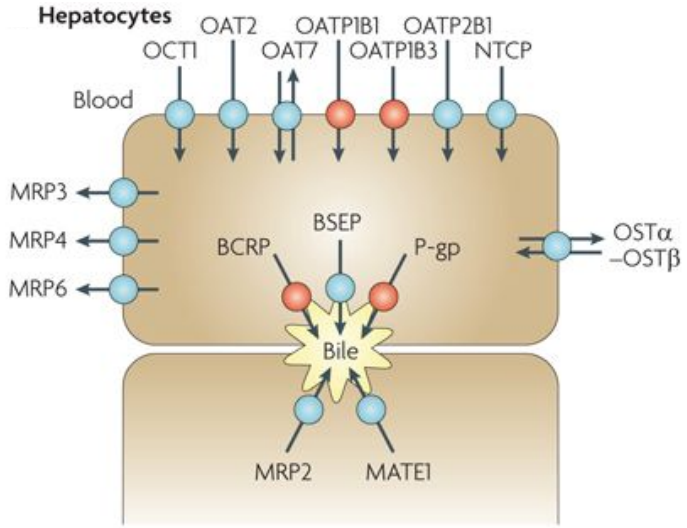
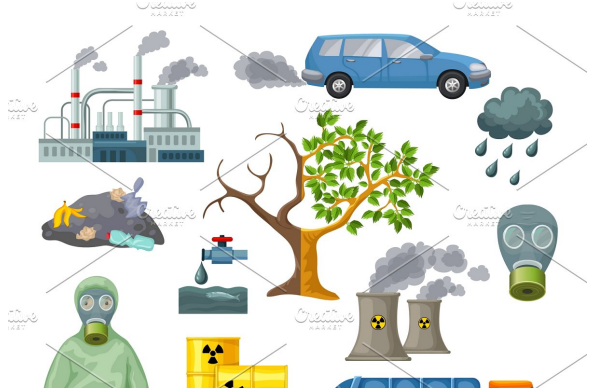
Inserm
La science pour la santé
From science to health



Hepatic drug transporters: Main actors of biliary drug secretion and pharmacokinetics

For drugs, interactions with hepatic drug transporters have been extensively studied and well-characterized

What about environmental chemicals, to which humans are largely exposed? Much less available data and studies than for drugs…

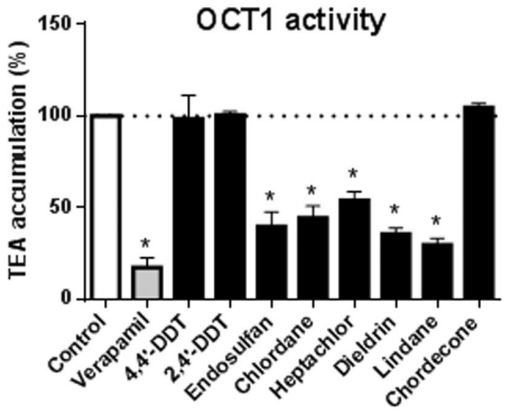


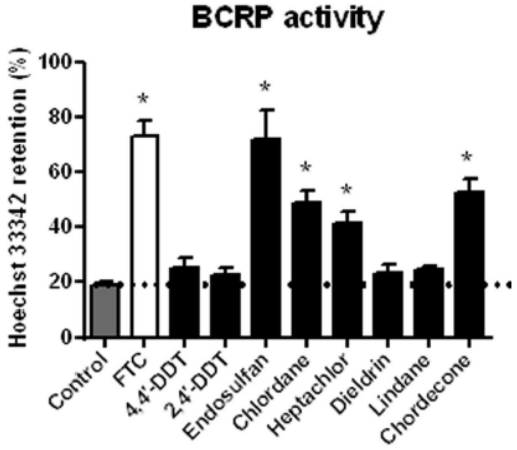
Aim of our studies: To characterize interactions of pollutants with hepatic drug transporters

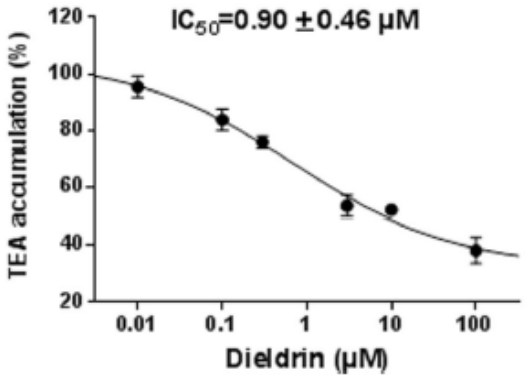
Regulation of drug transporter activity/expression by pesticides

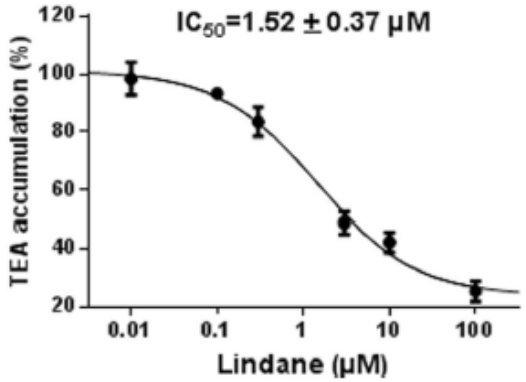
Pesticides belonging to various chemical classes can regulate hepatic drug transporter activity and/or expression

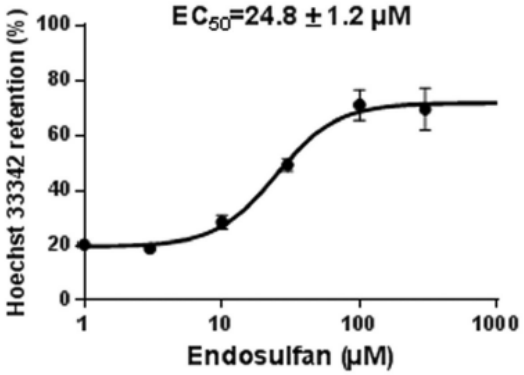
Organochlorine insecticides: Inhibition of *in vitro* hepatic transporter activity

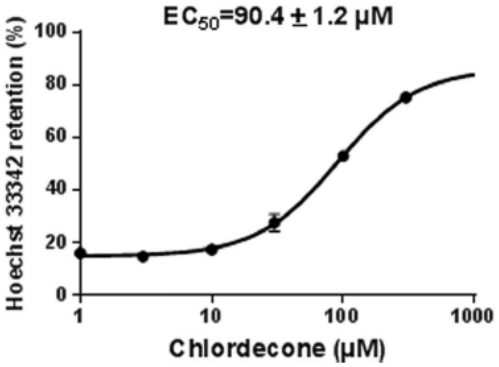








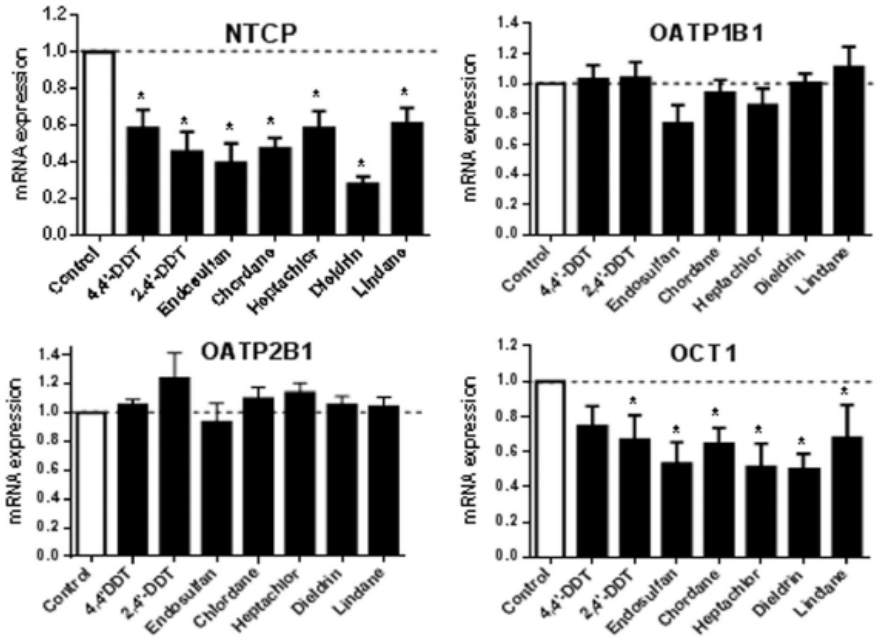


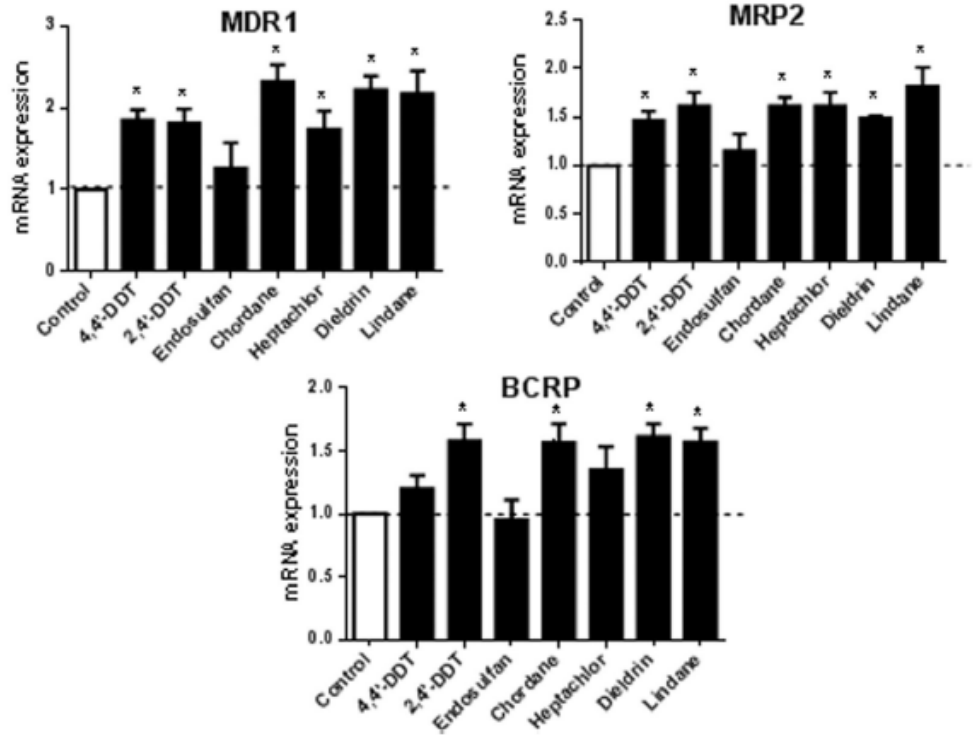


Bucher at al, 2014

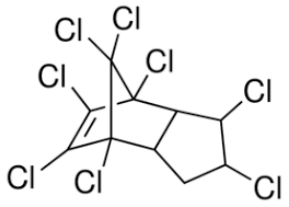
Organochlorine insecticides: Regulation of hepatic transporter expression

Differentiated human hepatoma HepaRG cells exposed to 10 µM OC pesticides for 48 h

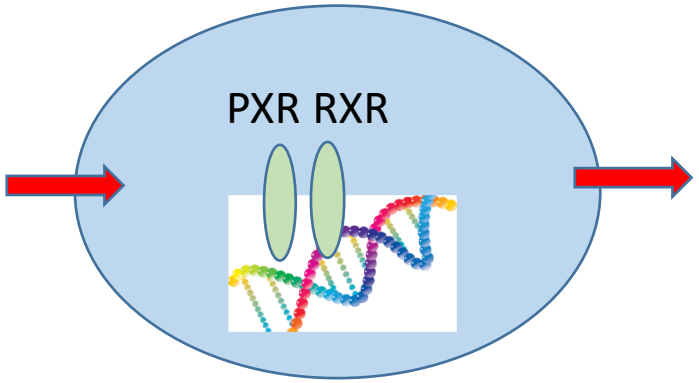




Organochlorine pesticides are agonists of drug-sensing receptors like PXR



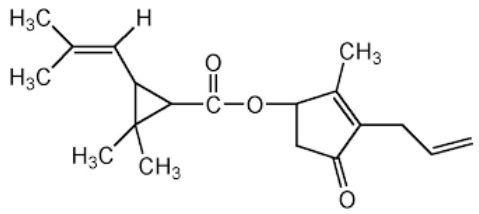
Chlordane



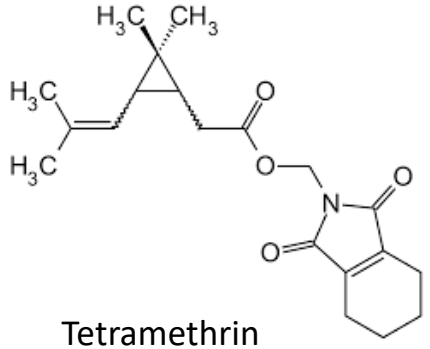
Up-regulation of MDR1 and MRP2 expression

Bucher at al, 2014

Pyrethroid insecticides: Inhibition of hepatic transporter activity



Allethrin



Tetramethrin

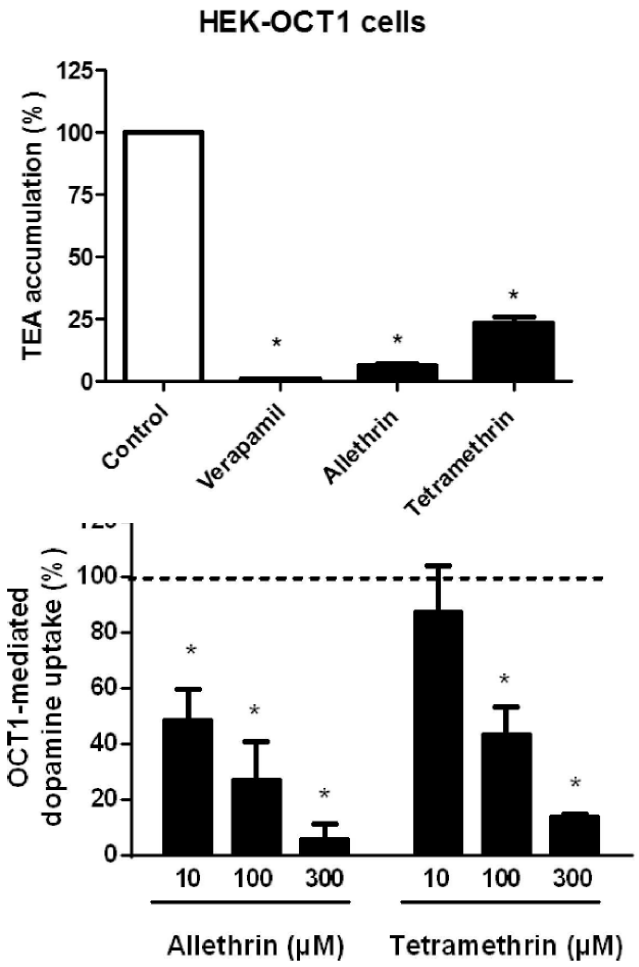
Table 3. Summary of allethrin and tetramethrin effects towards drug transporters.

Drug transporter		Allethrin	Tetramethrin
ABC transporter	P-gp	Inhibition (IC_{50}>100 μM)	Inhibition (IC_{50}>100 μM)
	MRP2	Inhibition (IC_{50} = 48.2 μM)	Inhibition (IC_{50} = 65.5 μM)
	BCRP	Inhibition (IC_{50} = 42.5 μM)	Inhibition (IC_{50} = 72.5 μM)
SLC transporter	OATP1B1	Inhibition (IC_{50} = 16.5 μM)	Inhibition (IC_{50} = 5.7 μM)
	OATP1B3	No effect (up to 100 μM)	No effect (up to 100 μM)
	OATP2B1	Stimulation (EC_{50} = 37.8 μM)	Stimulation (EC_{50} = 10.1 μM)
	OAT1	No effect (up to 100 μM)	No effect (up to 100 μM)
	OAT3	Inhibition (IC_{50} = 69.4 μM)	Inhibition (IC_{50} = 77.6 μM)
	MATE1	Inhibition (IC_{50} = 50.2 μM)	Inhibition (IC_{50} = 47.5 μM)
	MATE2-K	No effect (up to 100 μM)	No effect (up to 100 μM)
	OCT1	Inhibition (IC_{50} = 2.6 μM)	Inhibition (IC_{50} = 4.9 μM)
	OCT2	Inhibition (IC_{50} = 42.6 μM)	Inhibition (IC_{50} = 11.2 μM)

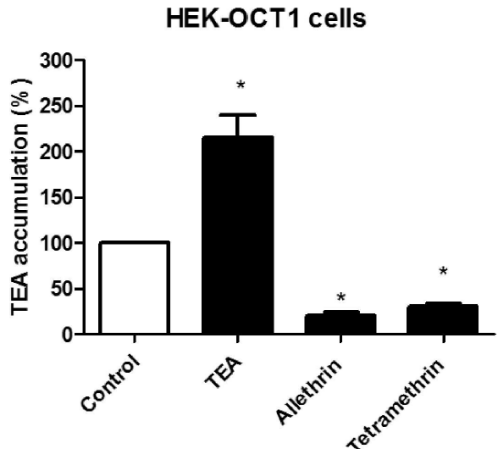
Chedik at al, 2017

Allethrin and tetramethrin are potent inhibitors of OCT1, but are not substrates

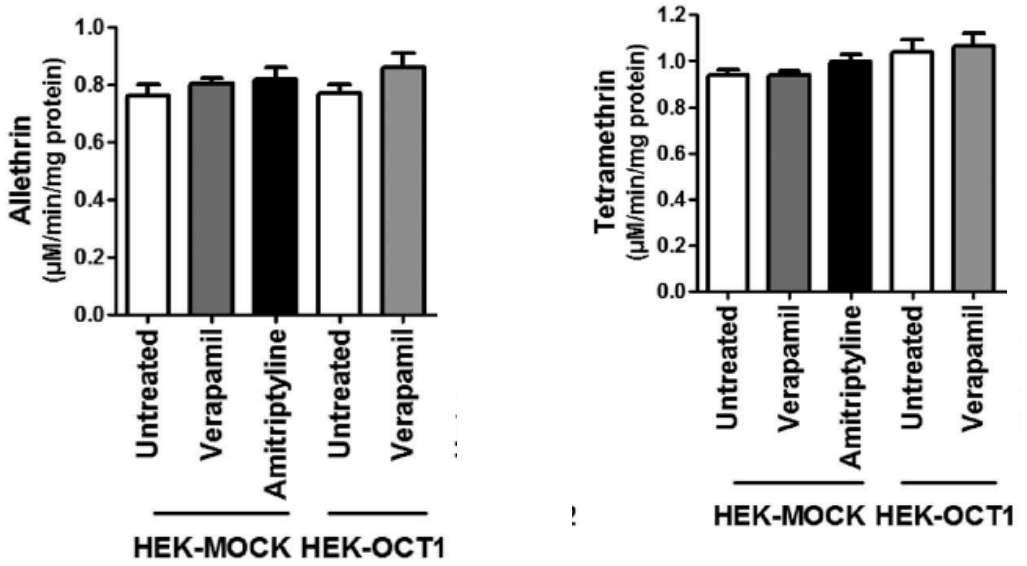
Cis-inhibition



Lack of trans-stimulation



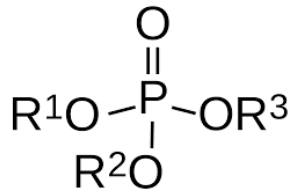
Lack of transport by OCT1

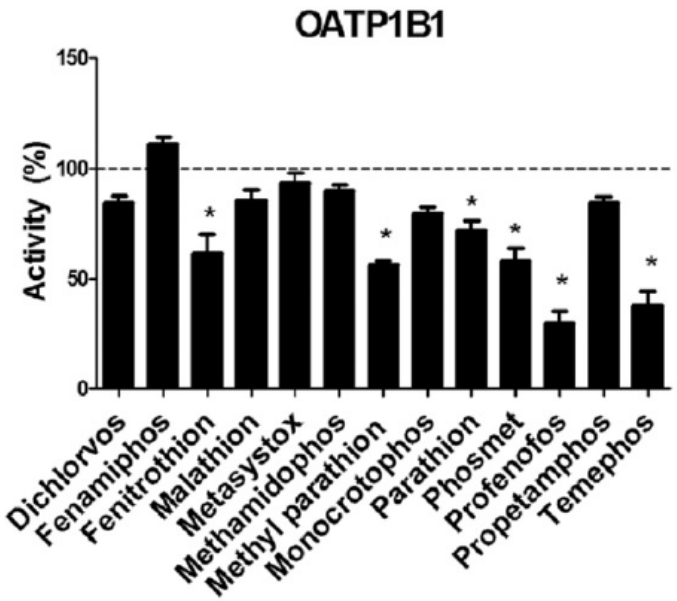


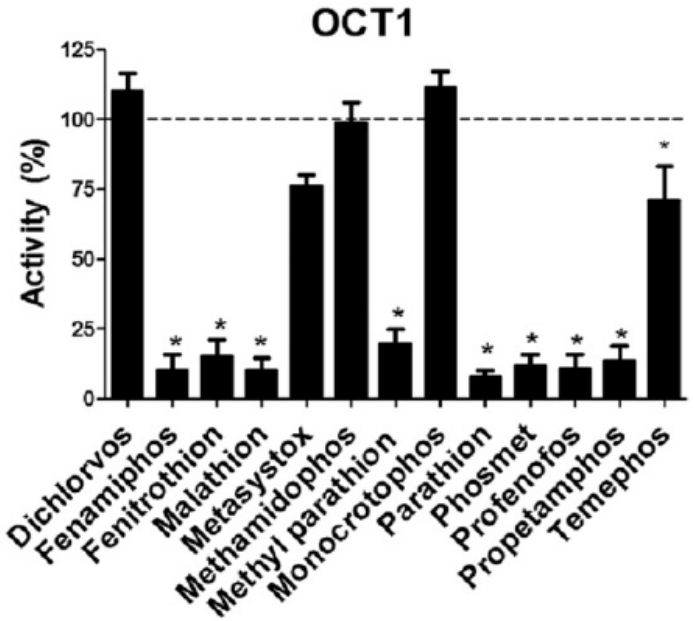
Chedik at al, 2017

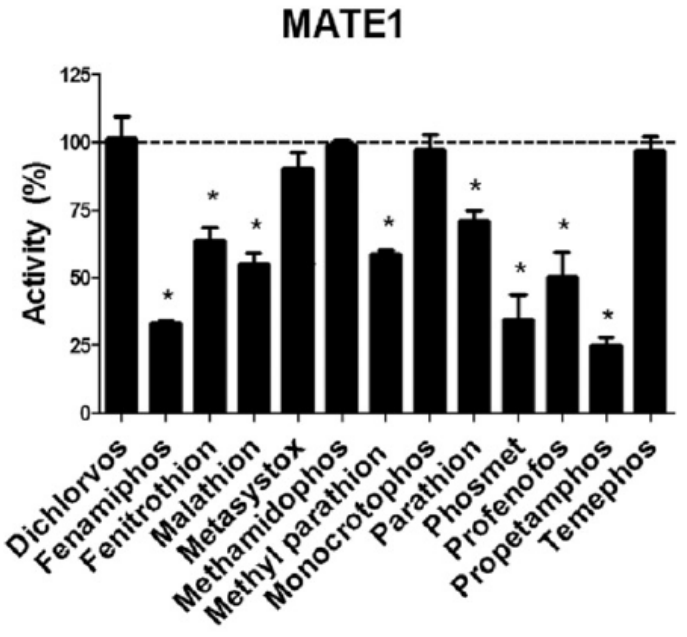
Organophosphate insecticides: Inhibition of hepatic transporter activity

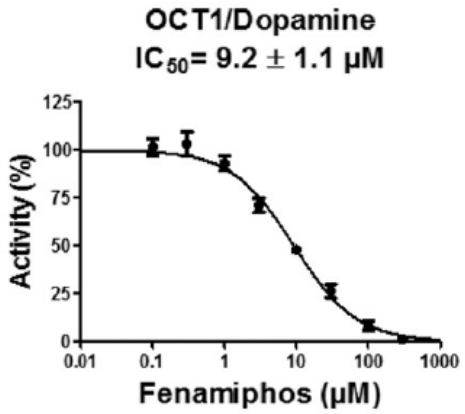
Chedik at al, 2019

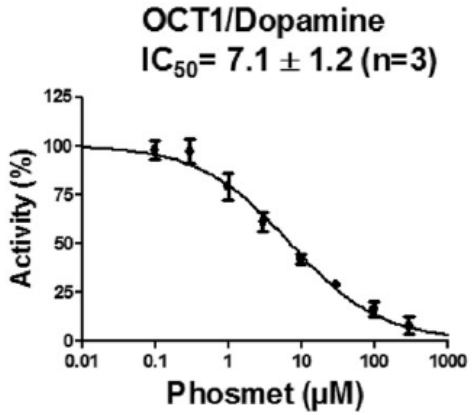


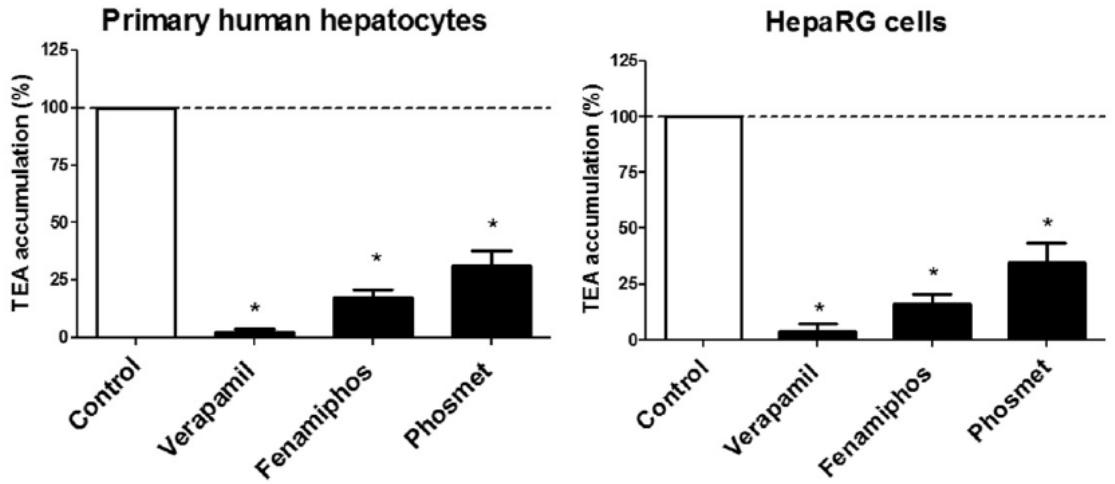


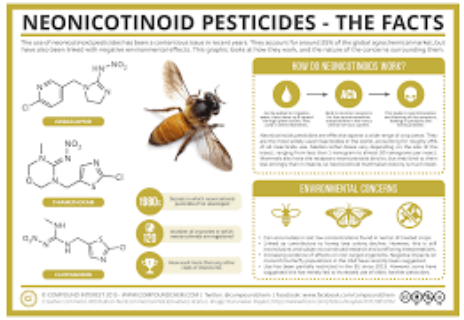






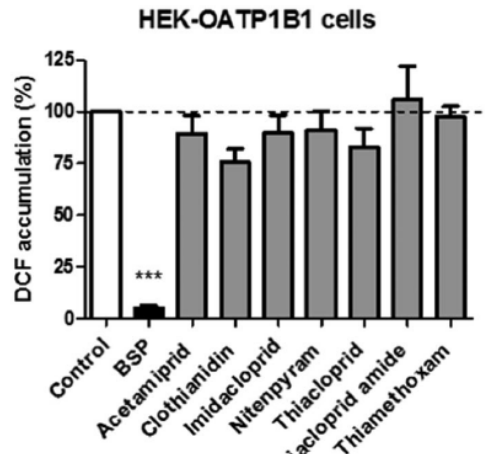


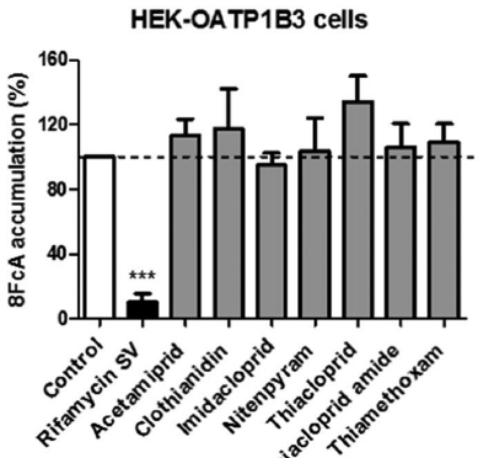


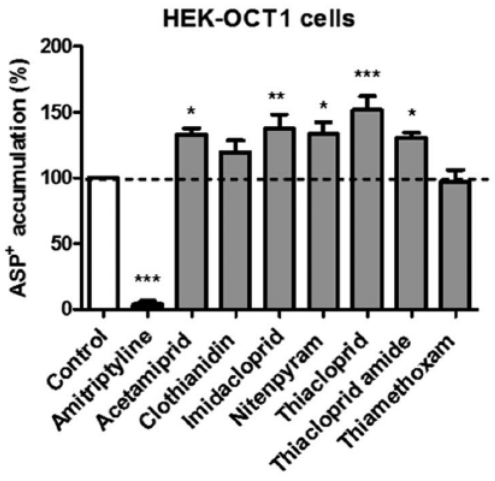


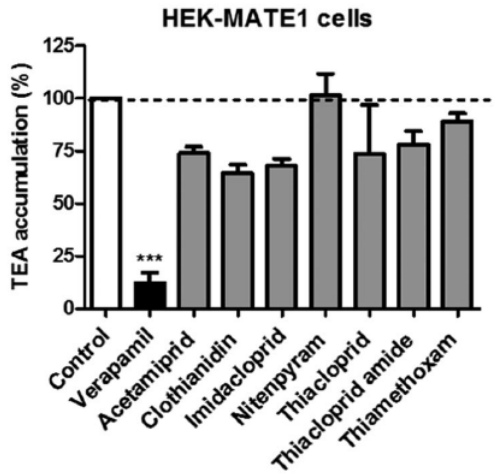
Neonicotinoid insecticides: No or poor inhibition of hepatic transporter activity

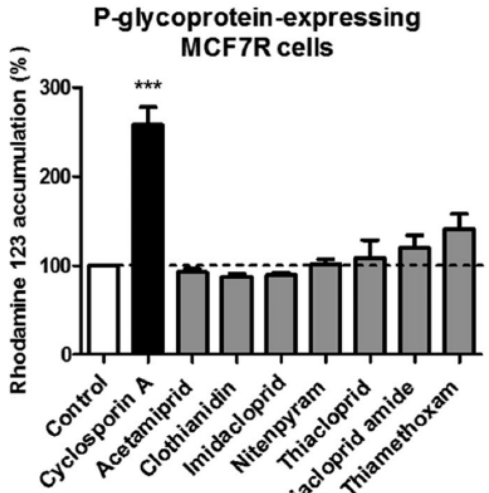
Le Vée et al, 2019

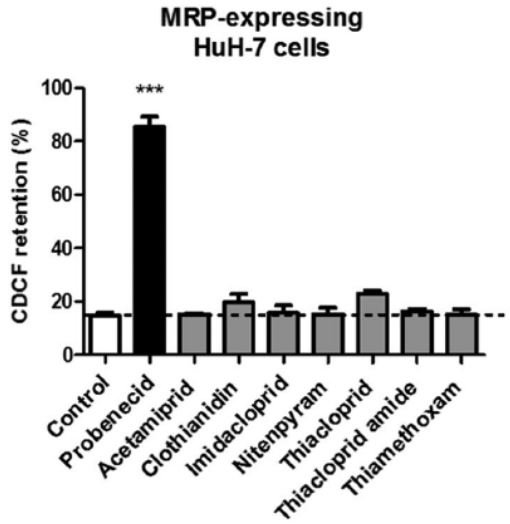


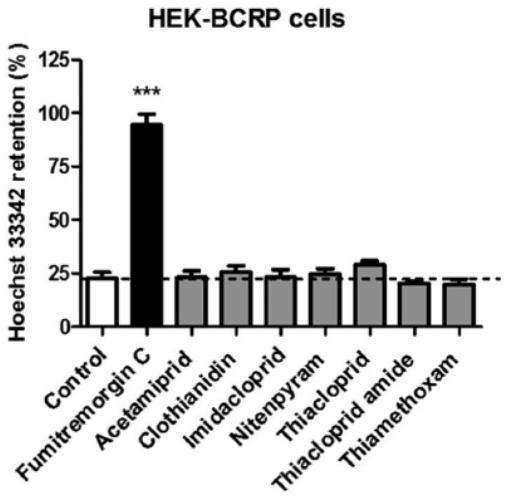






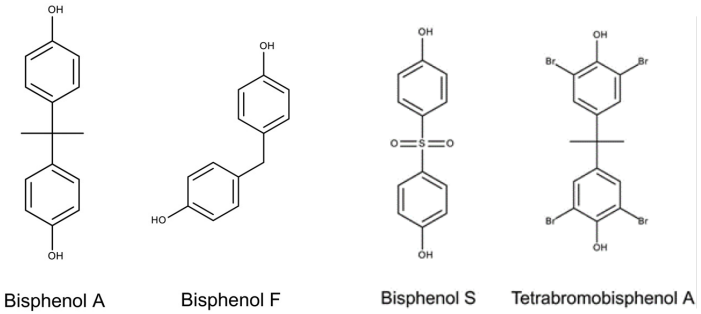


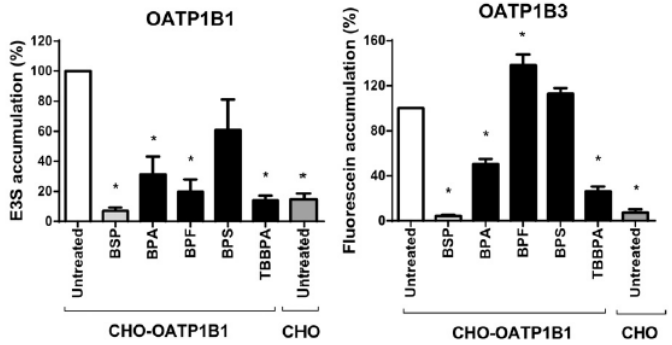


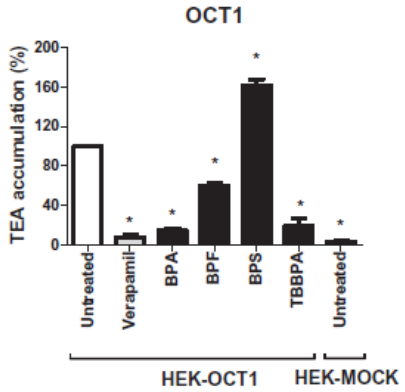


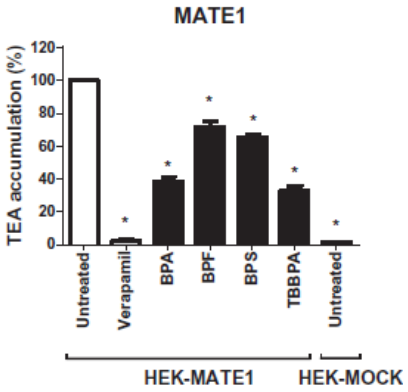
Not all pesticides block hepatic transporter activities….

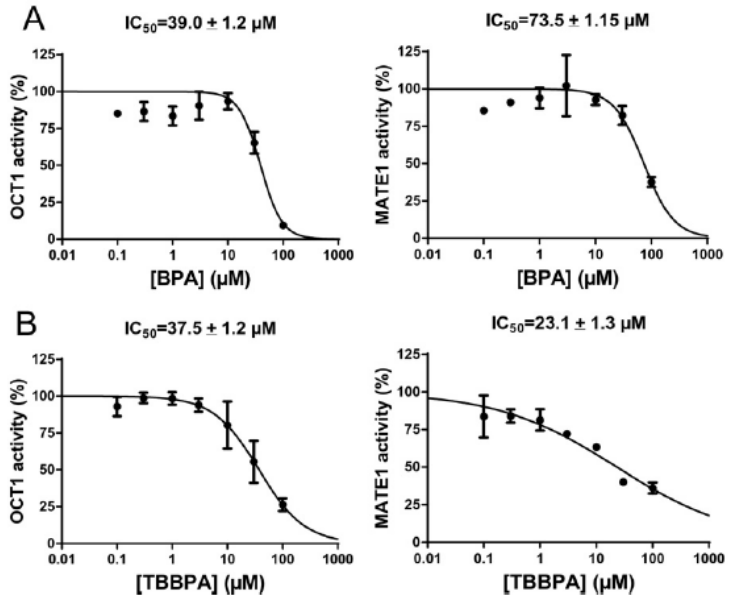
Regulation of hepatic drug transporter activity by bisphenols

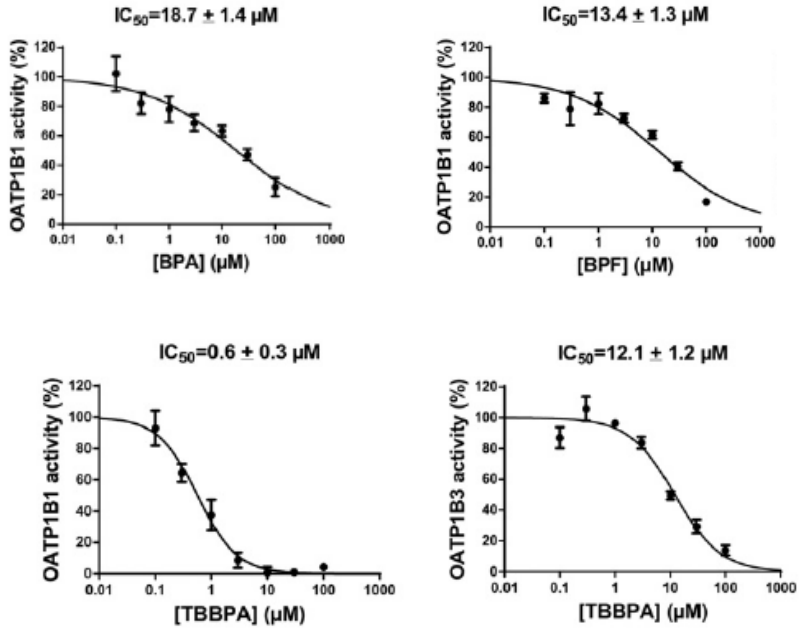








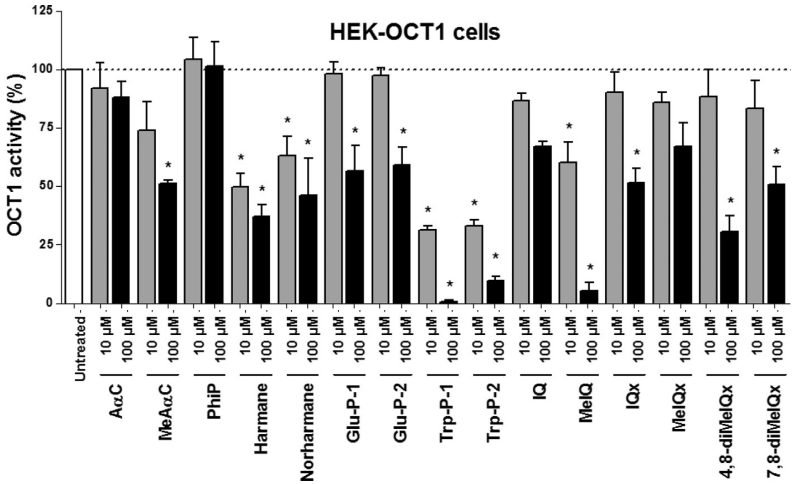


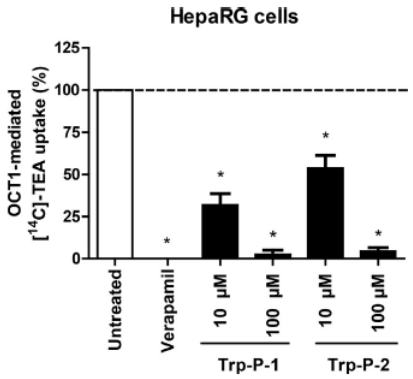


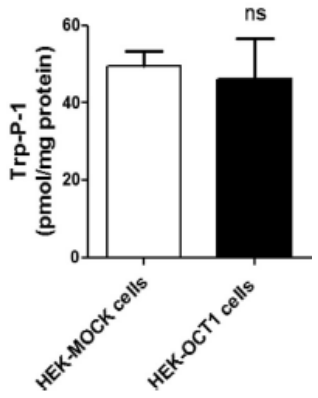
Bruyere at al, 2017

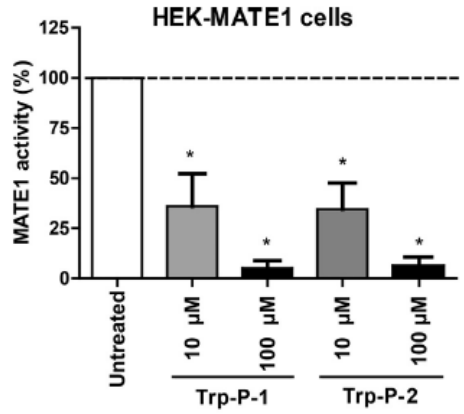
Regulation of hepatic drug transporter activity by heterocyclic aromatic amines (HAAs)

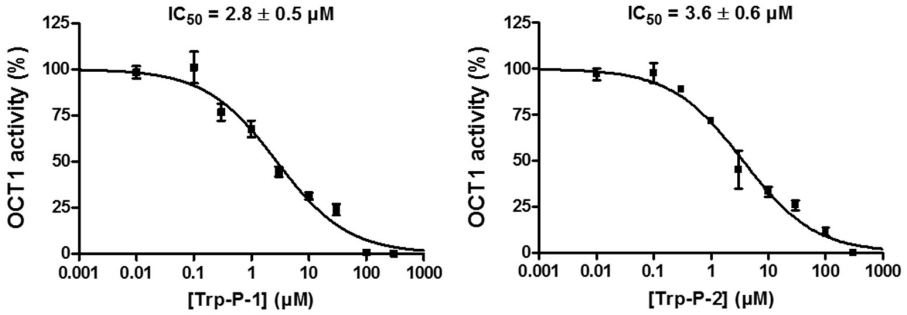
HAAs: carcinogenic chemicals found in grilled meat and cigarette smoke

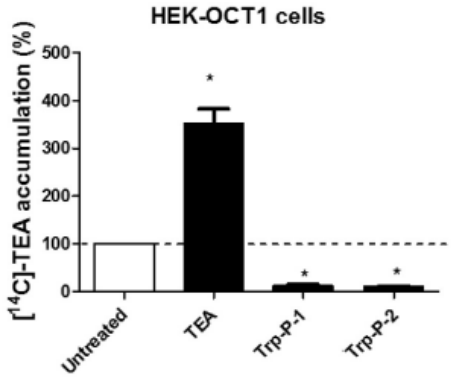


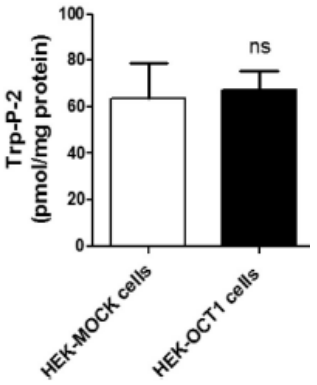


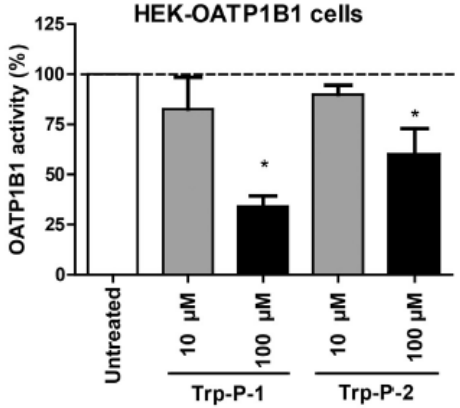












Trp-P-1 and Trp-P-2 are potent inhibitors, but not substrates, of OCT1

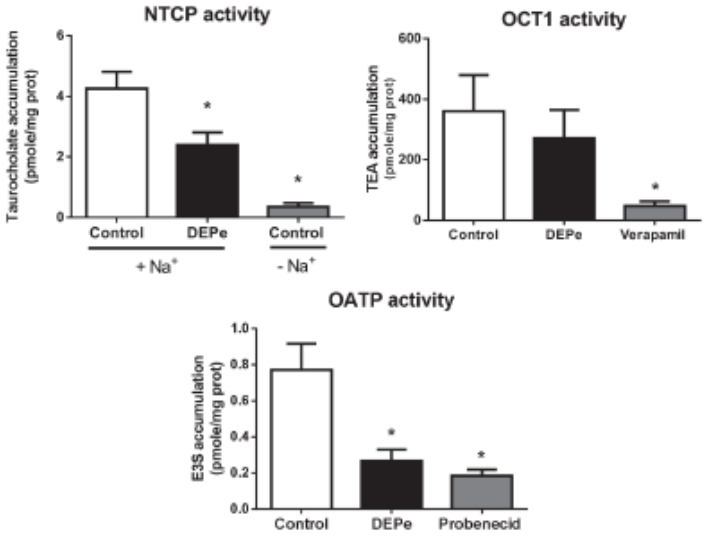
Sayyed at al, 2019

Regulation of hepatic drug transporters by complex pollutant mixtures

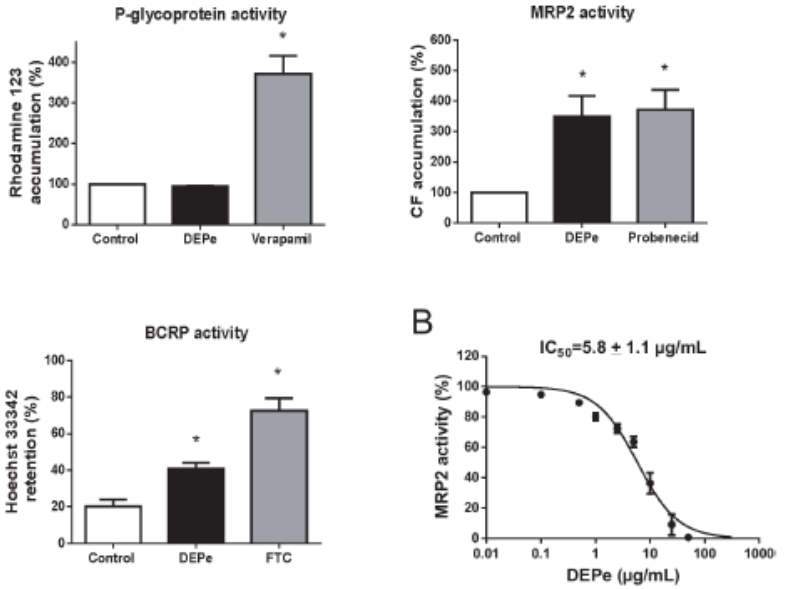
Diesel exhaust particles: Inhibition of *in vitro* hepatic transporter activity

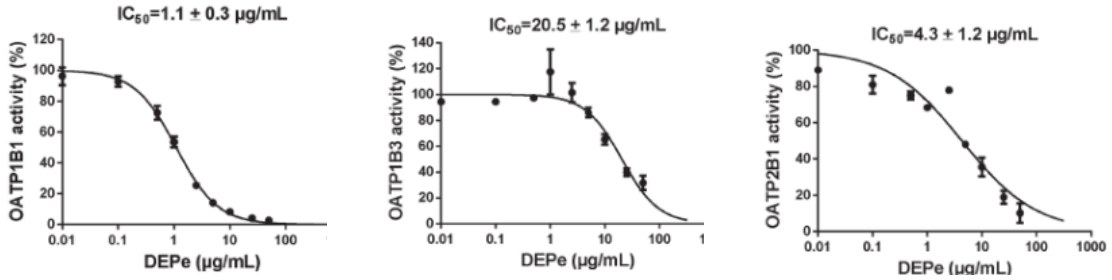
Diesel exhaust particle :
Hundreds of chemicals

SLC transporter activities

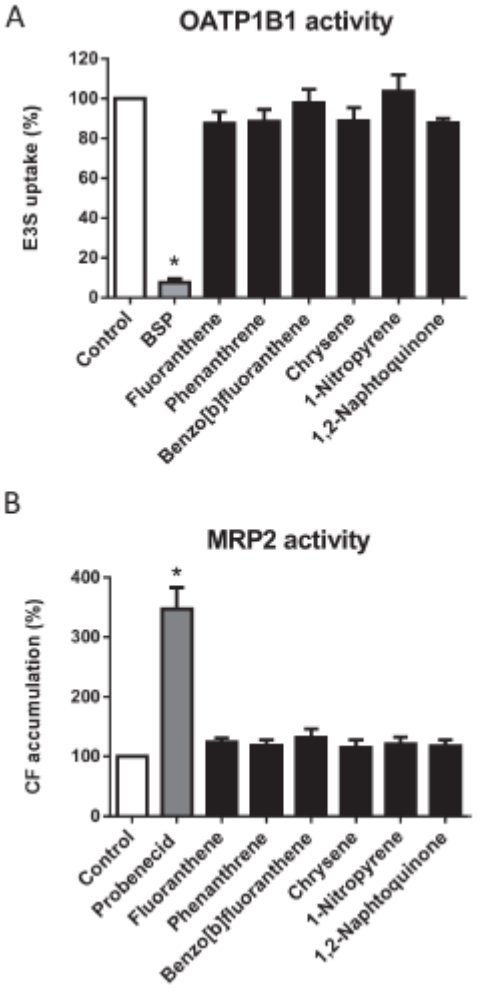


ABC transporter activities





Single DEP components

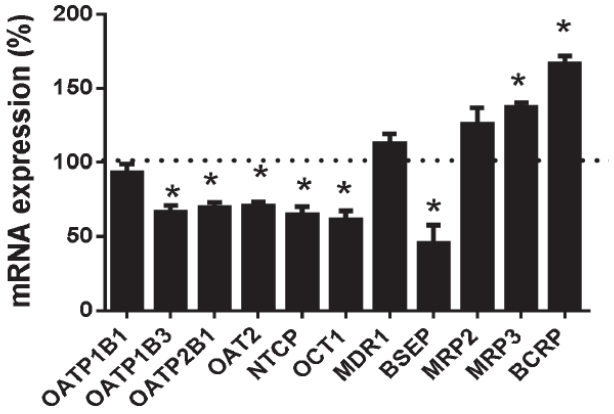


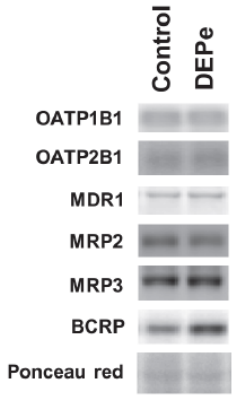
Le Vée et al, 2015

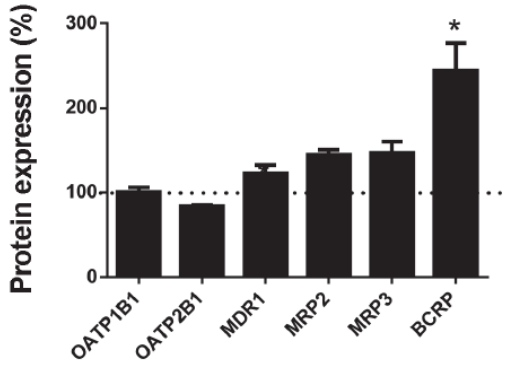
Diesel exhaust particles: Regulation of hepatic transporter expresssion

Le Vée et al, 2015

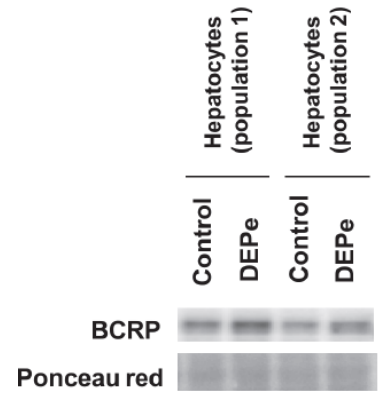
HepaRG cells were exposed to 25 µg/mL DEPe for 48 h



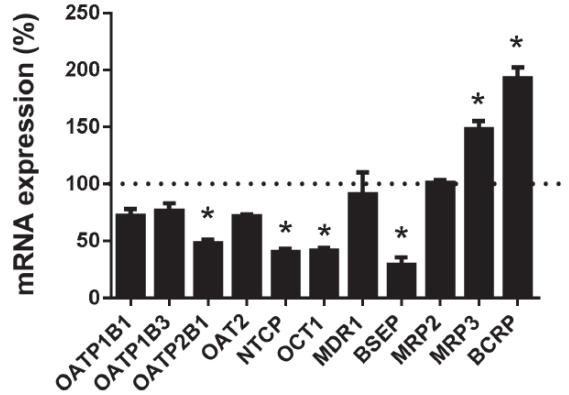




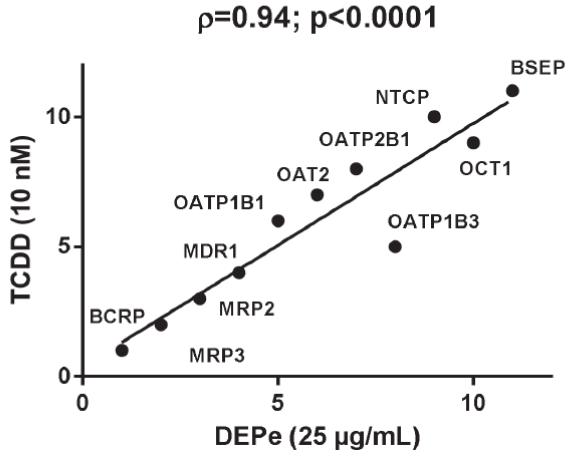
Human hepatocytes were exposed to 25 µg/mL DEPe for 48 h

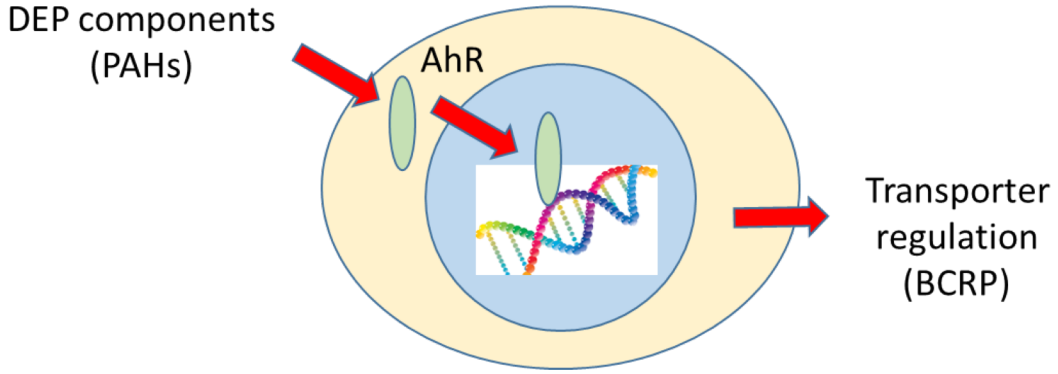


Effects of DEPe and TCDD on hepatic transporters are strongly correlated



Effects of TCDD





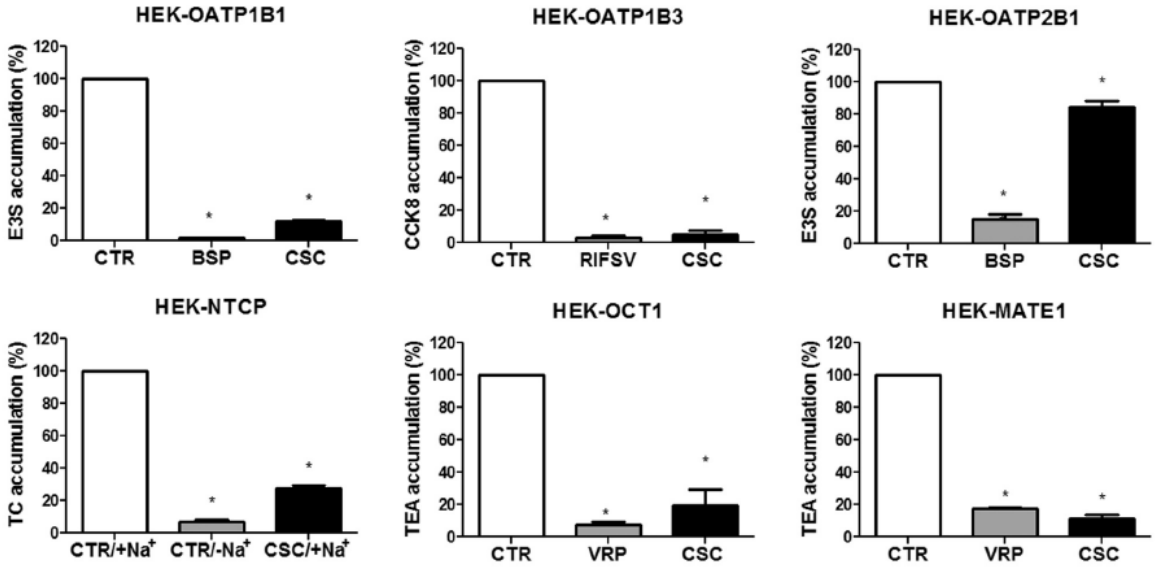
TCDD and DEPe may share the same molecular mechanism of regulation (The AhR pathway?)

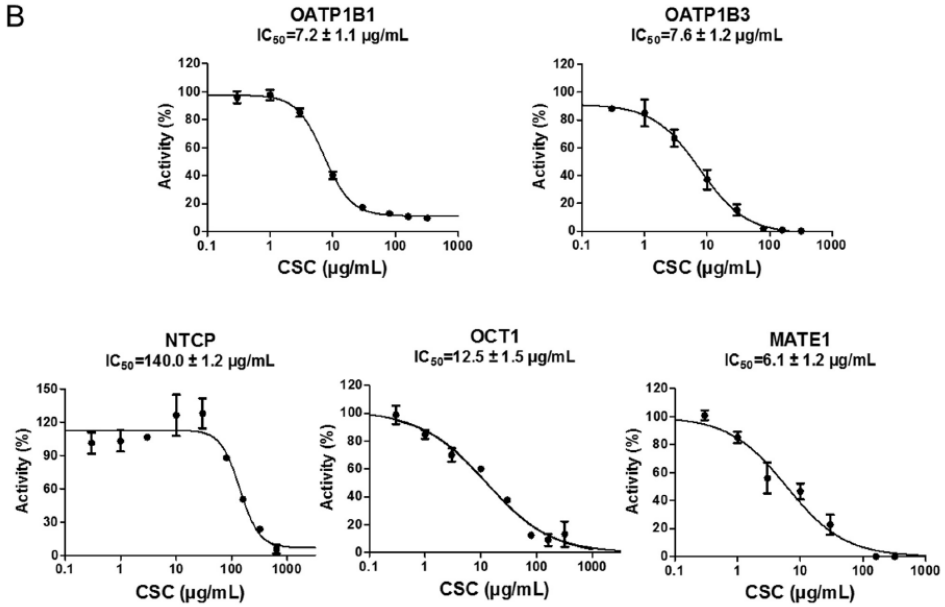
Regulation of hepatic drug transporters by complex pollutant mixtures

Cigarette smoke: Inhibition of *in vitro* hepatic transporter activity

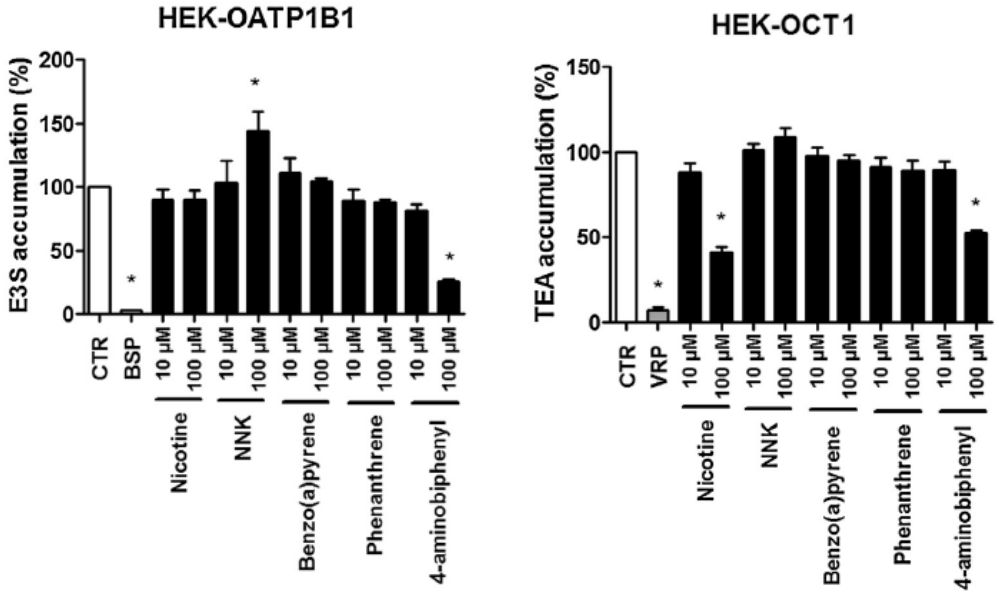
Cigarette smoke condensate (CSC):
Hundreds of chemicals

Hepatic SLC transporter activities





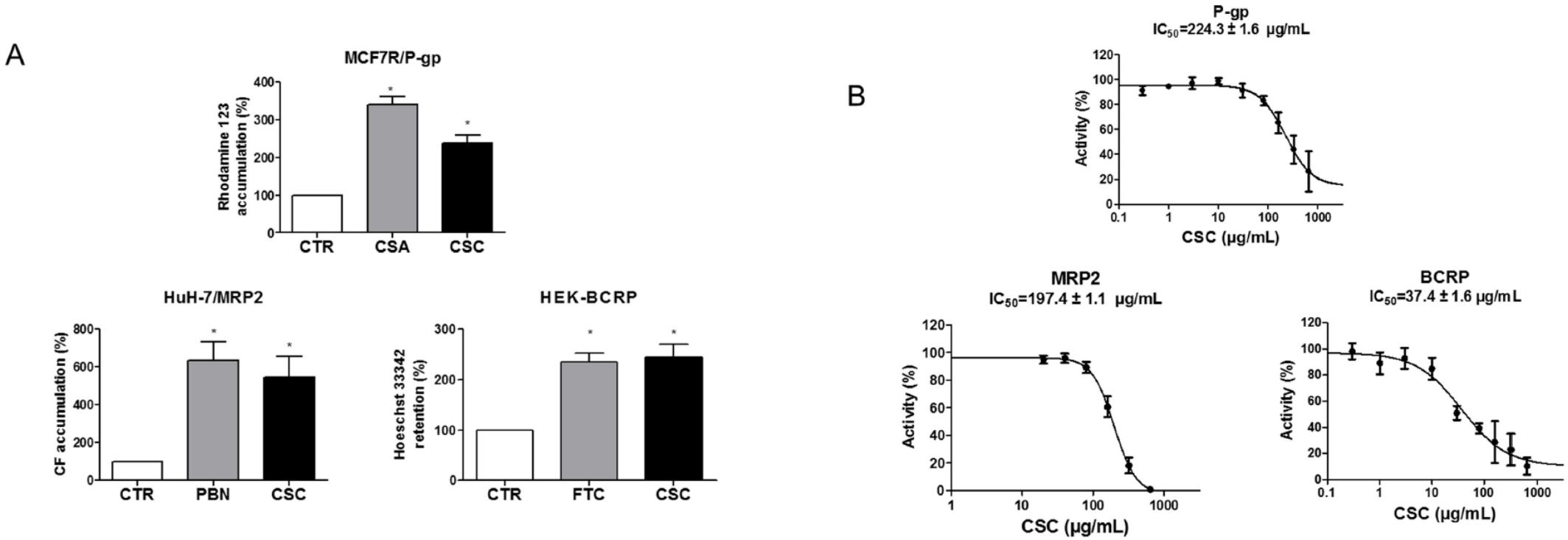
CSC components



Sayyed at al, 2016

Cigarette smoke: Inhibition of *in vitro* hepatic transporter activity

Hepatic canalicular ABC transporter activities

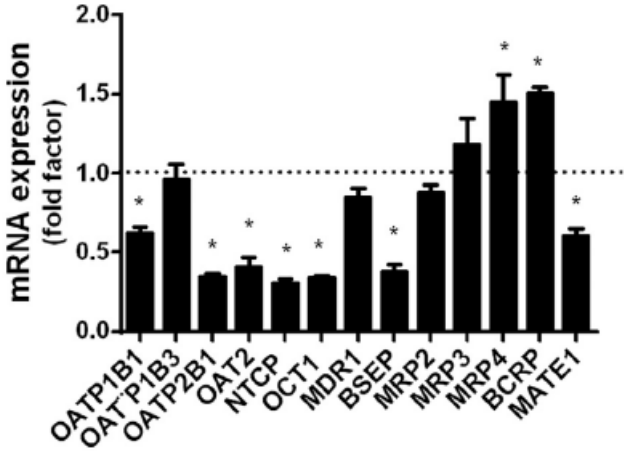


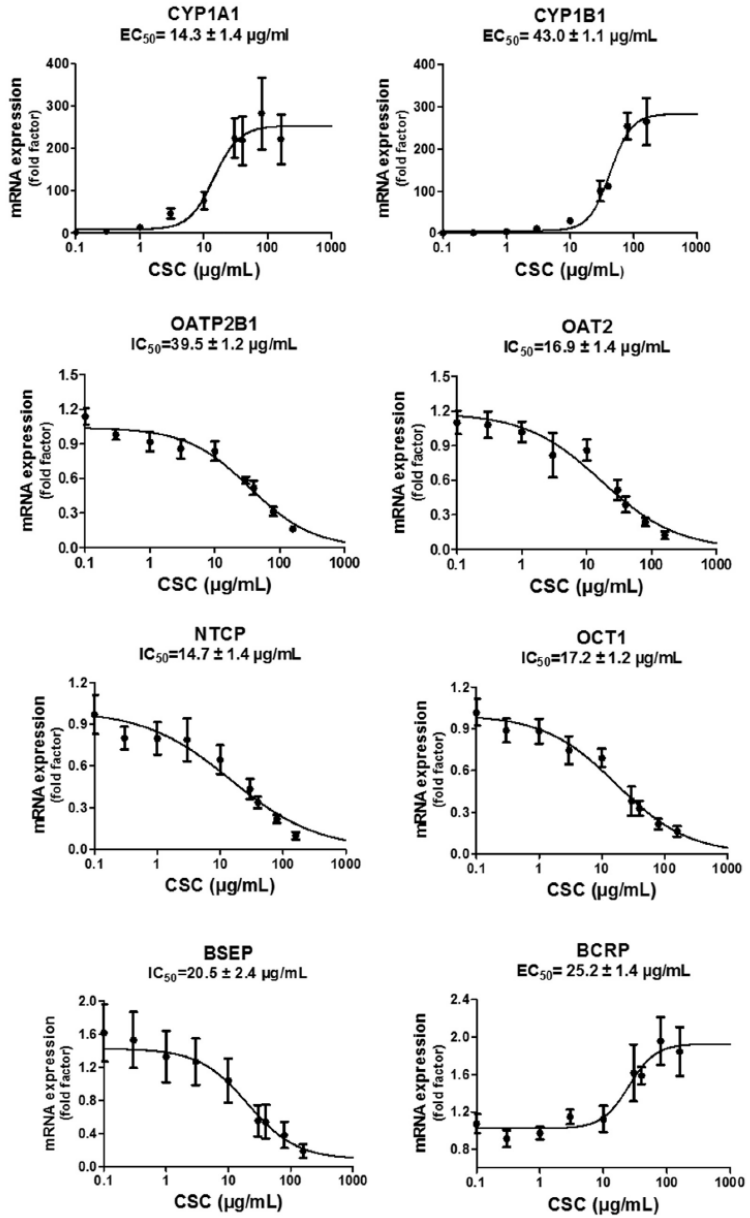
IC_{50} values for ABC transporters > IC_{50} values for SLC transporters

Cigarette smoke: Regulation of hepatic transporter expresssion

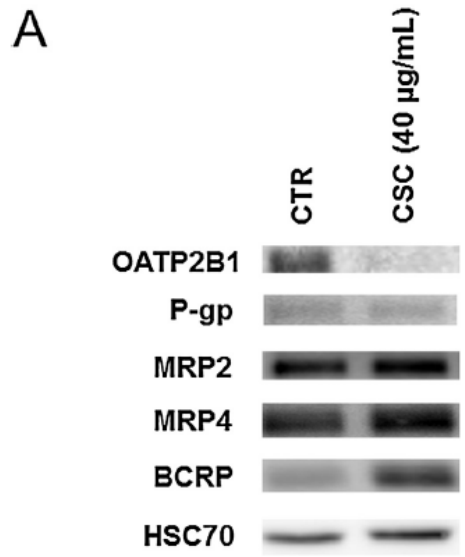
HepaRG cells were exposed to 40 µg/mL CSC for 48 h

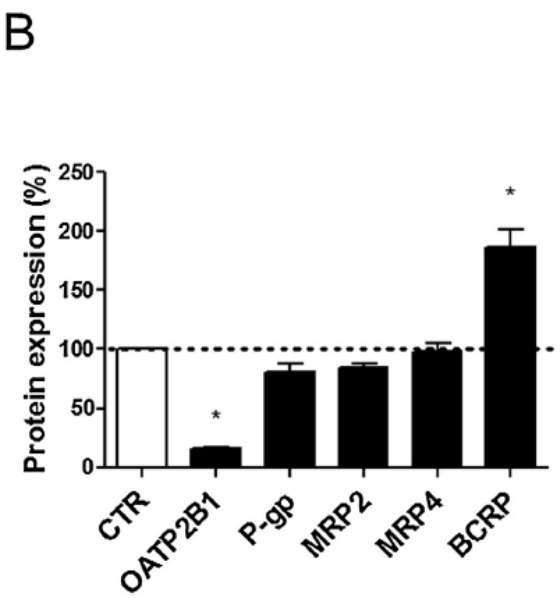
Transporter mRNA regulation





Transporter protein regulation

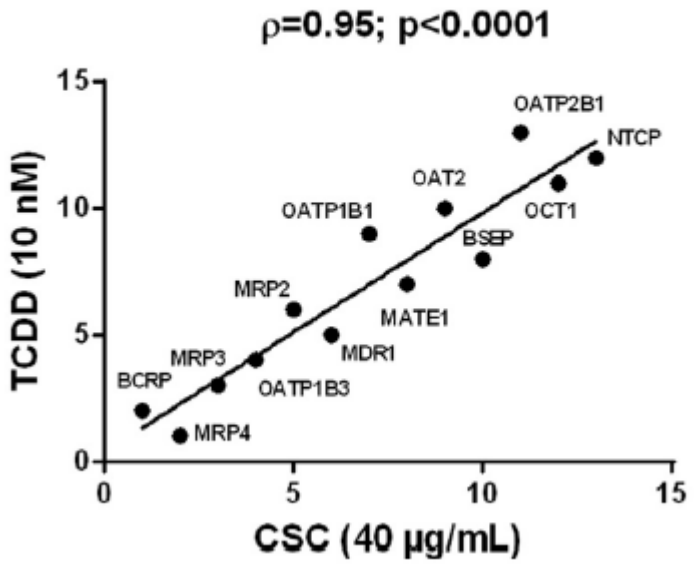


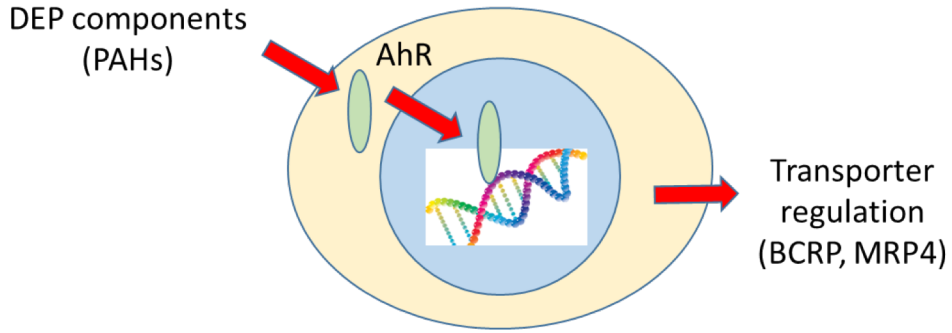


Sayyed at al, 2016

Cigarette smoke effects: Implication of the AhR pathway

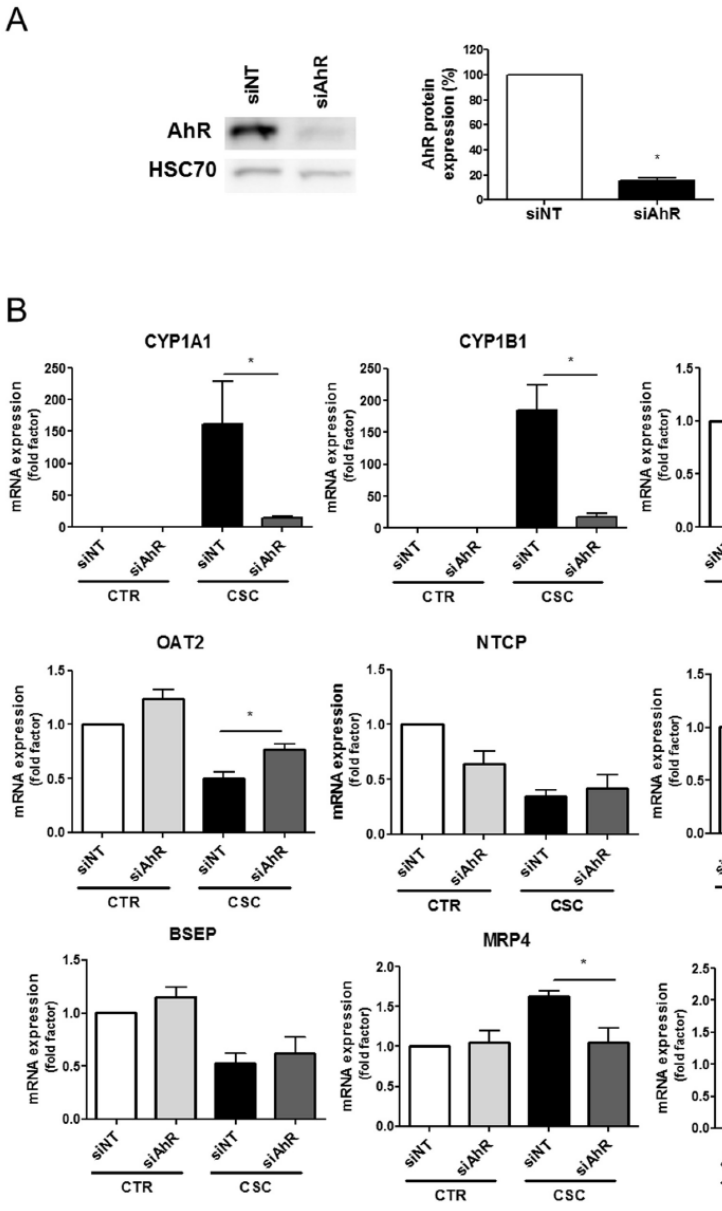
CSC and TCDD effects are highly correlated





Sayyed at al, 2016

Effects of AhR silencing in HepaRG cells



Various environmental chemicals can regulate hepatic drug transporter activity and/or expression in in vitro system, bringing the proof of the concept of pollutants-hepatic transporter interactions

What about in vivo clinical relevance of such interactions with hepatic transporters?

- For a **single chemical**, regulation of hepatic drug transporter activities and/or expression usually requires chemical concentrations in the µM range, much higher than those occurring in response to environmental exposure (in the pM or nM range): No expected *in vi*vo relevance for most of single pollutants ?

Prediction of potential drug-drug interactions (DDI) for BPA-mediated inhibitions of SLC drug transporters according to FDA criteria for plasma inhibitor concentration.[a]

SLC transporter	Effect of BPA on transporter activity	Ratio $[I_{BPA}]$/BPA IC_{50}		Prediction of potential DDI according to FDA criteria
		$[I_{BPA}] = 6.5$ nM[b]	$[I_{BPA}] = 44$ nM[c]	
OCT1	Inhibition ($IC_{50} = 39.0$ µM)	0.00017	0.00111	No DDI
OCT2	No effect	ND[d]	ND	No DDI
MATE1	Inhibition ($IC_{50} = 73.5$ µM)	0.00009	0.00060	No DDI
MATE2-K	No effect	ND	ND	No DDI
OATP1B1	Inhibition ($IC_{50} = 18.7$ µM)	0.00035	0.00216	No DDI
OATP1B3	Inhibition[e]	ND	ND	No DDI
OAT1	Stimulation	ND	ND	No DDI
OAT3	Inhibition ($IC_{50} = 9.2$ µM)	0.00071	0.00478	No DDI

Bruyere at al, 2017

- For **complex environmental mixtures (DEP, cigarette smoke)**, concentrations active *in vitro* may be reached *in vivo* : Contribution of drug transporters to well-established alterations of pharmacokinetics in smokers?

- For **single chemicals, mixtures** have also to be considered because (1) humans are commonly co-exposed to various chemicals and (2) inhibitory effects towards transporters may be synergistic.

Chedik at al, 2019

Table 2. Combination index (CI) values for OCT2 inhibition by combined treatment with fenamiphos and phosmet.

% Inhibition OCT2 activity	CI[a]	Mixture concentration (μM)[b]	Nature of effect[c]
10	0.43	0.38	Synergistic
20	0.51	1.00	Synergistic
30	0.58	1.90	Synergistic
40	0.64	3.21	Synergistic
50	0.71	5.19	Synergistic
60	0.79	8.40	Synergistic
70	0.90	14.18	Additive
80	1.05	26.85	Additive
90	1.34	70.22	Antagonistic

[a]CI values were calculated using CompuSyn software.
[b]The ratio [Fenamiphos]:[Phosmet] is 1:1.
[c]Synergistic effect: CI <0.8; additive effect: $0.8 \leq$ CI ≤ 1.2; antagonistic effect: CI >1.2.

- For **both single and mixtures of chemicals,** humans are commonly chronically exposed and potential time-dependent inhibition of transporter activities have therefore to be taken into account

Interactions of pollutants with (hepatic) drug transporters remain nevertheless rather poorly characterized

More than 1000 pesticides are used in the world and only few have been studied for interactions with transporters

Table 3. Inhibitory effects of pesticides toward drug transporter activities according to organic pesticide classes.

	Percentage of inhibitory pesticides[a] (n = total number of tested pesticides)				
Transporter	Organophosphorus pesticides	Organochlorine pesticides	Pyrethroids	Carbamates	Chloroacetanilides
P-gp	76.9% (n = 13) [17,19]	30.8% (n = 13) [12,17]	0.0% (n = 14) [18]	0.0% (n = 6) [17]	57.1% (n = 7) [28]
MRP1/MRP2	No data	50.0% (n = 8) [12]	14.3% (n = 14) [18]	No data	0.0% (n = 7) [28]
BCRP	66.7% (n = 3) [53]	50.0% (n = 8) [12]	14.3% (n = 14) [18]	100% (n = 2) [53]	0.0% (n = 7) [28]
OCT1	61.5% (n = 13) [59]	62.5% (n = 8) [12]	23.5% (n = 17) [18]	No data	No data
OCT2	61.5% (n = 13) [59]	No data	23.5% (n = 17) [18]	No data	No data
MATE1	23.1% (n = 13) [59]	No data	14.3% (n = 14) [18]	No data	No data
MATE2-K	0.0% (n = 13) [59]	No data	0.0% (n = 14) [18]	No data	No data
OATPs	15.4% (OATP1B1) 0.0% (OATP2B1) (n = 13) [59]	0.0% (Total OATP activity) (n = 8) [12]	14.3% (OATP1B1), 0.0% (OATP1B3) (n = 14) [18]	No data	No data
OAT1	0.0% (n = 13) [59]	No data	0.0% (n = 17) [18]	No data	No data
OAT3	23.1% (n = 13) [59]	No data	23.5% (n = 17) [18]	No data	No data

[a]Pesticide concentrations are usually set at 100–250 µM

Chedik at al, 2018

Complementary/additionnal studies are needed…

Thanks

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Sponsors

Thank you very much for your attention

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