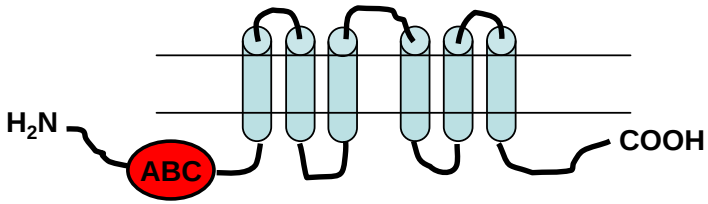


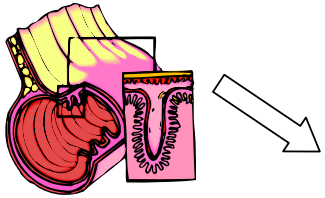

BCRP: Breast cancer resistance protein

Risiken erkennen – Gesundheit schützen

# Können Pflanzeninhaltsstoffe den biochemischen Schutz des menschlichen Darmes gegenüber Lebensmittelkontaminanten verstärken?

**Alfonso Lampen, Stefanie Hessel**

# Resorption, biotransformation and elimination of B[*a*]P from enterocytes



Resorption

Export to lumen

ABC-Transporter:
- p-Glycoprotein
- MRP2 (Multidrug Resistance Protein)
- BCRP

apical membrane

ABC-Transporter

Oxidation

Xenobiotica

CYP‘s

1A1,1B1

Conjugation

Transformation product

transferases

PAPS
GSH
UDPGlcUA

Conjugate

?

blood

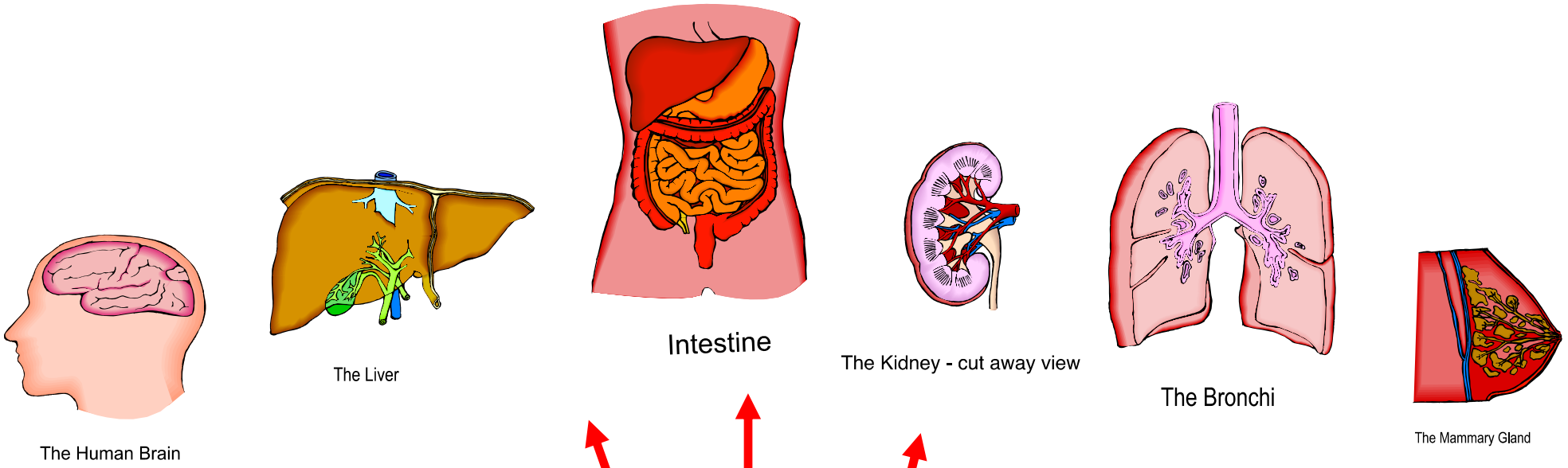
$H_2N$

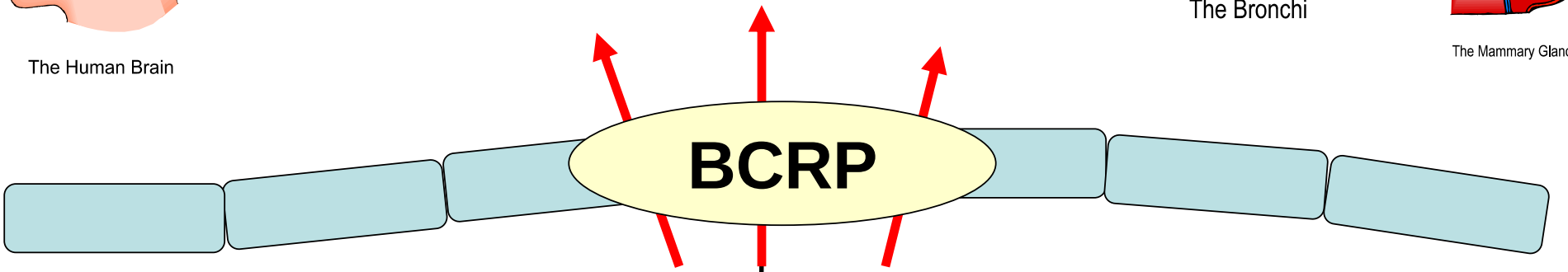
ABC

BCRP

COOH

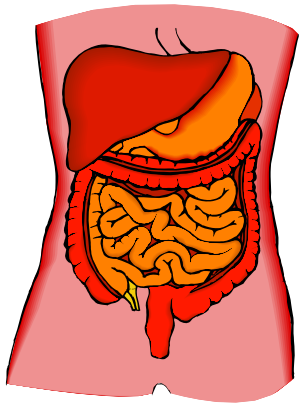
# Expression von BCRP



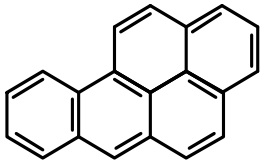

| Tissue | Function |
|---|---|
| stomach, duodenum, colon | reduction of resorption of xenobiotica, drugs |
| liver, kidney | hepato-biliar excretion, renal excretion |
| brain | protection against xenobiotica? |
| placenta | protection of fetus |
| **mammary gland** | **???** |

# Metabolisierung des Lebensmittelkontaminanten Benzo[*a*]pyren; eine Modellsubstanz mit hohem karzinogenen Potential

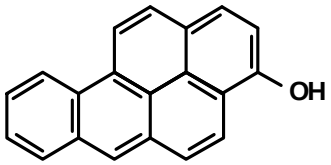


Intestine

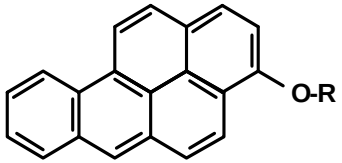
Benzo(a)pyren



CYPs

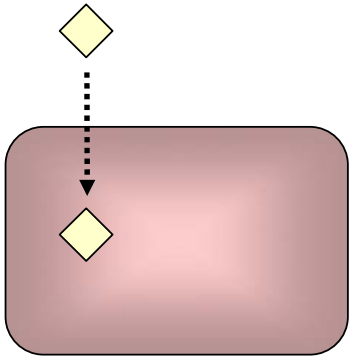



Phase II-Enzyme



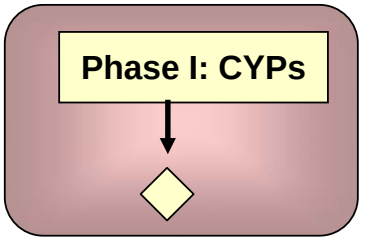

***1. Lipophiler Fremdstoff:***

**freie Diffusion durch Membranen**



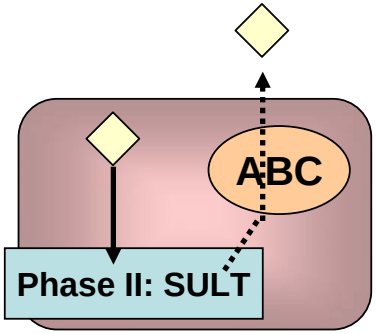
***2. Hydroxylierung von B[a]P:***

**Bildung potentieller Substrate für Phase II Enzyme; Bioaktivierung zu mutagenen Derivaten**

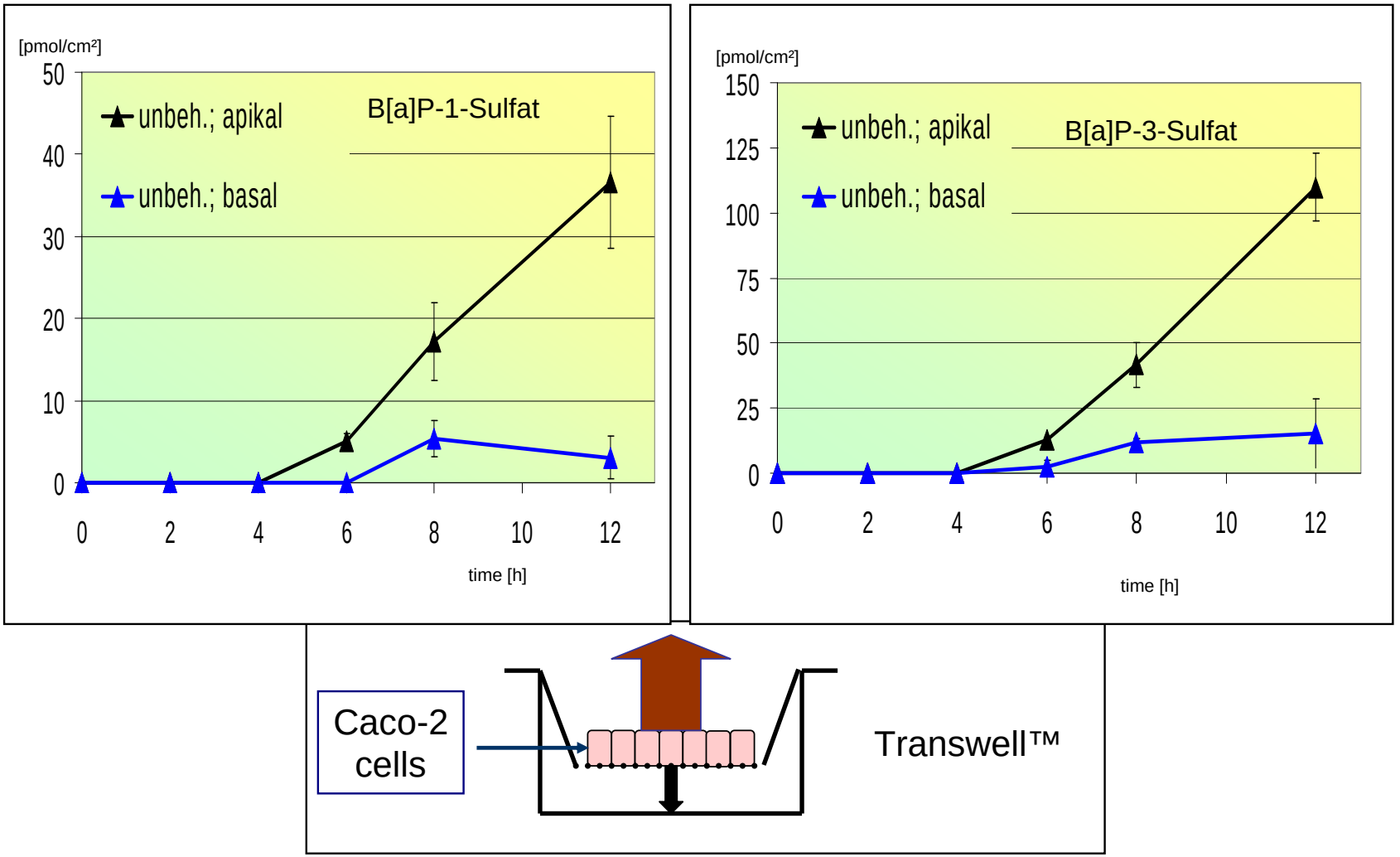



***3. Hydrophiler Phase II-Metabolit:***

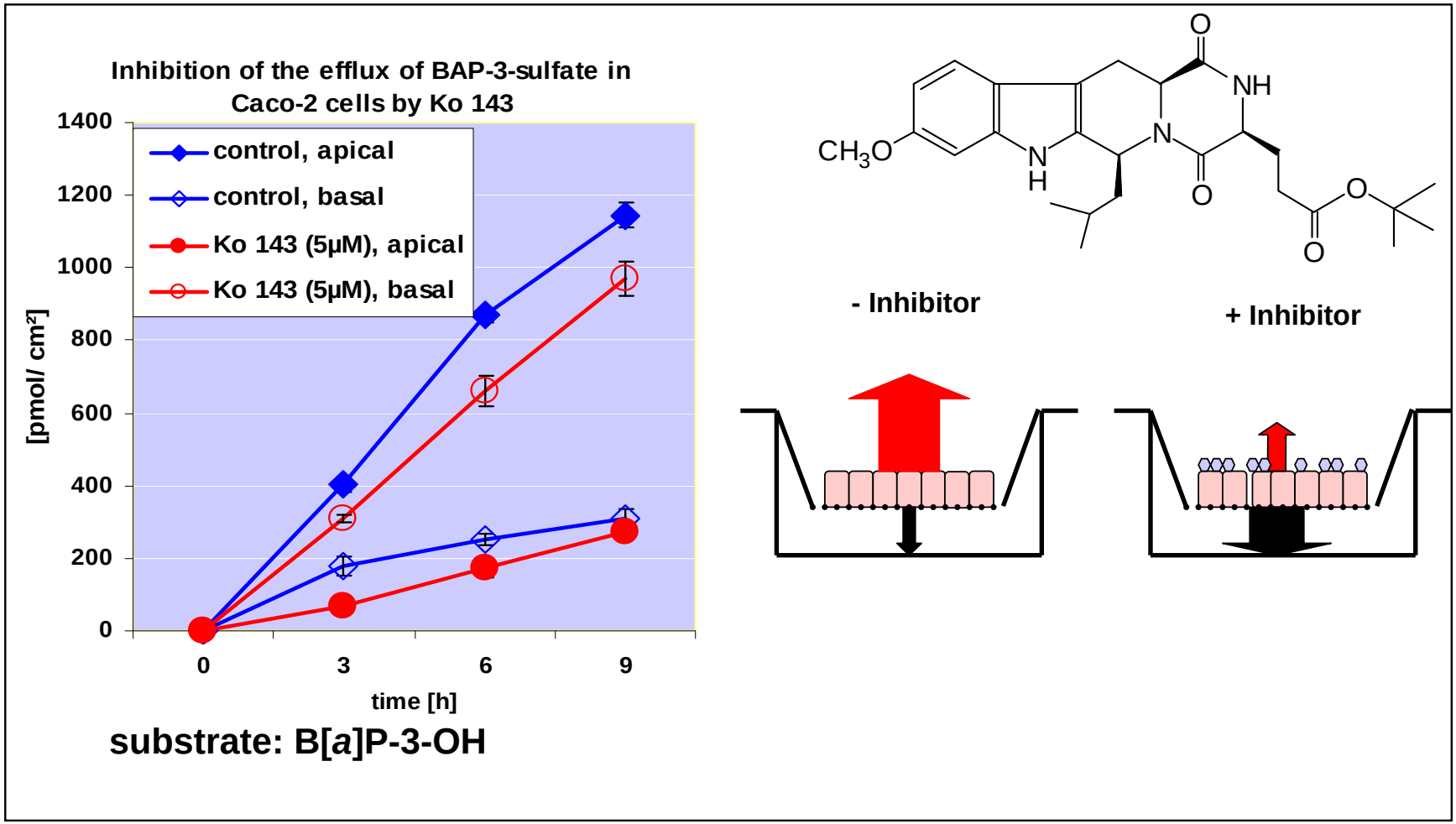
**aktiver Transport aus der Zelle notwendig**



# Transepithelial efflux of B[*a*]P-1-sulfate and B[*a*]P-3-sulfate in human intestinal Caco-2 cells

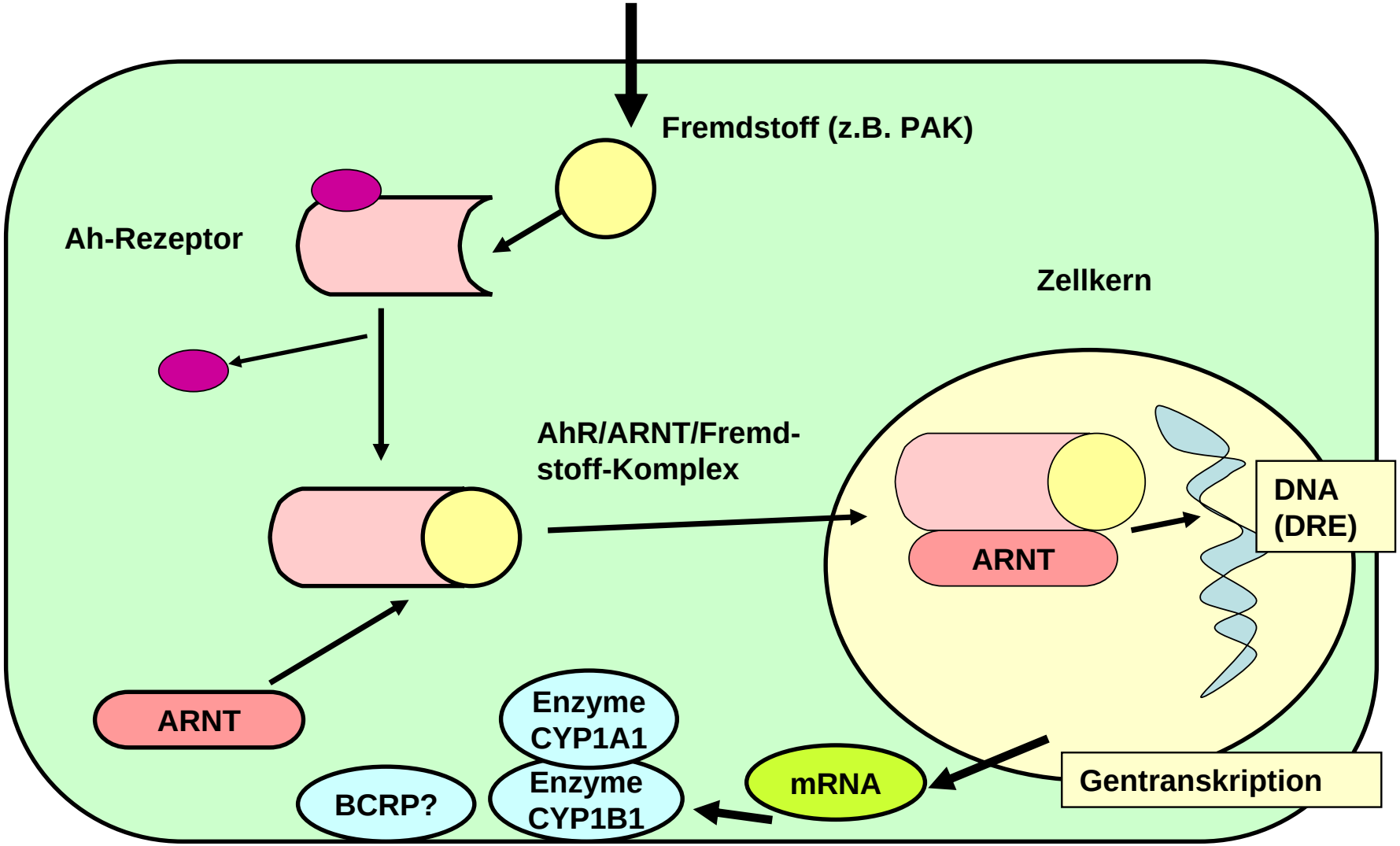


# BCRP is responsible for the transepithelial transport of B[a]P-sulfates in Caco-2 cells



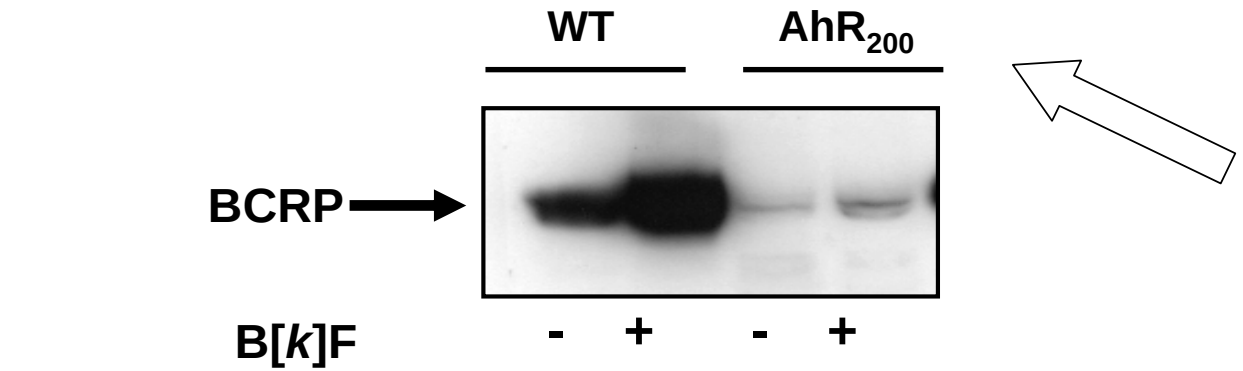
# Ah-Rezeptor Aktivierung durch B[a]P führt zu einer Induktion von CYP1A1/1B1

Kernrezeptor: Arylhydrocarbon-Rezeptor AhR

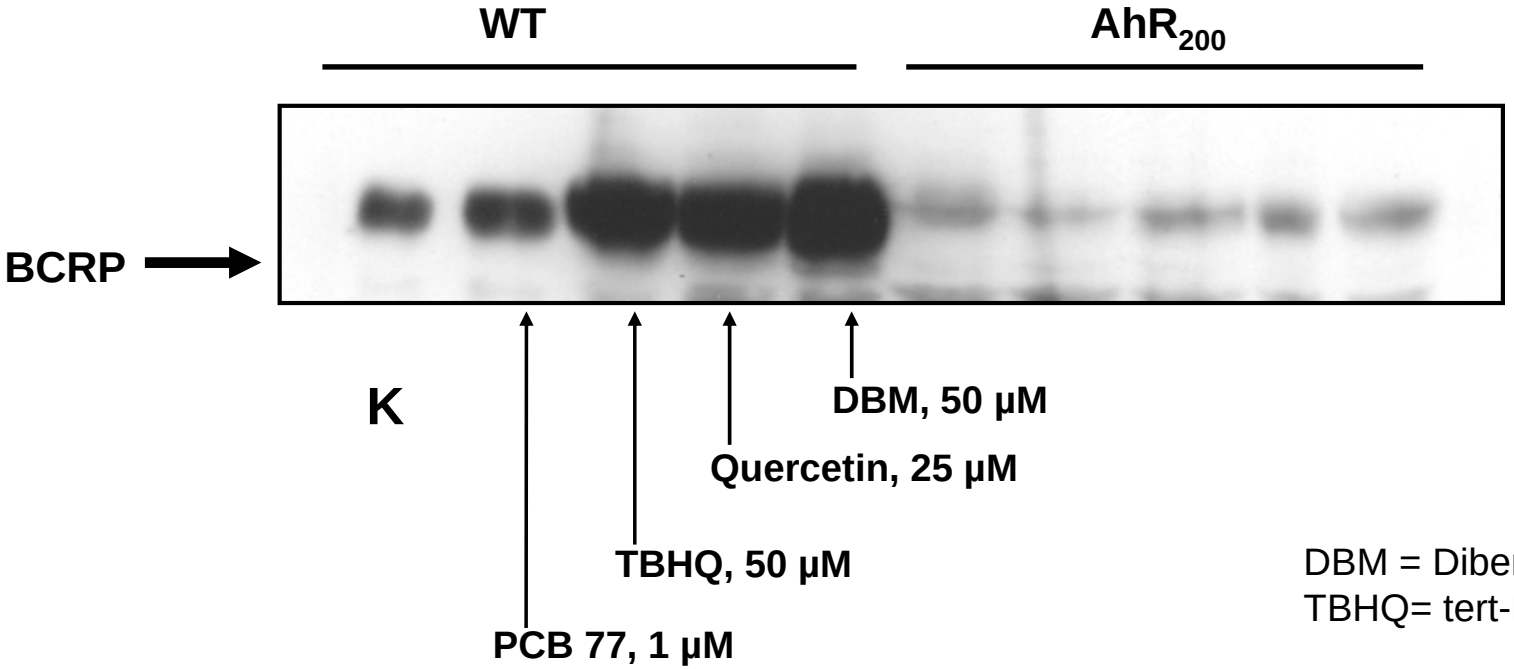



(DRE = Dioxin response element, Promoter)

# The role of AhR: expression of BCRP-protein in MCF-7 cells

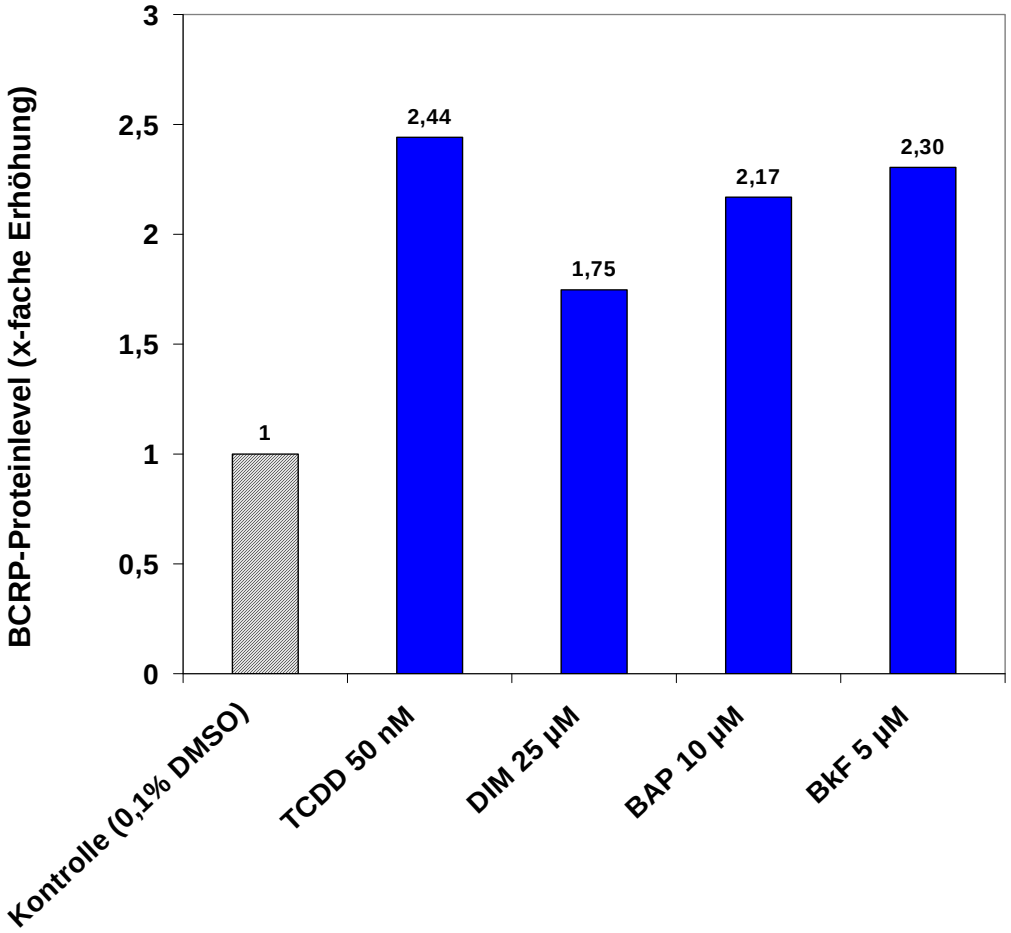


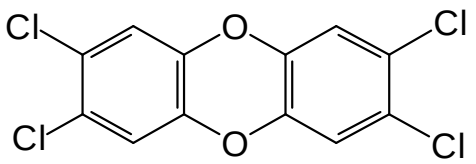

**$AhR_{200}$ : AhR-deficient (Yeh *et al*., 1999): small basal expression of BCRP**



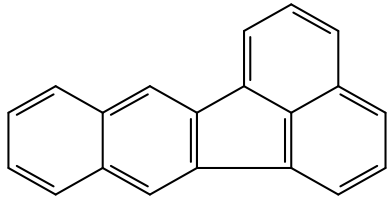

DBM = Dibenzoylmethan
TBHQ= tert-Butyl-hydrochinon

# Induction of BCRP by AhR-agonists in Caco-2 cells

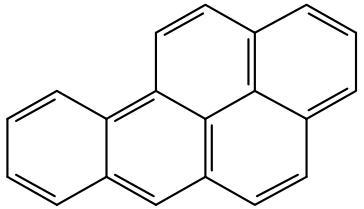


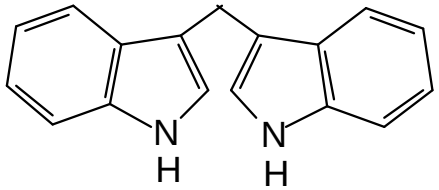

**TCDD**



**BkF**

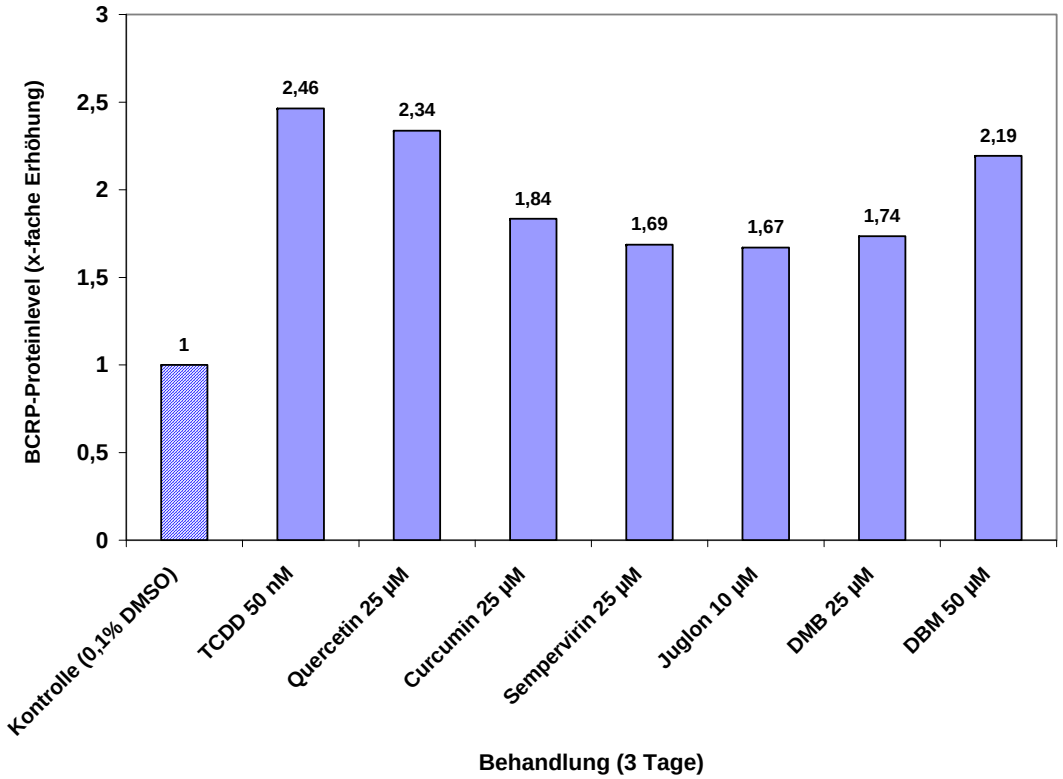


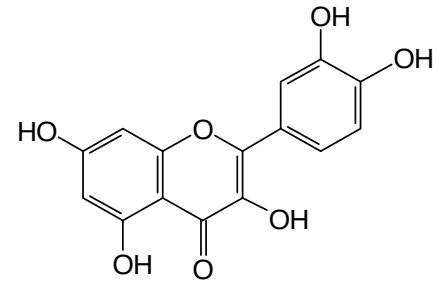
**BaP**



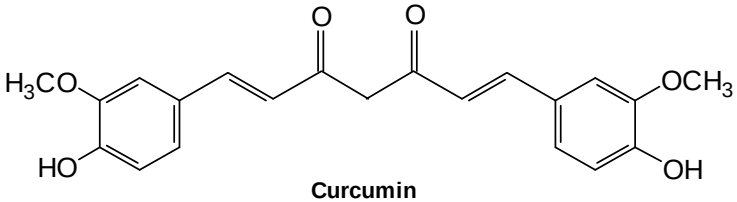

**DIM = 3,3`-Diindolylmethan**

# Induction of BCRP expression by phytochemicals in Caco-2 cells

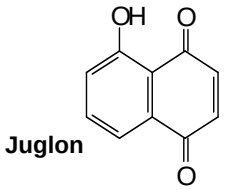


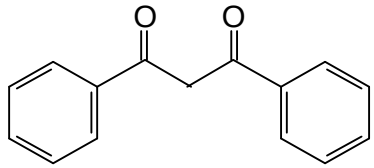

Quercetin




Curcumin

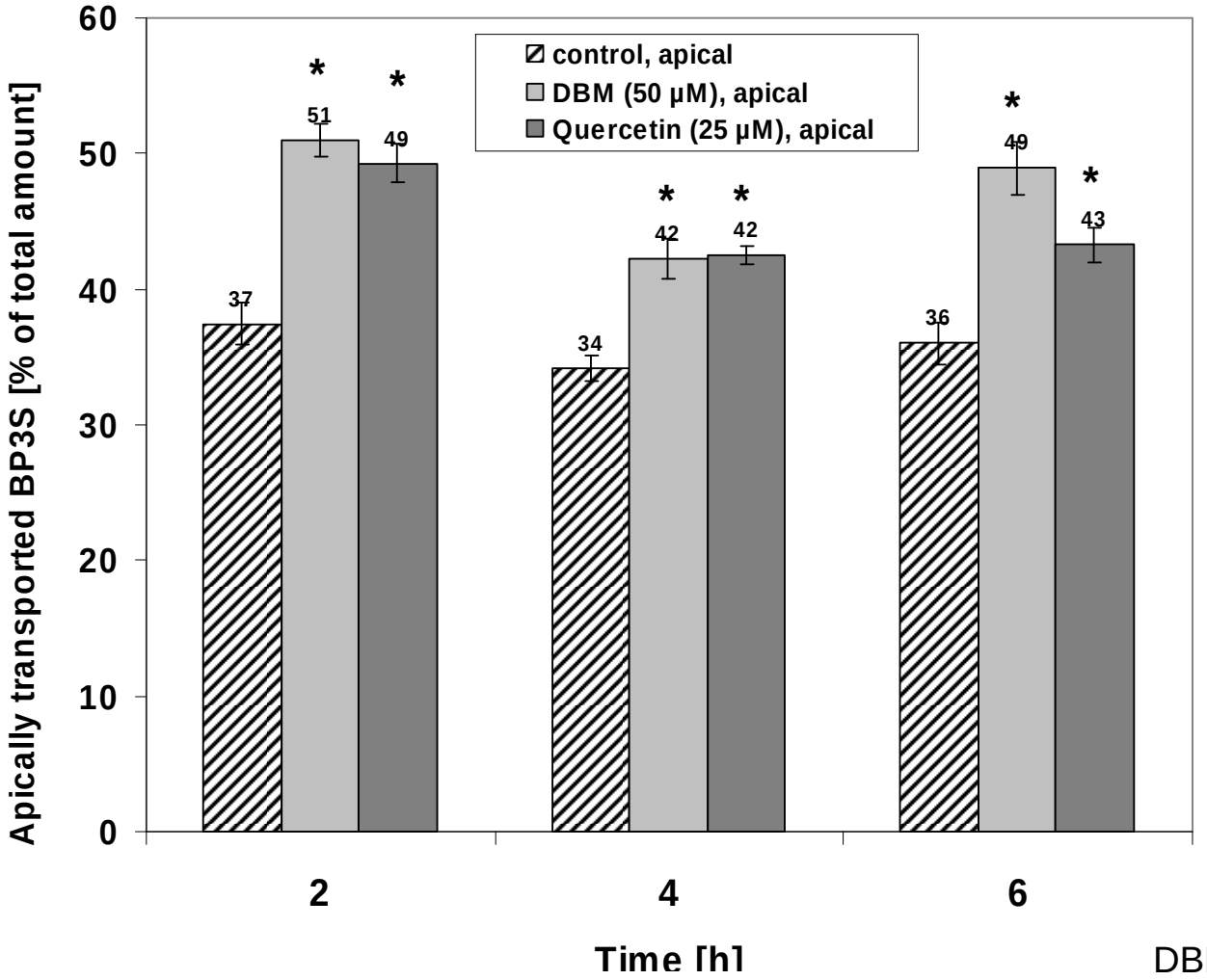




Juglon




Dibenzoylmethan

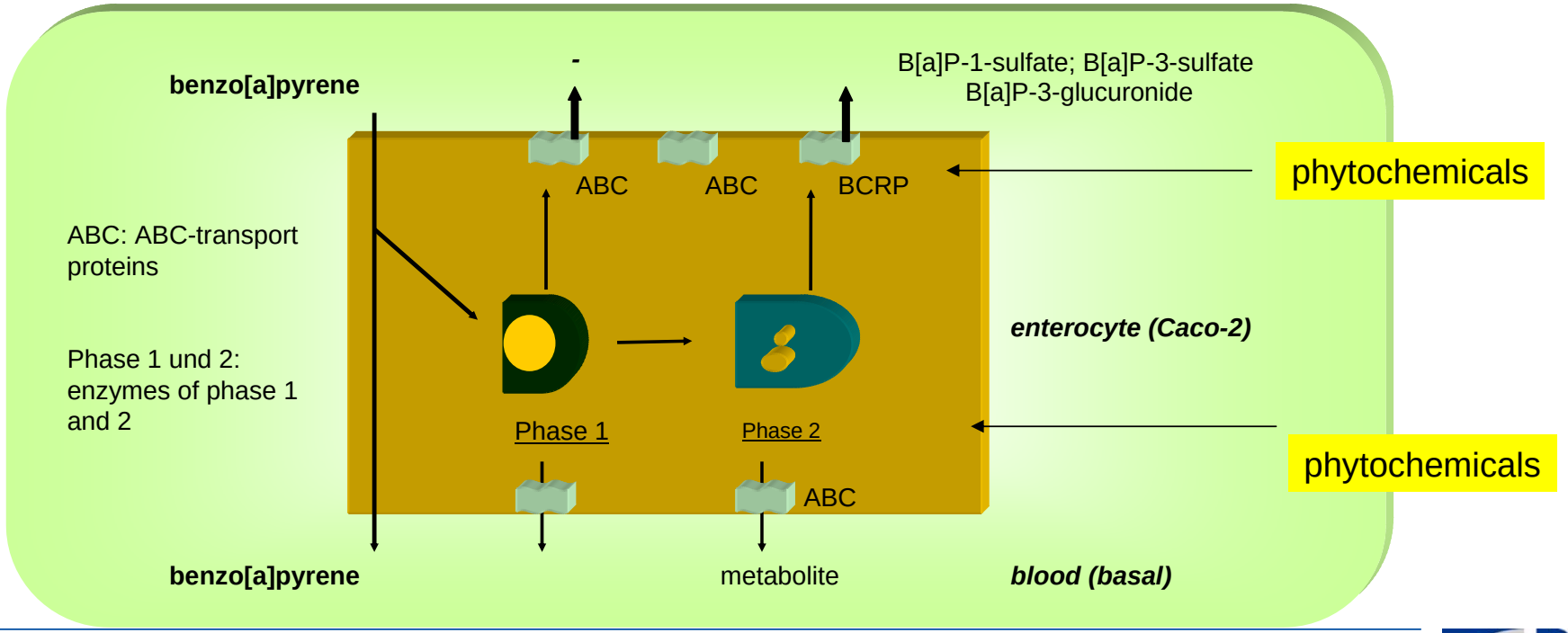
# Effect of DBM and Quercetin on the transport of B[a]P-sulfate in Caco-2 cells




DBM = Dibenzoylmethan
(aus Süßholzpflanze)

# Conclusions

- There is a functional interplay between metabolism of CYP1A1/CYP1B1 substrates (PAHs), Phase II and the transport of metabolites by BCRP
- The ABC-transporter BCRP is responsible for the transport of B[a]P-sulfates und B[a]P-glucuronides
- AhR Agonists induce the gene- and protein expression of the responsible CYPs and BCRP.
- Regulation of BCRP-transporter is most likely AhR dependent.
- Phytochemicals that are AhR-agonist do have an impact on gene/protein expression of BCRP and on its functonal transport of potential toxic phase II metabolites.
- Phytochemicals may influence bioavailability of potential toxic compounds and protect the body against toxic metabolites.



# Acknowledgment


**Dr. Bettina Ebert**
**Dr. Lutz Stumkat**
**Yan Li (Ch), Ph.D**
**Roland Büsen,Ph.D**
**Melissa Mock (AUS) Ph.D**
**Fachgruppe 56 des BfR**

**PD Dr. Albrecht Seidel**
**Biochemisches Institut für Umweltkarzinogene,**
**Prof. G. Grimmer-Foundation, Großhansdorf**

**Prof. A. Schinkel, University of Amsterdam, Netherlands**

**Prof. H.R. Glatt**
**DIFE, Rehbrücke, Potsdam**


# Thank you for your attention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