Xenobiotic Bioavailability: Role of Intestinal Disposition

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Bioavailability and Fraction Dose Absorbed

- Bioavailability (*F*) – measurement of the rate and extent of therapeutically active drug that reaches the systemic circulation and is available at the site of action *(Shargel & Yu, 1999)*
- Fraction Dose Absorbed (f_a) – fraction of oral dose that traverses the intestine intact

Intestinal Disposition

- Intestinal permeability, metabolism, solubility, stability and dissolution of a xenobiotic
- Inhibition of membrane transporters and/or metabolizing enzymes
- Modulation of the expression of membrane transporters and/or metabolizing enzymes

Factors Affecting Oral Bioavailability

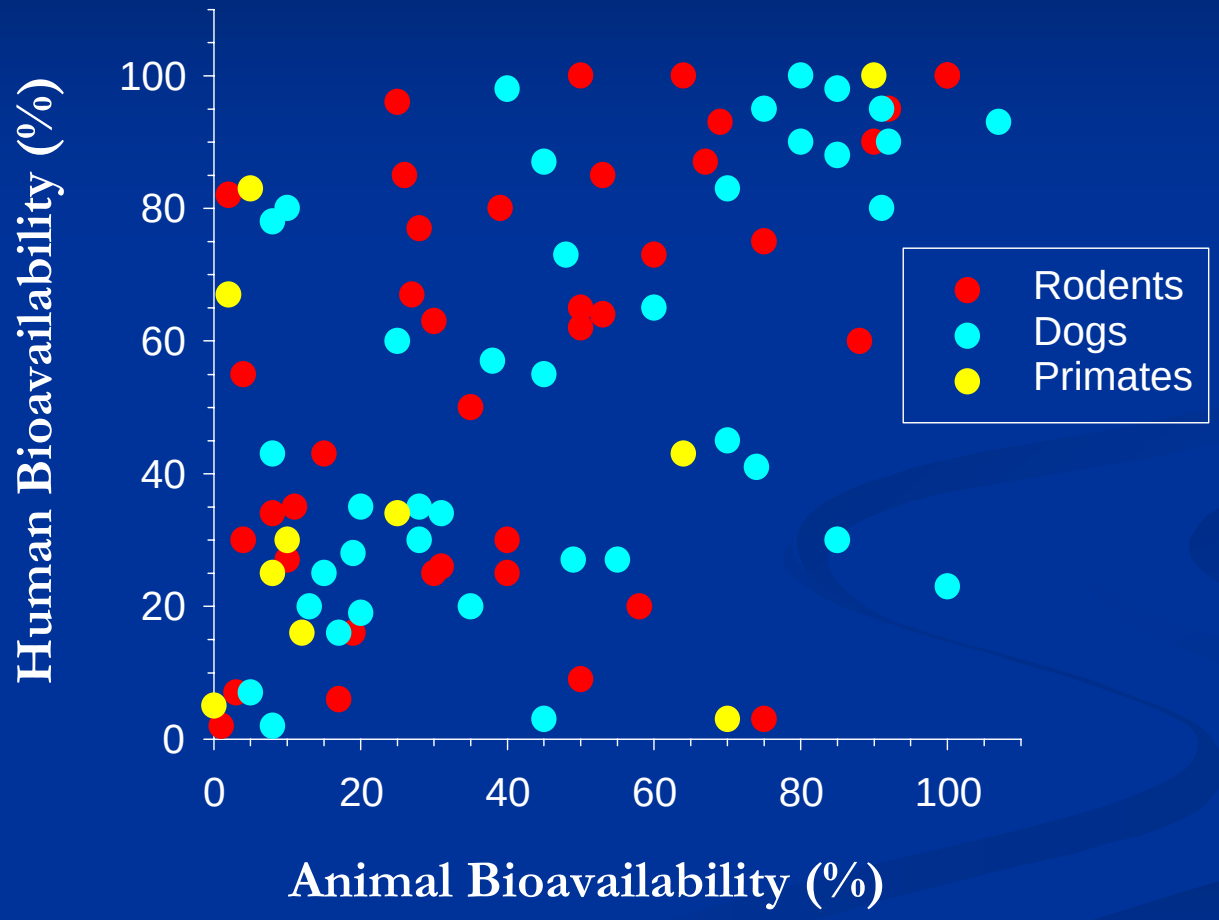
Physicochemical

- Solubility
- Ionization
- Dissolution Rate
- Chemical Stability
- Diffusion (intra-lumenal)

Physiological

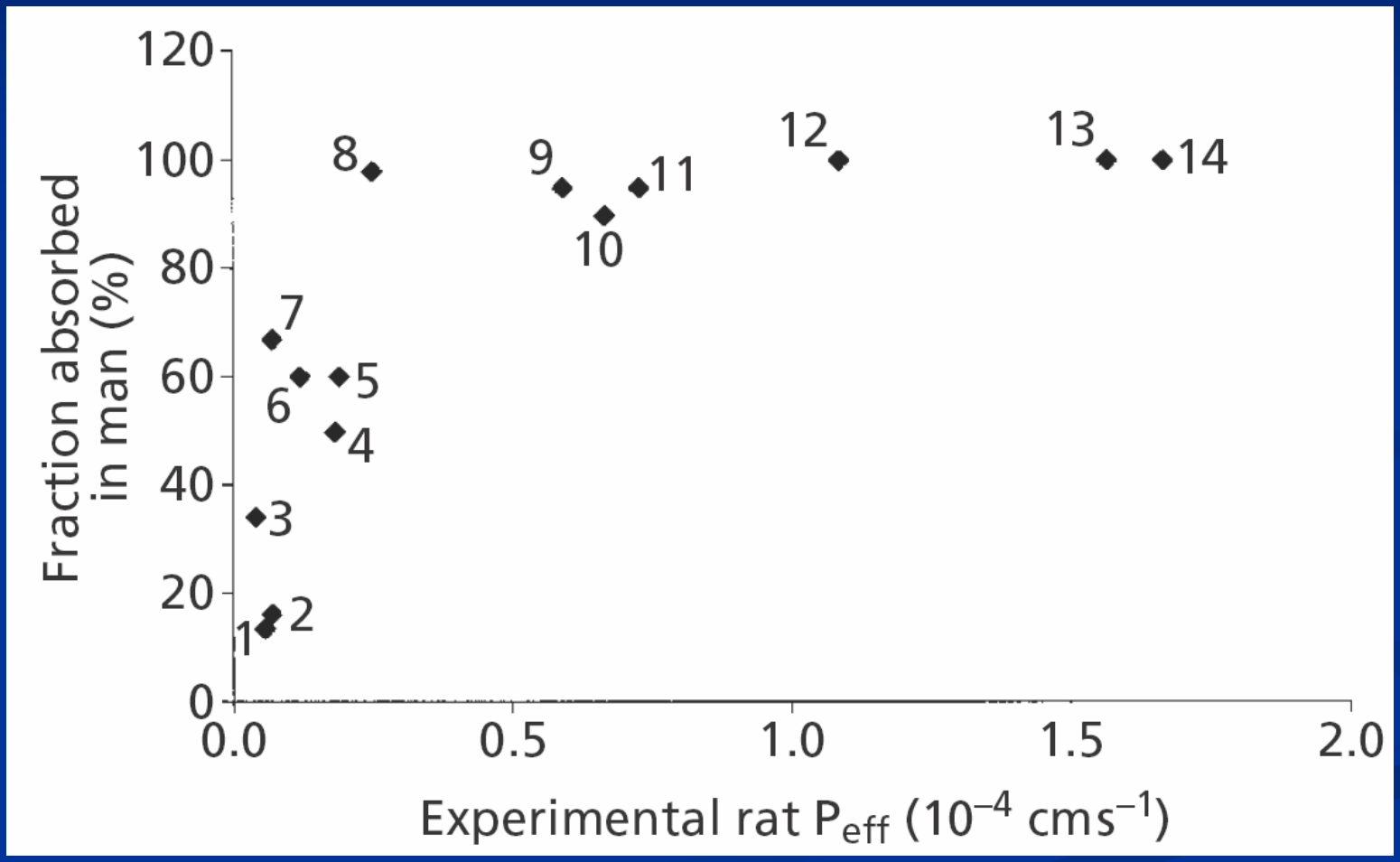
- GI Transit
- Bile Secretion
- Transport Mechanisms
- Metabolism
- Regional Effects
- Polymorphism of Transporters/Enzymes

Oral Bioavailability Comparison



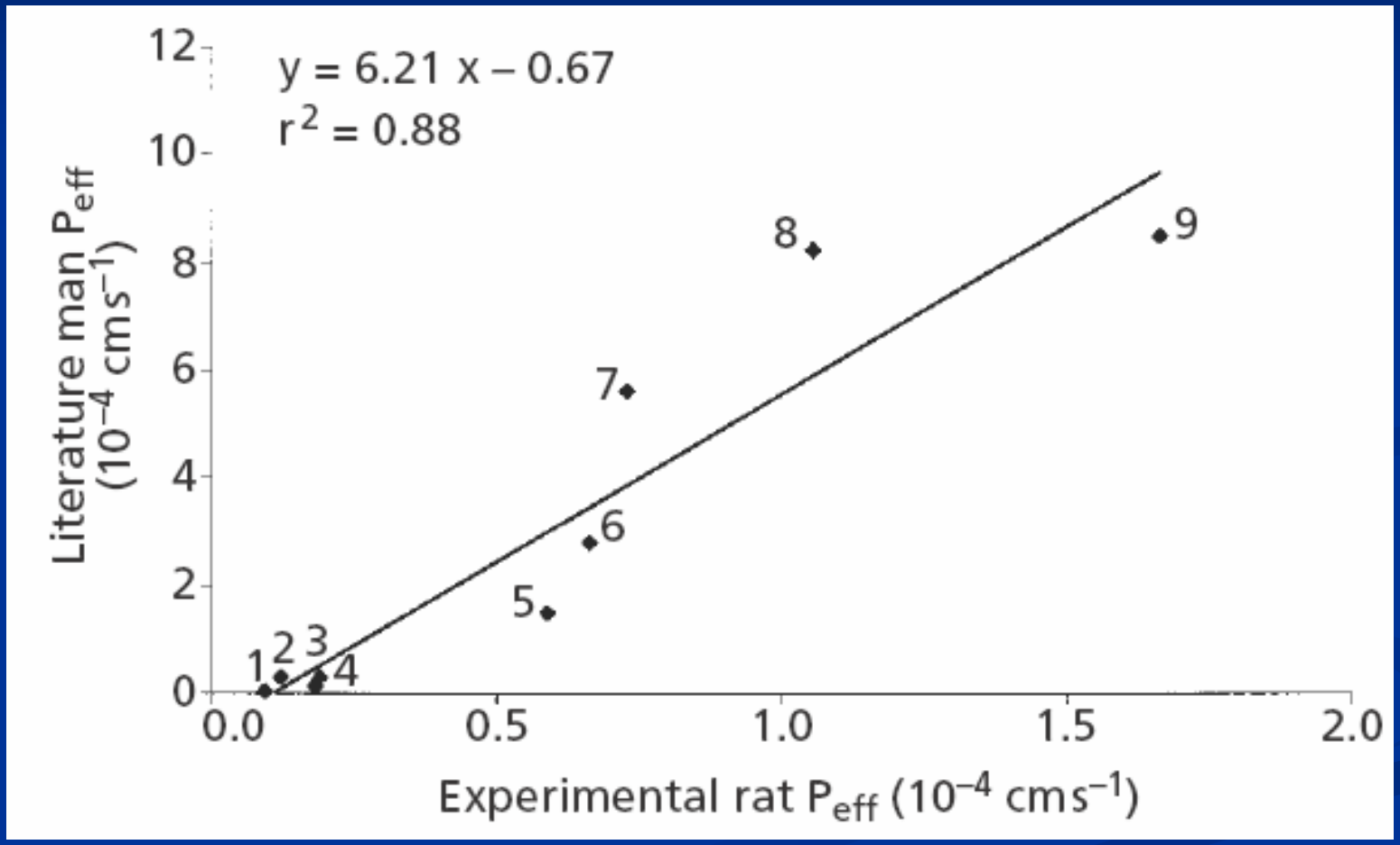
Adapted from: W.K. Sietsema, *Int. J. Clin. Pharmocol. Ther. Toxicol.*, **27**:179-211 (1989)
G. Grass

Fa – Permeability Comparison



From: L. Salphati, et. al., *J. Pharmacy Pharmocol.*, **53:**1007-1013 (2001)

Permeability – Permeability Comparison



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Intestinal Transport and Metabolism

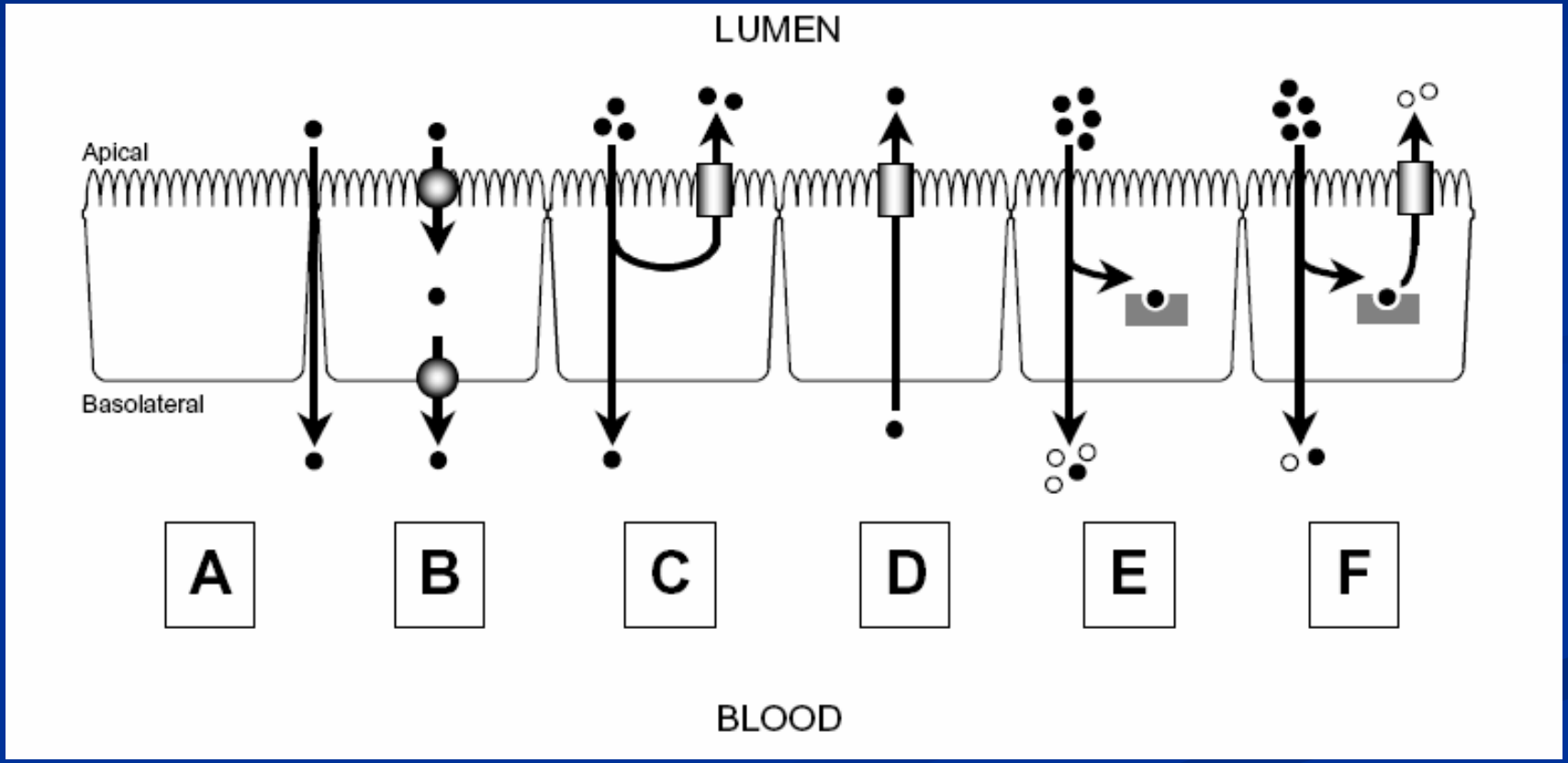


Figure from *Eur J Pharm Sci* **21**: 25, 2004

Proteins Involved in Intestinal Disposition

- Influx Transporters
  - Peptide, bile acid, nucleoside, amino acid, etc.
- Efflux Transporters
  - P-gp, MRP2, BCRP, etc.
- Metabolizing Enzymes
  - Phase I – CYP isoforms (primarily 3A4, 2D6,
  - Phase II – GSTs, UGTs, sulfotransferases
- Nuclear Hormone Receptors
  - CAR, PXR, PPAR, RXR, etc.

Intestinal Disposition

- Permeability
- Metabolism

Also

- Inhibition
- Induction

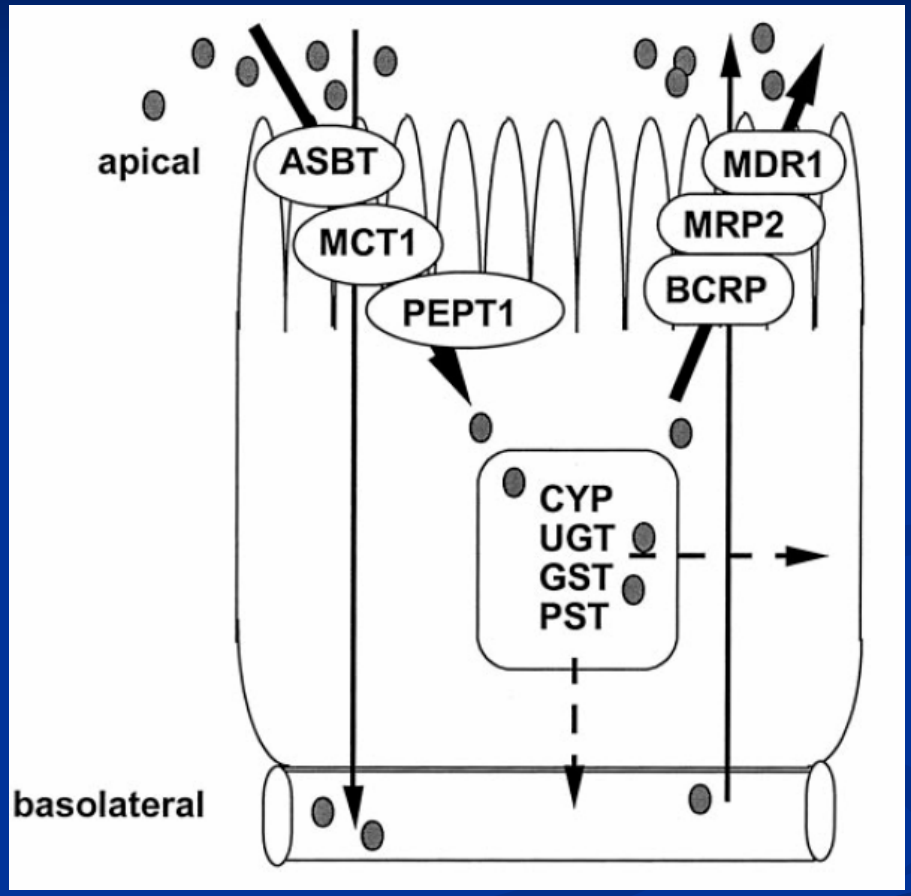
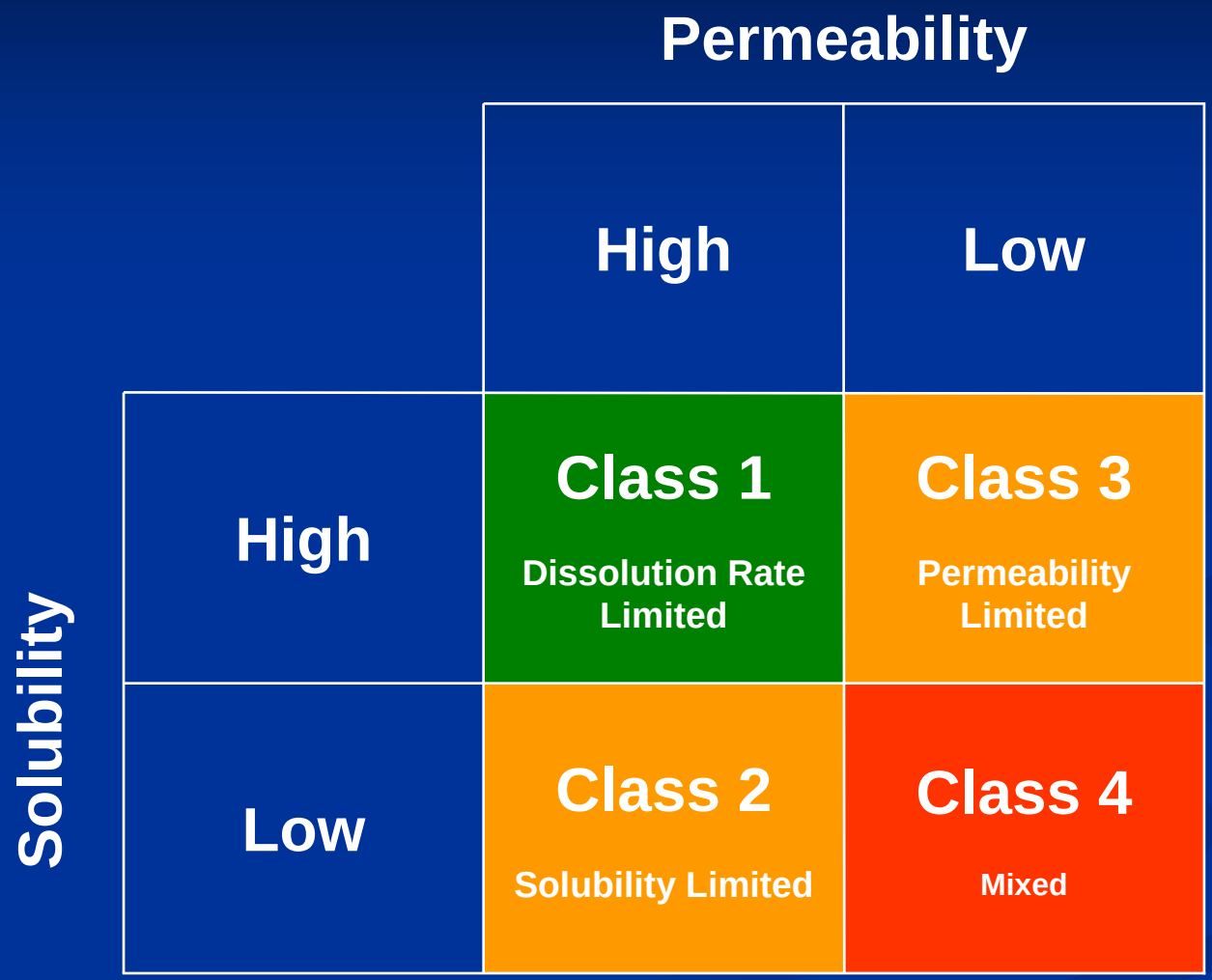
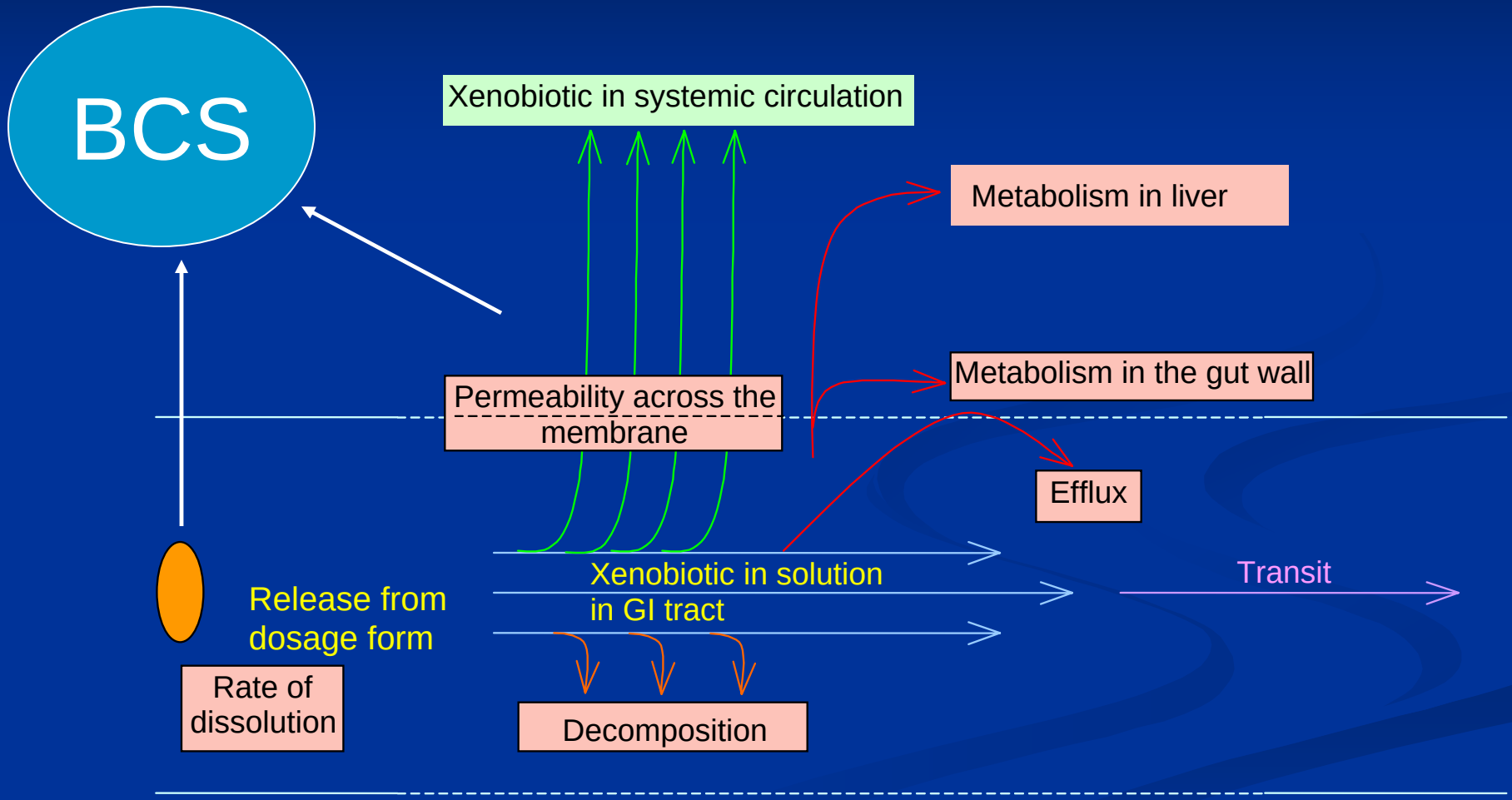


figure from *Drug Metab Dispos* **31**: 1507, 2003.

Biopharmaceutical Classification System



Factors affecting rate and extent of oral absorption



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Clinical Intestinal Metabolism Drug Interactions

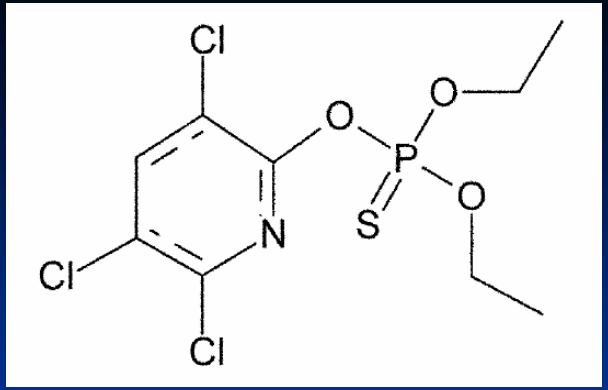
Drug	Interacting agent	Effect on relative bioavailability	Inhibition or induction	Clinical significance
Immunosuppressants				
Cyclosporin	Ketoconazole	↑ × 2.5	Inhibition	High cyclosporin concentrations, enabling a reduction in dosage
	Erythromycin	↑ × 2.0	Inhibition	
	Grapefruit juice	↑ × 0.6	Inhibition	
Tacrolimus	Rifampicin	↓ × 2.7	Induction	Therapeutic failure: transplant rejection
	Ketoconazole	↑ × 2	Inhibition	High concentrations: dosage reduction
Antivirals				
Saquinavir	Grapefruit juice	↑ × 2	Inhibition	High concentrations: dosage reduction
Indinavir	St John's wort	↓ × 2	Induction	Therapeutic failure
Cardiac				
Nifedipine	Rifampicin	↓ × 8	Induction	Therapeutic failure
	Grapefruit juice	↑ × 2.8	Inhibition	Potential toxicity
Felodipine	Erythromycin	↑ × 2.5	Inhibition	Increased toxicity: low blood pressure
	Grapefruit juice	↑ × 1-2	Inhibition	
	Itraconazole	↑ × 6	Inhibition	
Other				
Simvastatin	Itraconazole	↑ × 5	Inhibition	Potential for increased skeletal muscle pain
	Grapefruit juice	↑ × 16	Inhibition	
	Erythromycin	↑ × 4	Inhibition	
Lovastatin	Grapefruit juice	↑ × 15	Inhibition	Potential for increased skeletal muscle pain
	Cyclosporin	↑ × 20	Inhibition	
	Itraconazole	↑ × 20	Inhibition	

(adapted from:
Doherty, M.M. and Charman, W.N., *Clin Pharmacokinet*, **41**:235-253, 2002)

Preclinical Methods for Intestinal Disposition

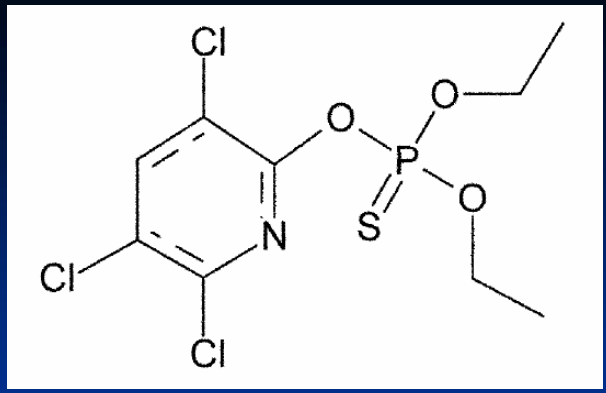
- Intestinal permeability studies
  - Perfusion
  - Diffusion chamber (excised tissue or cultured cells)
  - Everted gut sac
  - PAMPA
- Intestinal metabolism
  - Perfusion
  - Microsomes
- Oral PK studies
  - P-gp, CYP inhibitors
  - Knockout animals

Chlorpyrifos



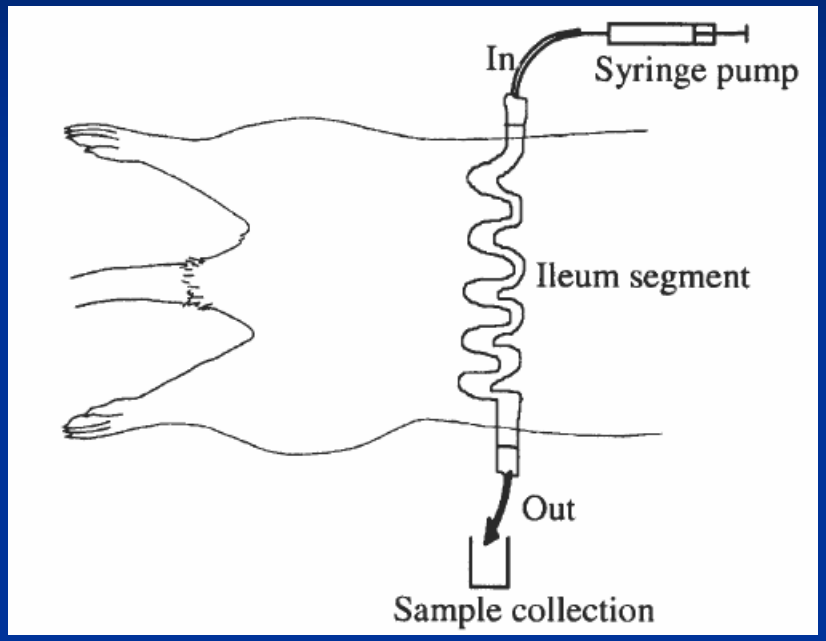
- Organophosphate pesticide
- Potential exposure routes
- Limited human bioavailability studies
- Goals
  - Determine intestinal permeability as a function of region and concentration
  - Determine effect of chlorpyrifos on expression and function of membrane transporters

Chlorpyrifos



- Single-pass Intestinal Perfusion (SPIP)
  - Regional permeability as a function of concentration
- Exposure studies in Caco-2 cells
  - Competitive PCR assay for MDR1
  - Effect on membrane efflux function

Single Pass Intestinal Perfusion



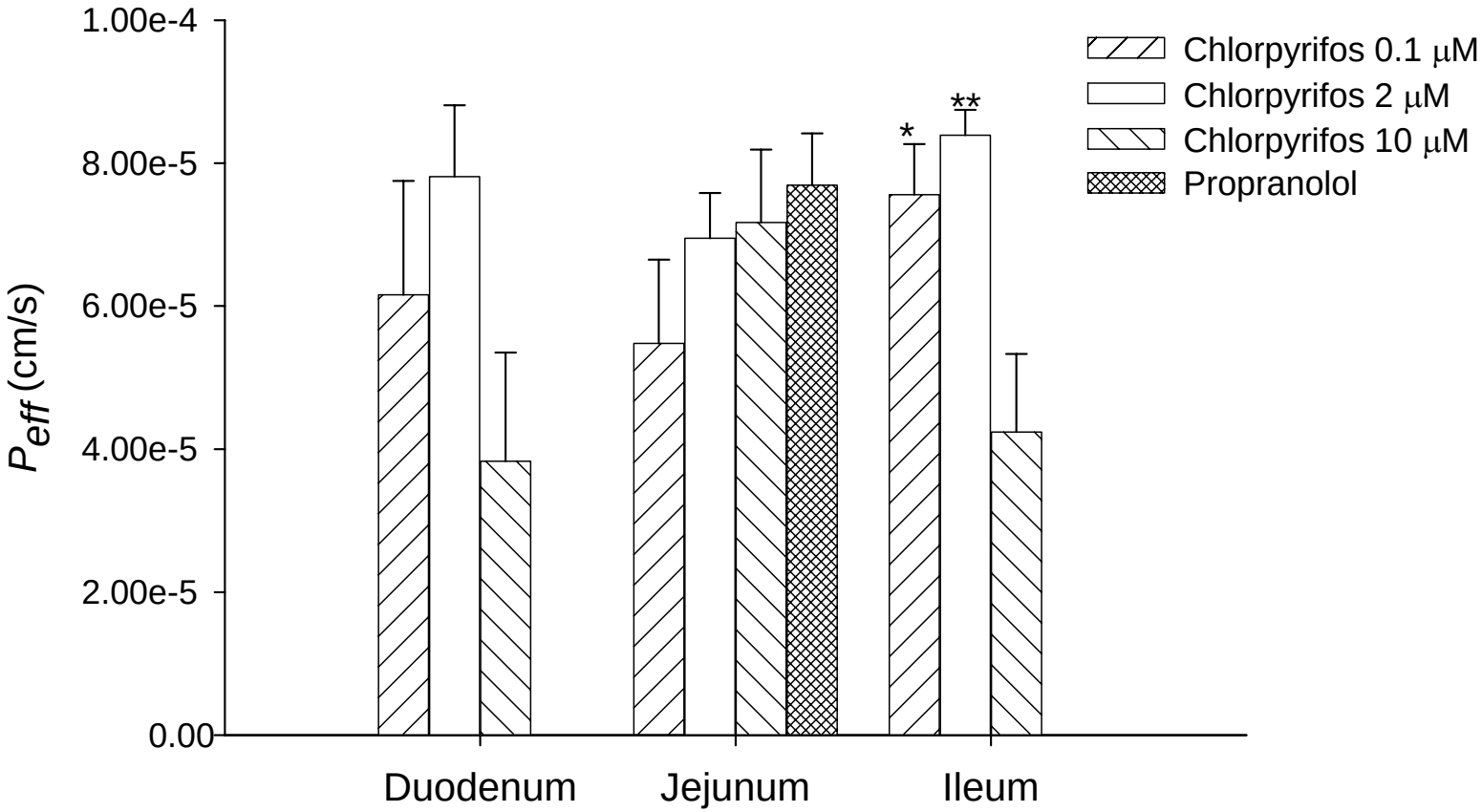
- Permeability determined by loss from perfusate

$$P_{eff} = \frac{-Q}{2\pi r l} \ln\left(\frac{C_{out}}{C_{in}}\right)$$

- Correct for adsorption, stability, accumulation

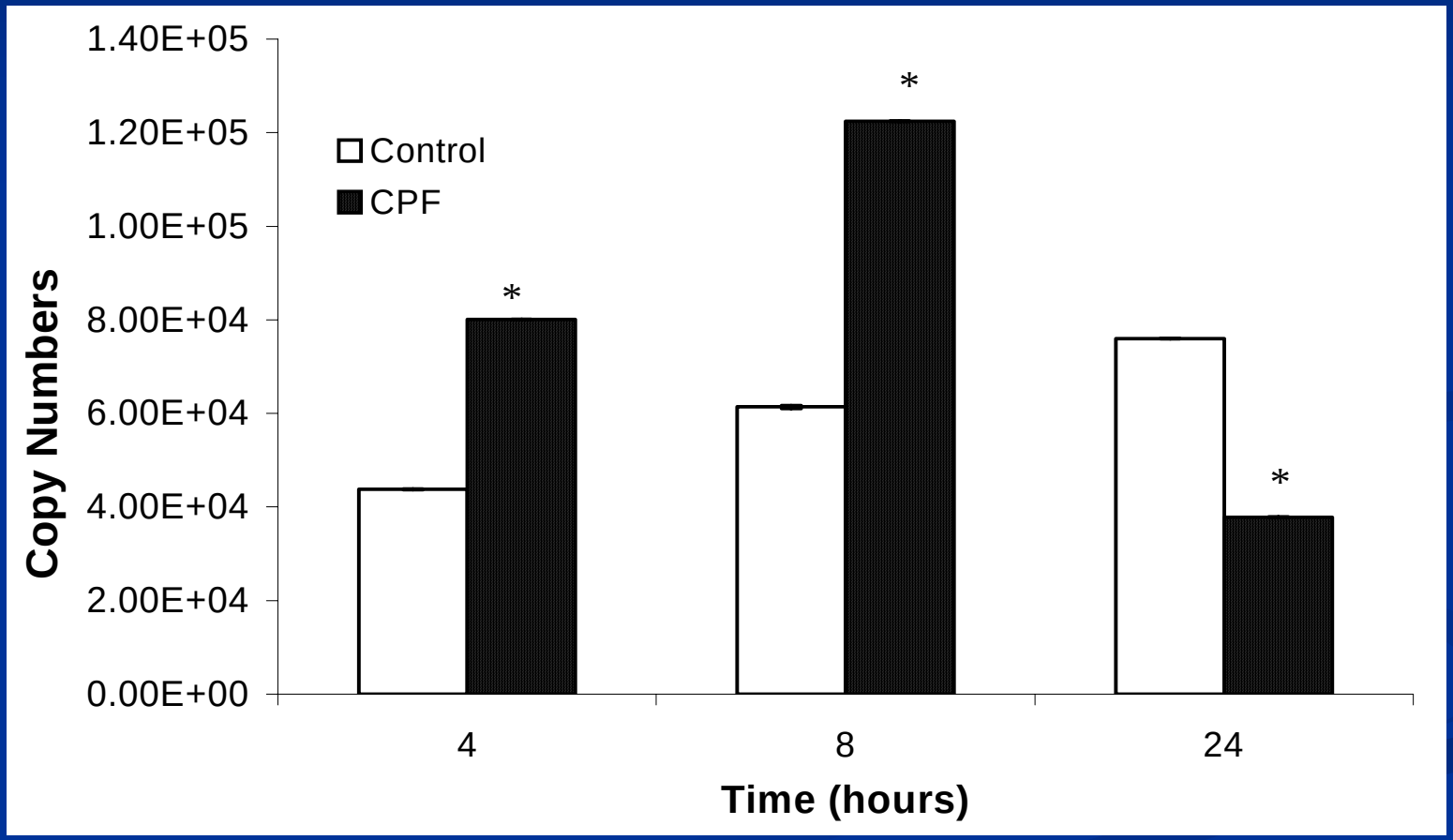
Figure from: Salphati, et al, JPP 2001, **53**: 1007–1013

Results – Permeability



T.J. Cook and S.S. Shenoy, *Toxicology*, **184**:125-133, 2003

Results – Effect of CPF on MDR1 Expression in Caco-2 Cells



S. Agarwala, W. Chen and T.J. Cook, *Toxicol. In Vitro*, **18**:403-409 (2004)

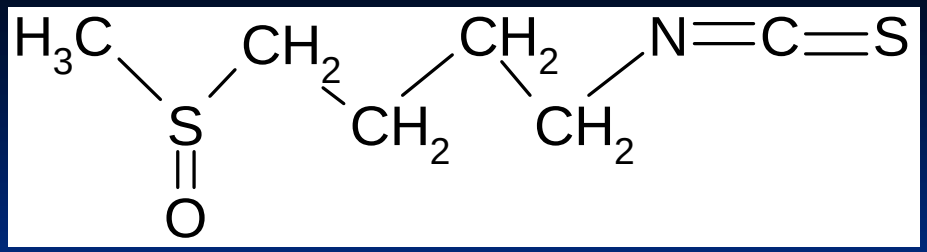
Results

Effect of CPF on Efflux Function in Caco-2 Cells

	VL	*VC*	*VH*
Control	2.87	3.40	4.44
8 hr CPF pre-incubation	3.65	4.18	5.01
Increase	27%	23%	13%

S. Agarwala, W. Chen and T.J. Cook, *Toxicol. In Vitro*, **18**:403-409 (2004)

Sulforaphane



- Isothiocyanate from cruciferous vegetables
- Potential chemopreventive agent
- Mechanism of action
  - Induction of Phase II metabolizing enzymes and efflux transporters, e.g., MRP2
- Goal: Determine intestinal disposition and effect of SFN on expression of Phase II enzymes and MRP2 in intestine

SPIP-MV

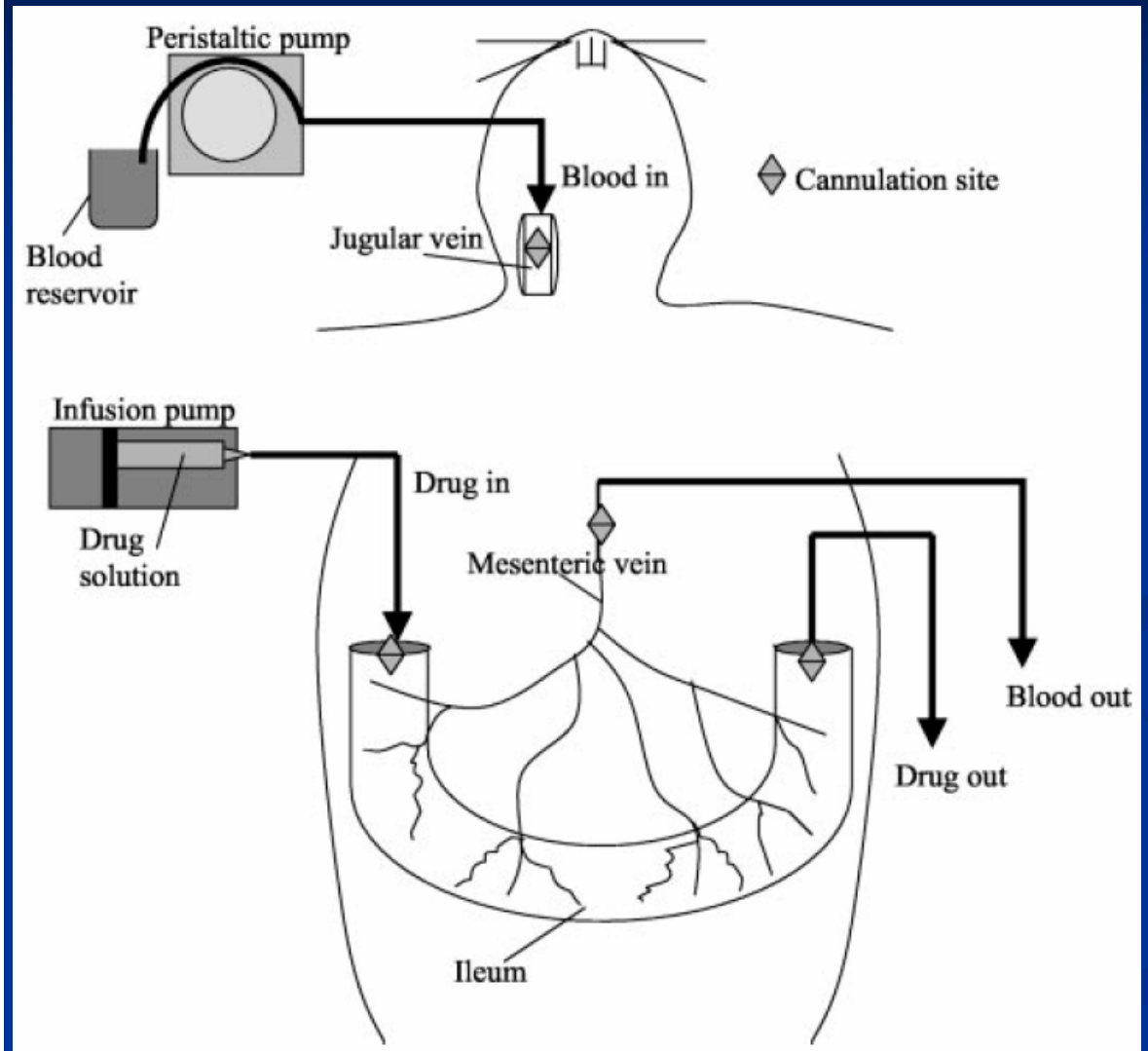
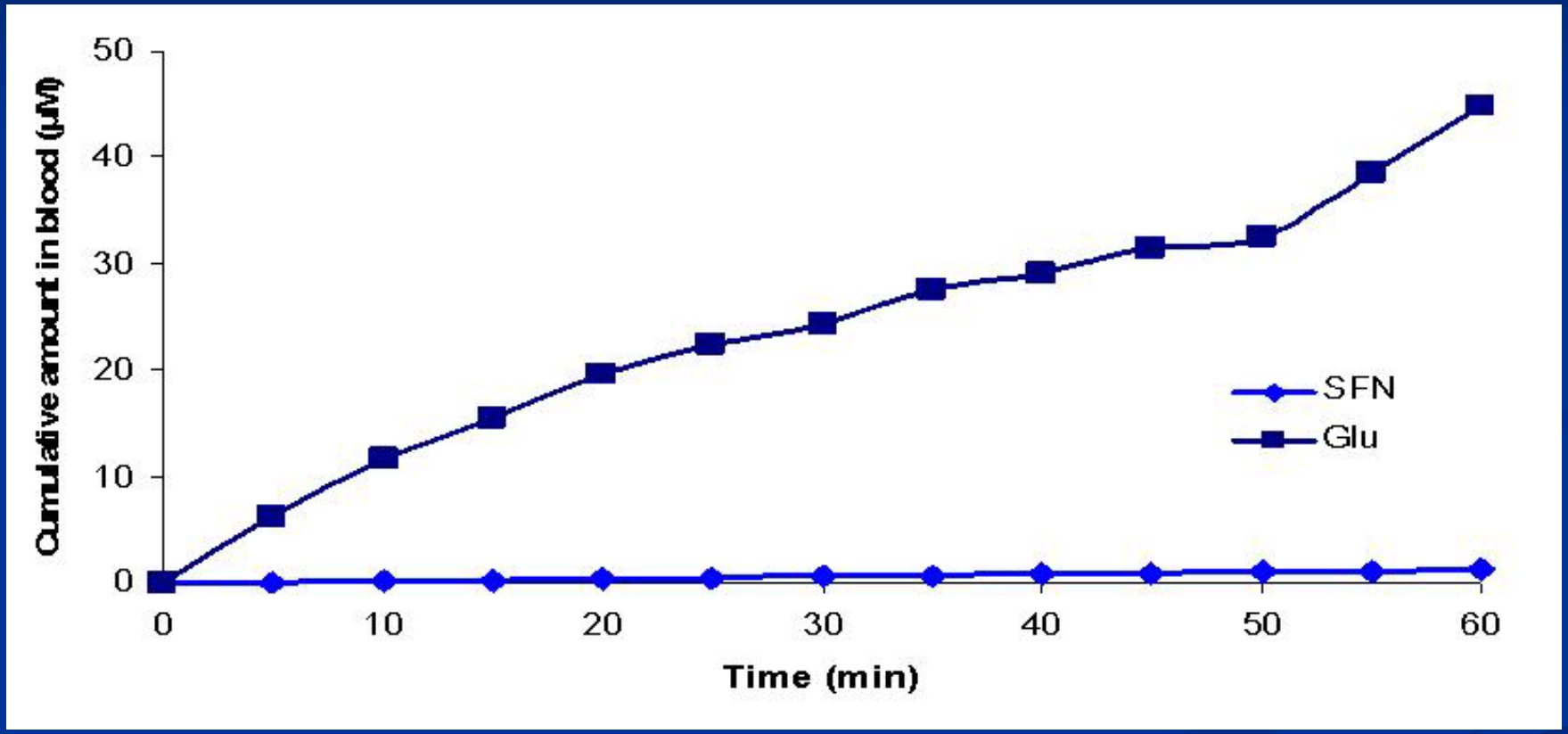


Fig. 1. Illustration of the experimental setup for single-pass intestinal perfusion with mesenteric cannulation and continuous infusion of blood through the jugular vein.

- Permeability Determination
  - Lumenal
  - Blood
- Bioanalytical

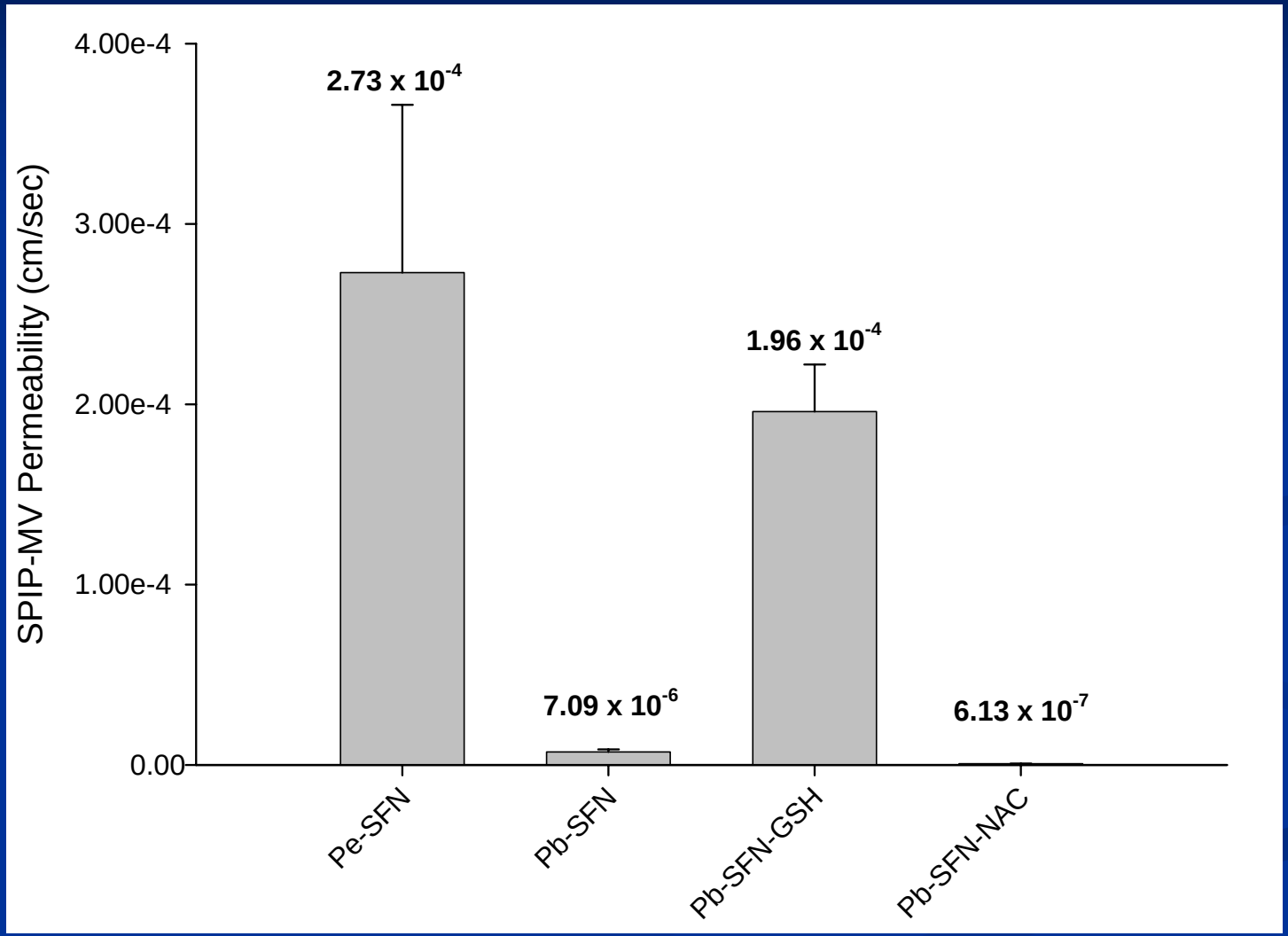
Figure from Cummings, et al, *JPET*, **305**:306, 2003.

SFN and SFN-GLU in Mesenteric Blood



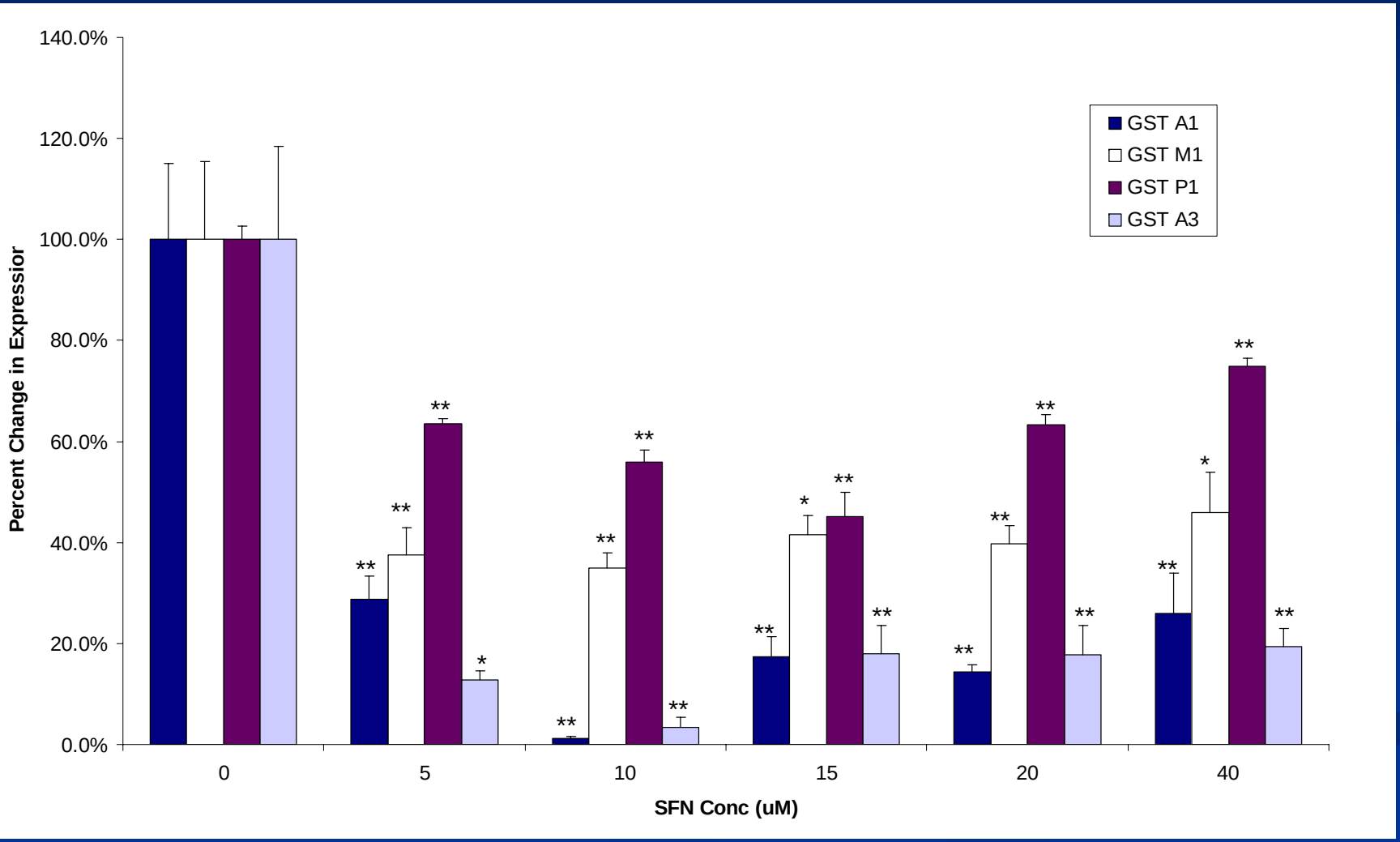
Agrawal, S., Tsao, Y., Hu, P., and Cook, T.J., Intestinal Disposition of Sulforaphane, In Preparation, 2005.

Permeability of SFN and Metabolites



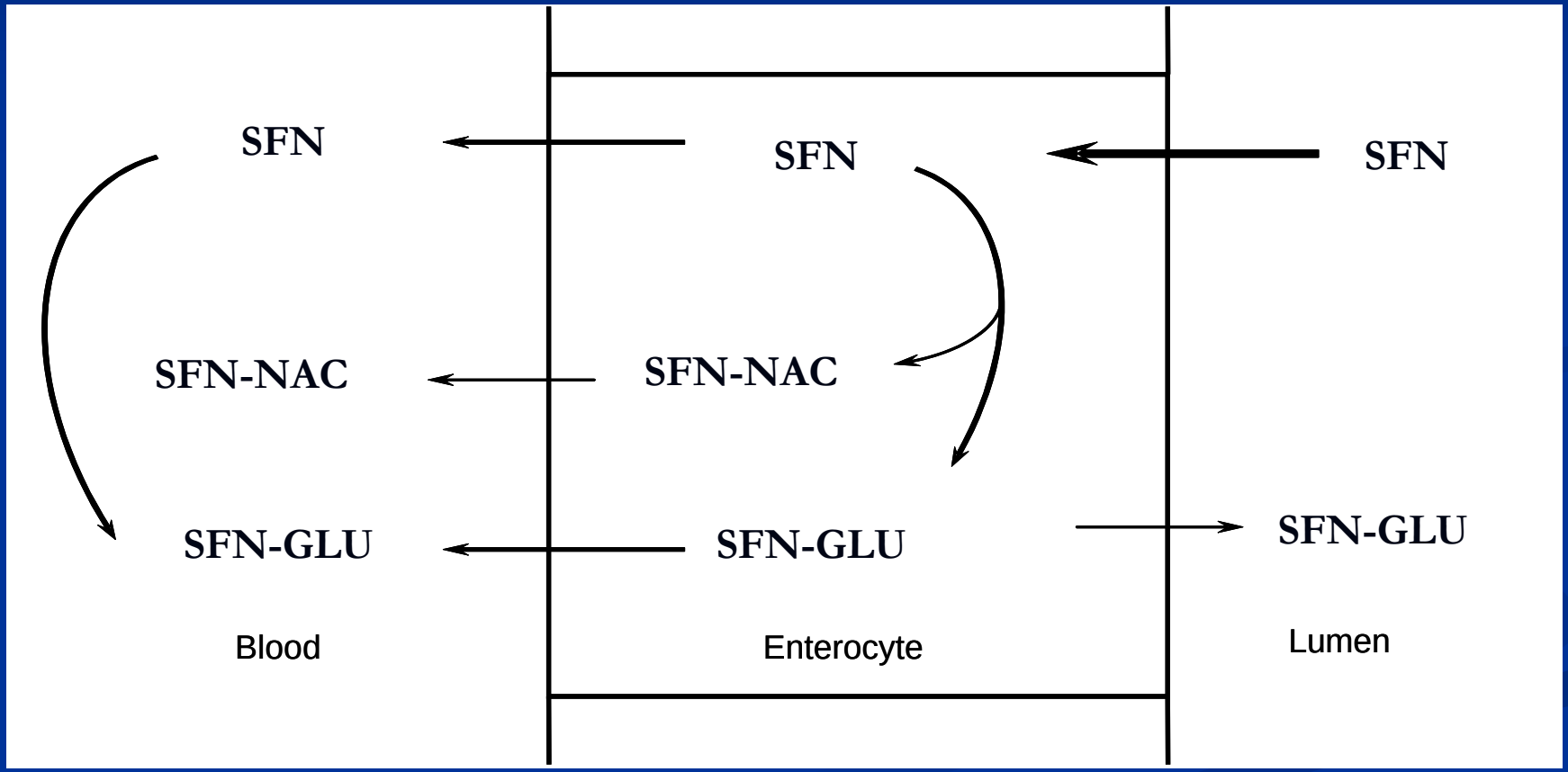
Agrawal, S., Tsao, Y., Hu, P., and Cook, T.J., Intestinal Disposition of Sulforaphane, In Preparation, 2005.

Effect of SFN on GST Expression in Rat Ileum



Tsao, Y., Hu, P., and Cook, T.J., AACR Frontiers in Cancer Prevention Research, #A133, 2004.

Model of SFN Intestinal Disposition



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Relevance

- Depends on:
  - Metabolic pathways
  - Therapeutic index of drug
  - Toxicity of xenobiotic
  - Variability in intestinal metabolism
- Xenobiotic – Drug Interactions
  - Induction of expression
  - Relative affinity for transporter/enzyme
  - Concentration, etc
  - Exposure

Summary

- Intestinal disposition is critical for the bioavailability of orally administered compounds *(but may not be the limiting factor)*
- Interactions with transporters/enzymes (modulation of expression and/or function) should be considered
- Dietary factors (e.g., grapefruit juice) can contribute to variability in oral drug bioavailability
- "Baseline" expression of patients may change based on dietary factors
- Potential contribution of unidentified transporters and enzyme isoforms

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