A Framework to Prioritize Trace Organics for Human and Eco-Toxicity Studies

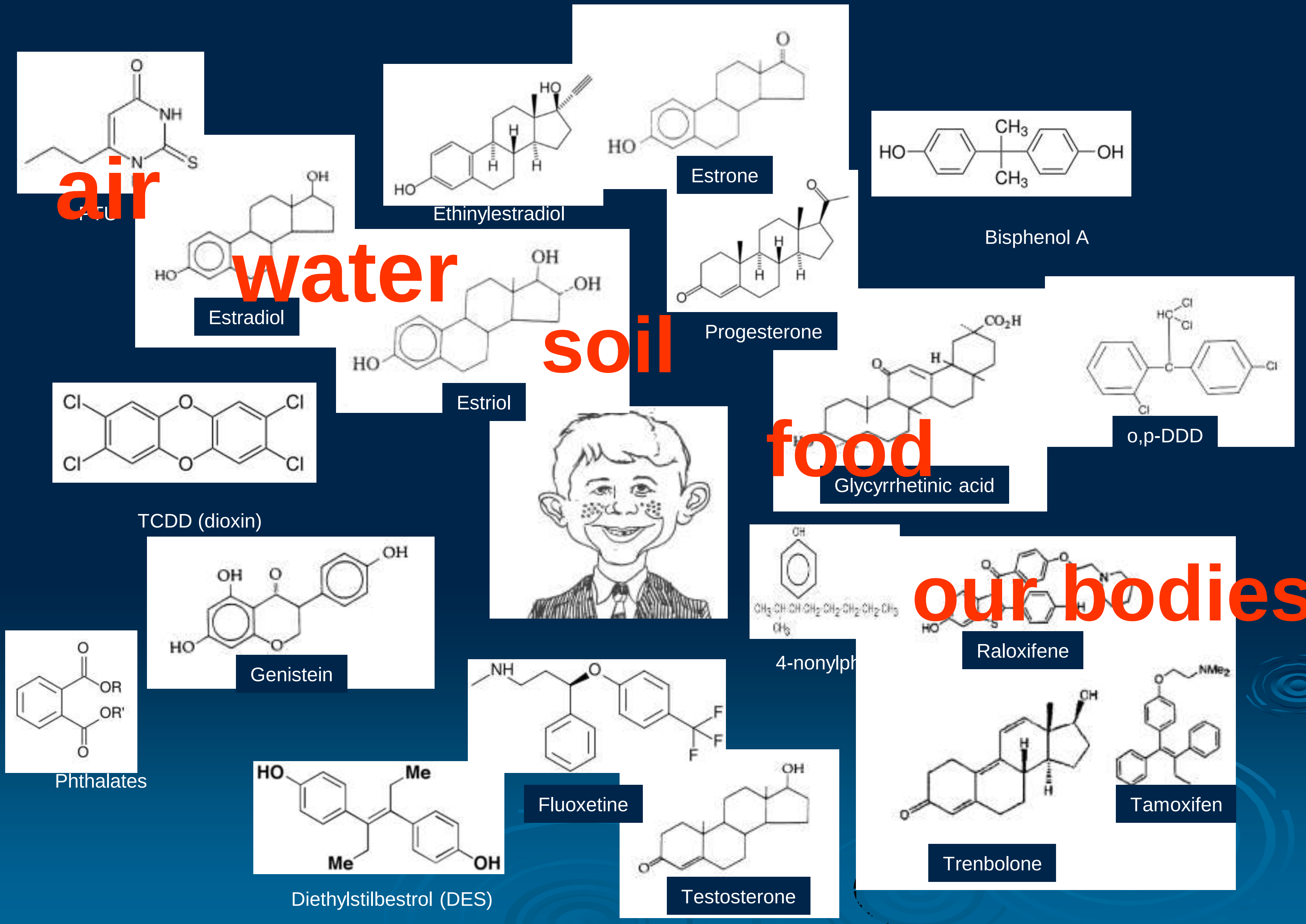
Kuldip Kumar

MWRD Chicago

Email: Kuldip.Kumar@mwrd.org

Ph.: 708.588.3579

The Chemical Sea Around Us



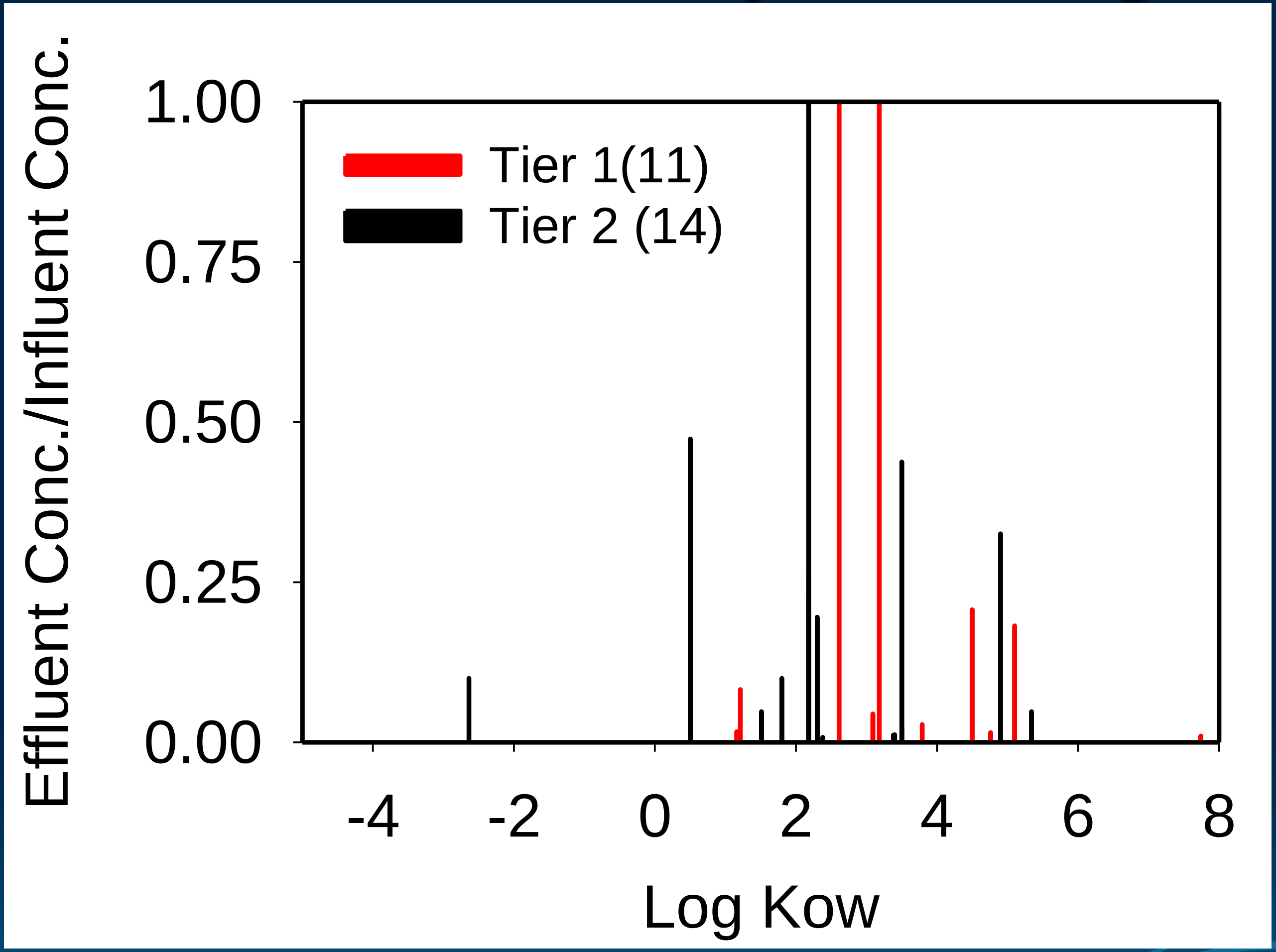
Highlights of 2006-2007 TNSSS

Pharmaceutical	Use	# Detects (out of 84)	Conc Range μg/kg
Triclocarban	Antimicrobial	84	187-441,000
Ciprofloxacin	Antibiotic	84	75-47,500
Diphenhydramine	Antipsychotic	84	37-5,730
Ofloxacin	Antibiotic	83	74-58,100
Tetracycline	Antibiotic	81	38-5,270
Azithromycine	Antibiotic	80	10-6,530
Carbamazepine	Anticonvulsant	80	9-6,030
Triclosan	Antibacterial	79	430-133,000
Gemfibrozil	Cholesterol lowering	76	12-2,650
Cimetidine	Anti-acid	74	8-9,780
Ibuprofen	Anti-inflammatory	54	100-11,900
Minocycline	Antibiotic	32	351-8,650
Diltiazem	Hypertension	69	2-225
Fluoxetine	Antidepressant	79	12-3,130

Highlights of 2006-2007 TNSSS

Steroids/hormones	Use	# Detects (out of 84)	Conc Range μg/kg
Estrone	Estrogen	60	27-965
Androsterone	Testosterone	50	21-1,030
Andostenedione	Testosterone	32	108-1,520
Flame retardants			
Tri & Tetra BDEs	Reduce flammability	84	77-5,126
Penta-BDEs		84	23-5,250
Hexa-BDEs		84	21-1,010
Deca-BDEs		83	150-17,000
PAHs			
Phthalates	Plasticizer	84	657-310,000
Fluoranthene		77	45-12,000
Pyrene		72	44-14,000

Removal Efficiency vs. Log Kow



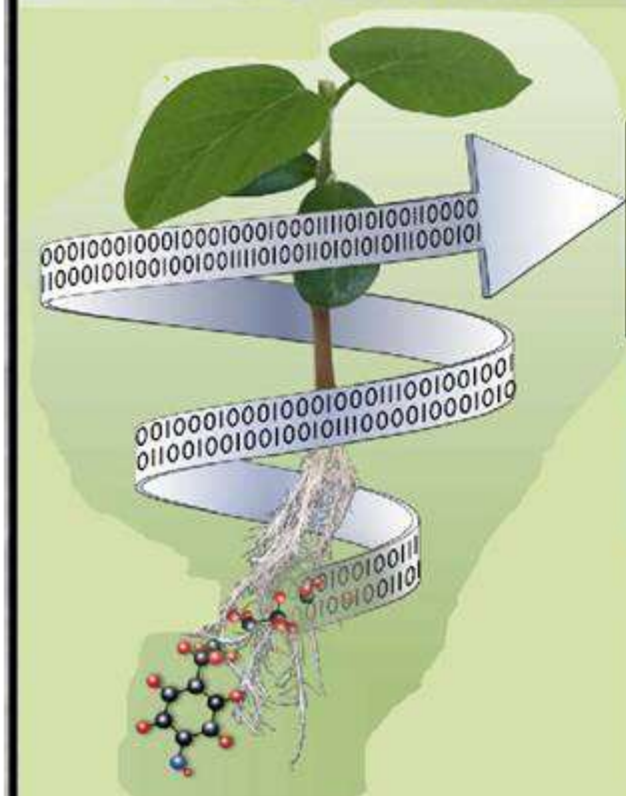
MW

Tier 1= 138-290 Except 1 compd. 642

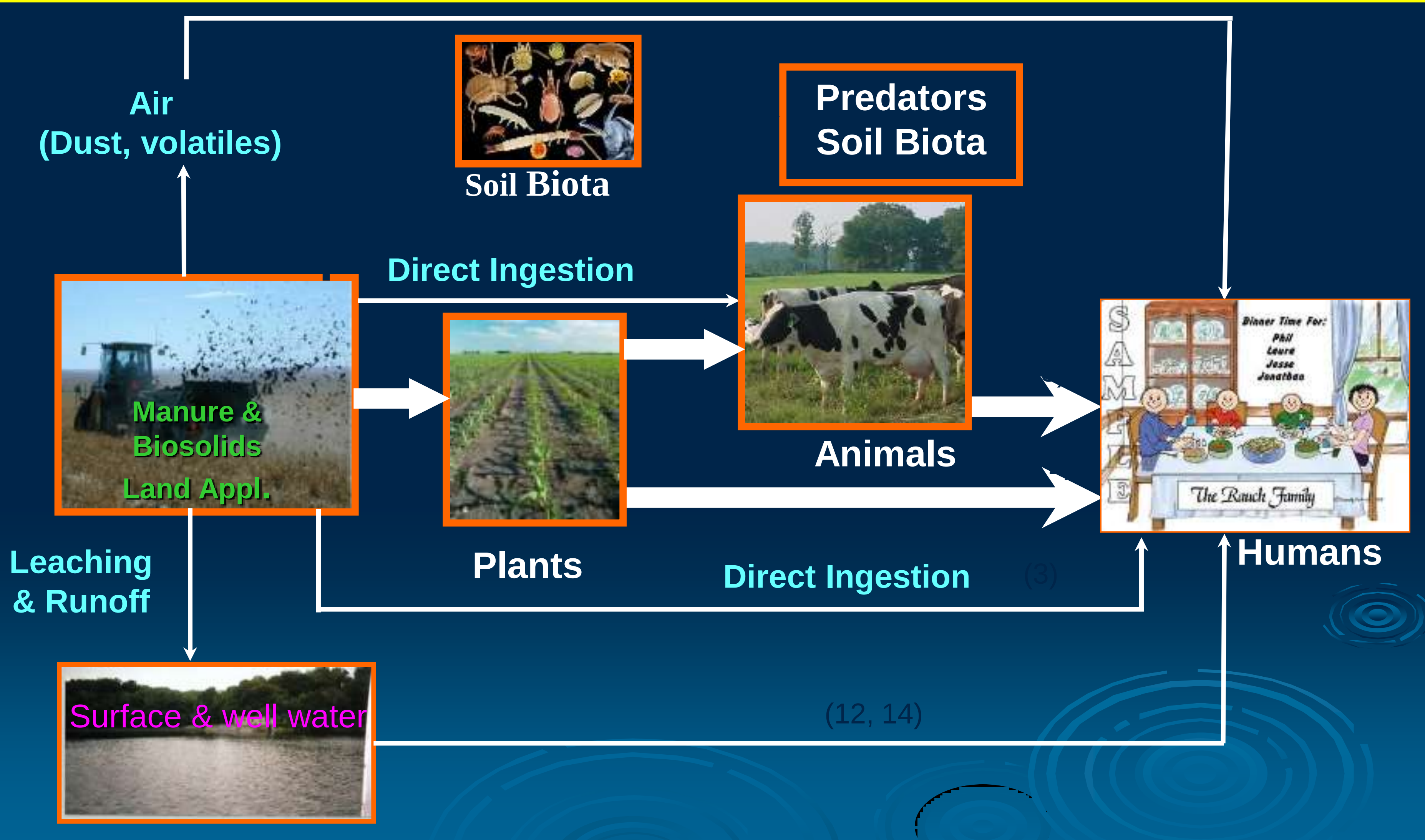
Tier 2= 124-362

Why is Plant Uptake Important

- Risk Assessment
- Phytoremediation
- Pesticide Management



Risk Assessment



Which of ~100,000 Compounds to Study

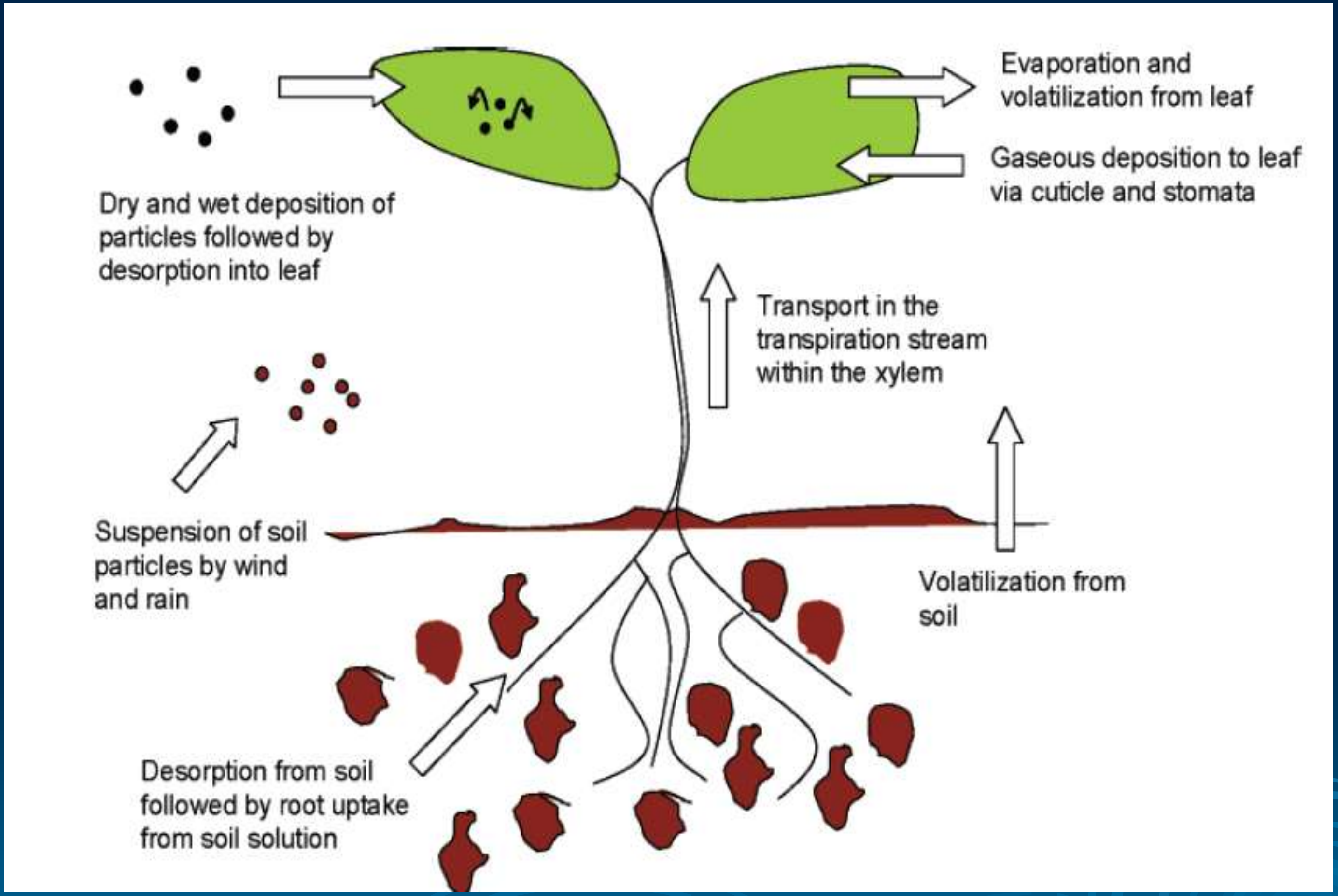
You All Are Going Back Home as Experts on Trace Organics Prioritization for Human and Eco-Tox Risk Assessment

Outline

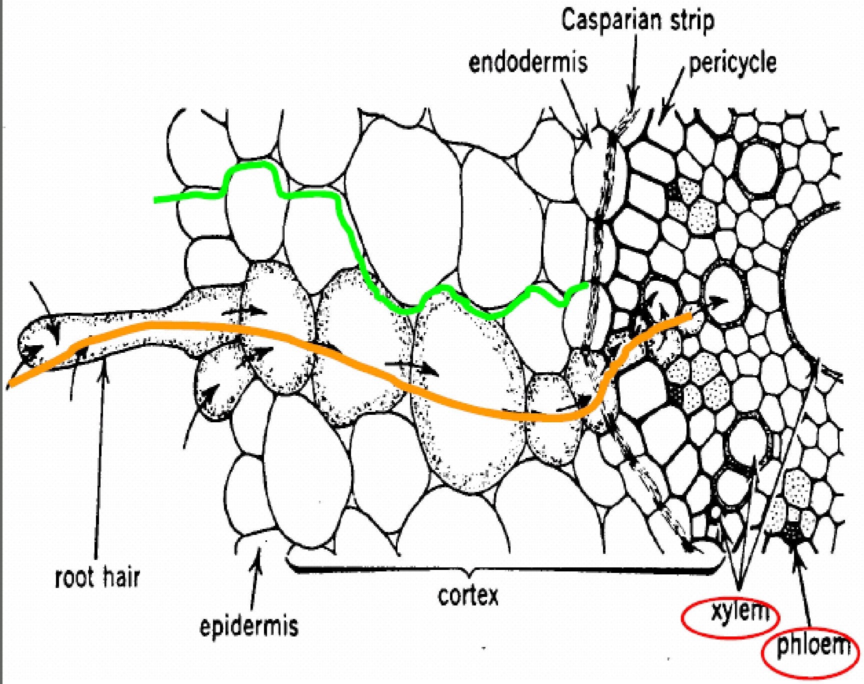
Brief Review and Discussion of Current Knowledge on:

- Routes and processes of uptake of organic chemicals by plant
- The relationships between physico-chemical properties of compounds and their partitioning and transport in plant tissues
  - Permeability of PPCPs in Drug Discovery Setting
- Development and application of a simple framework to predict PPCPs uptake
  - Manure, Biosolids, & Wastewater Reuse

Principal Uptake Pathways of Uptake of Organic Chemicals by Plants



Basic properties of drugs and possible routes of uptake and transport in plants



rapp, McFarlane 1995)

Apoplasmatic Transport :

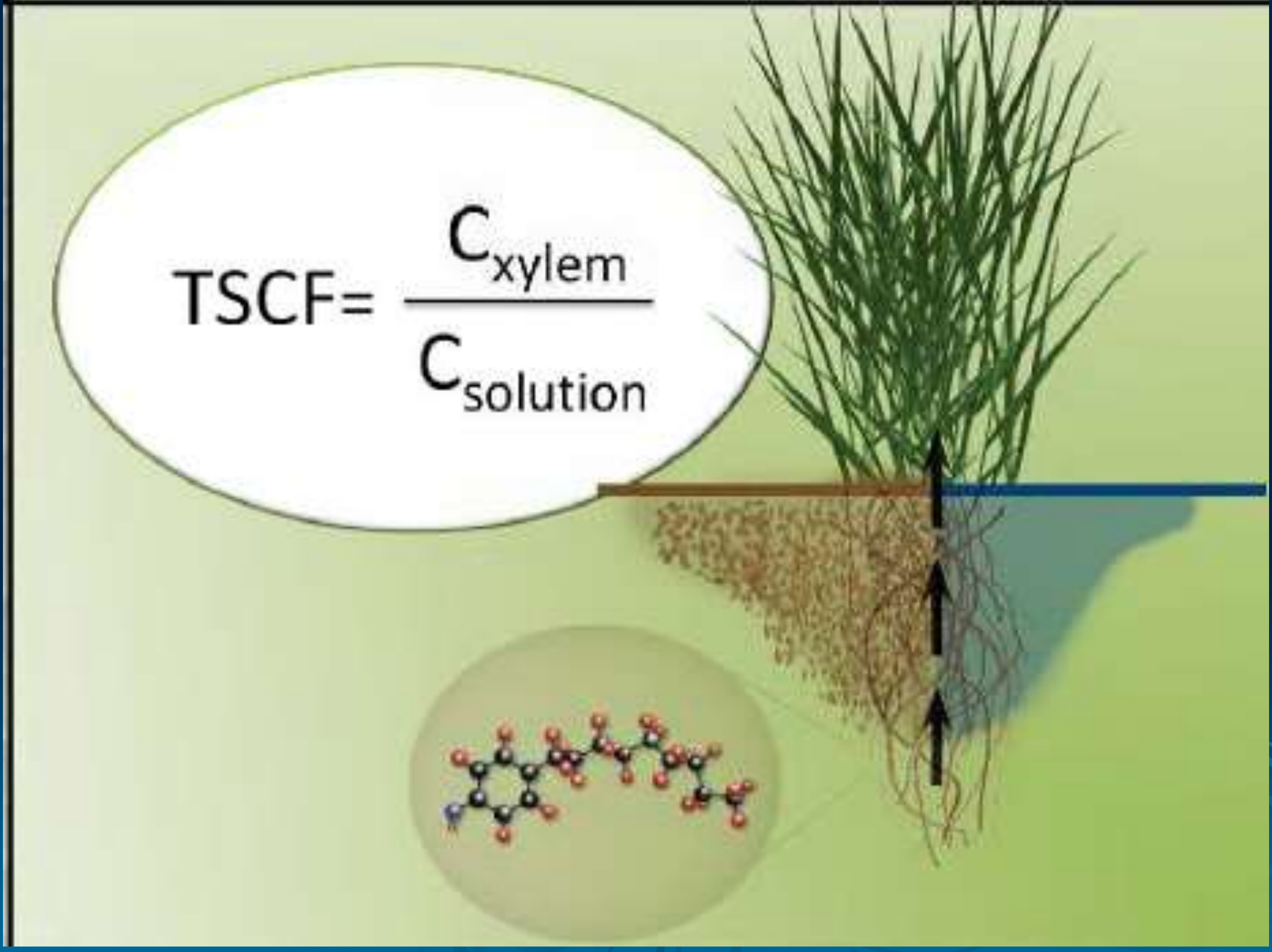
- lower lipophily
- lower log $K_{o/w}$

(*Partition coefficient octanol/water*)

Symplasmatic Transport :

- higher lipophily
- higher log $K_{o/w}$

Uptake Descriptor



Factors Affecting Chemical Uptake and Distribution within Plant Parts

- Physico-chemical properties of the compound such as:
  - Water solubility, vapor pressure, molecular weight, octanol/water partition coefficient
- Environmental Characteristics
  - Temperature, organic and mineral matter and water content of soil
- Plant Characteristics
  - Type of roots, shape and chemical characteristics of leaves, and lipid content

Paterson et al., 1990

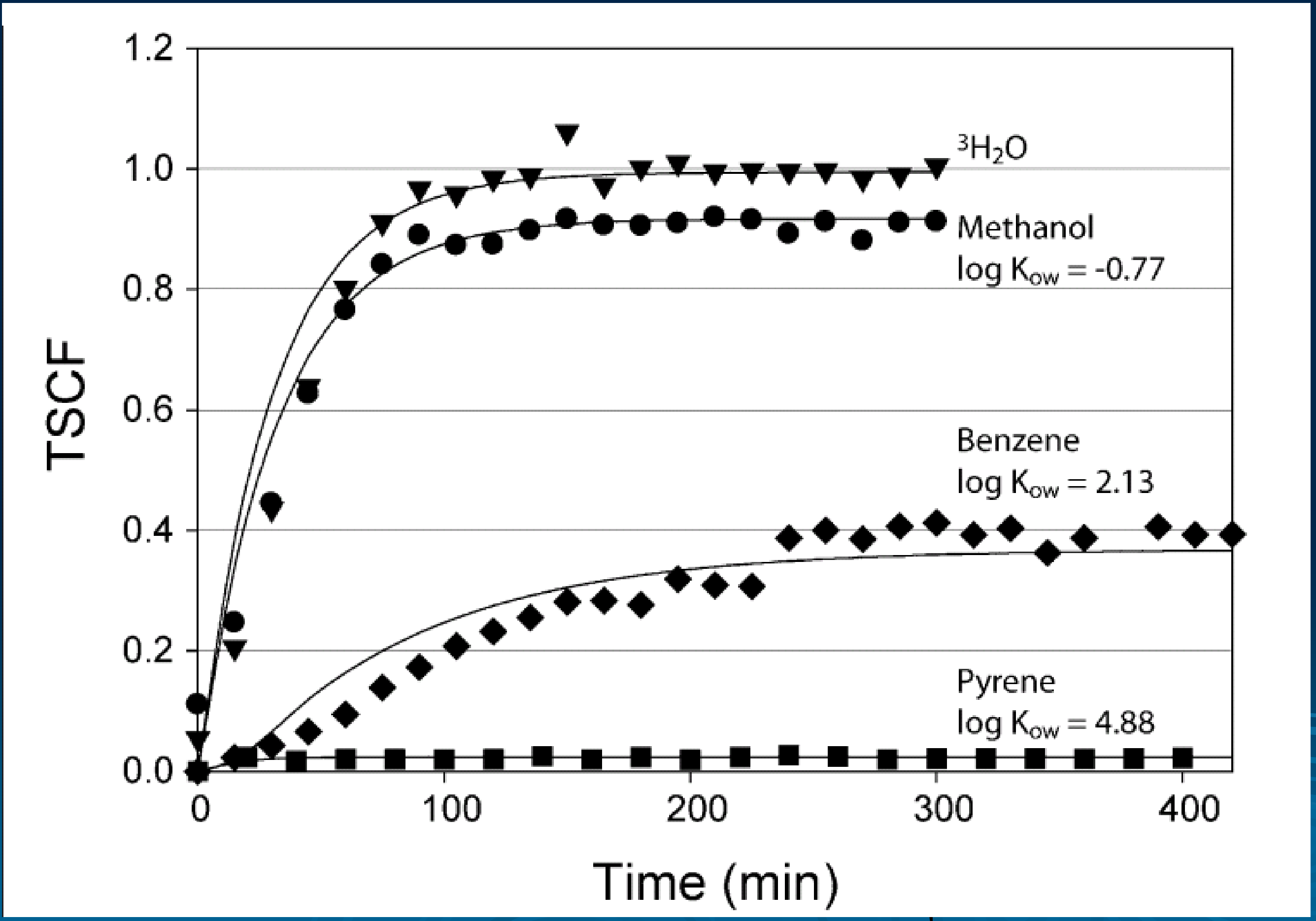
Physico-chemical Properties Affecting Membrane Permeability

- Lipophilicity
- Molecular Weight
- H-bond Donors
- H-bond Acceptors

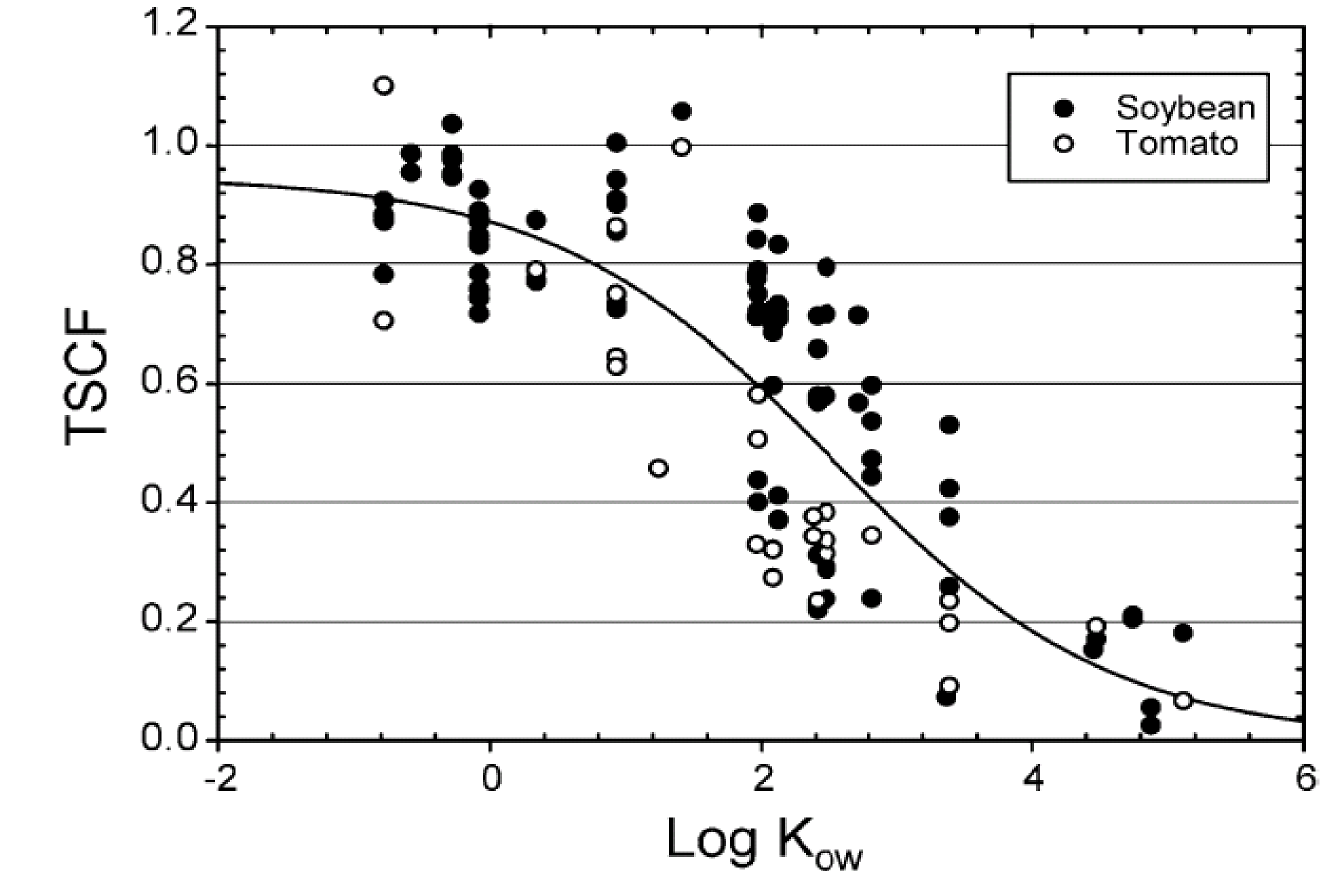
Lipophilicity: Log Kow

- Expressed as a ratio of octanol solubility to aqueous solubility appears in some form in almost every analysis of physico-chemical properties related to absorption.

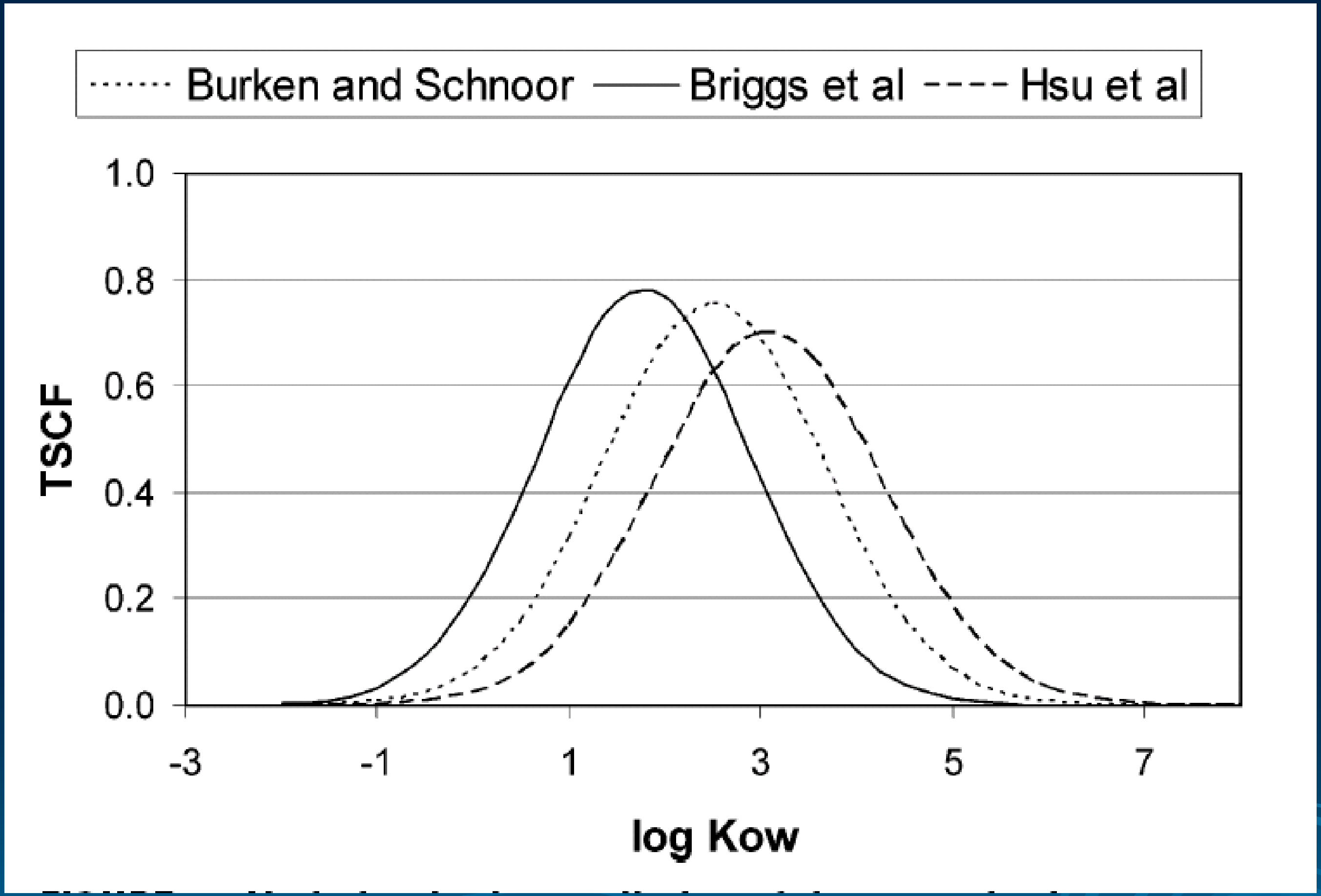
Effect of Log Kow of Chemicals on TSCF (Dettenmaier et al., 2008)



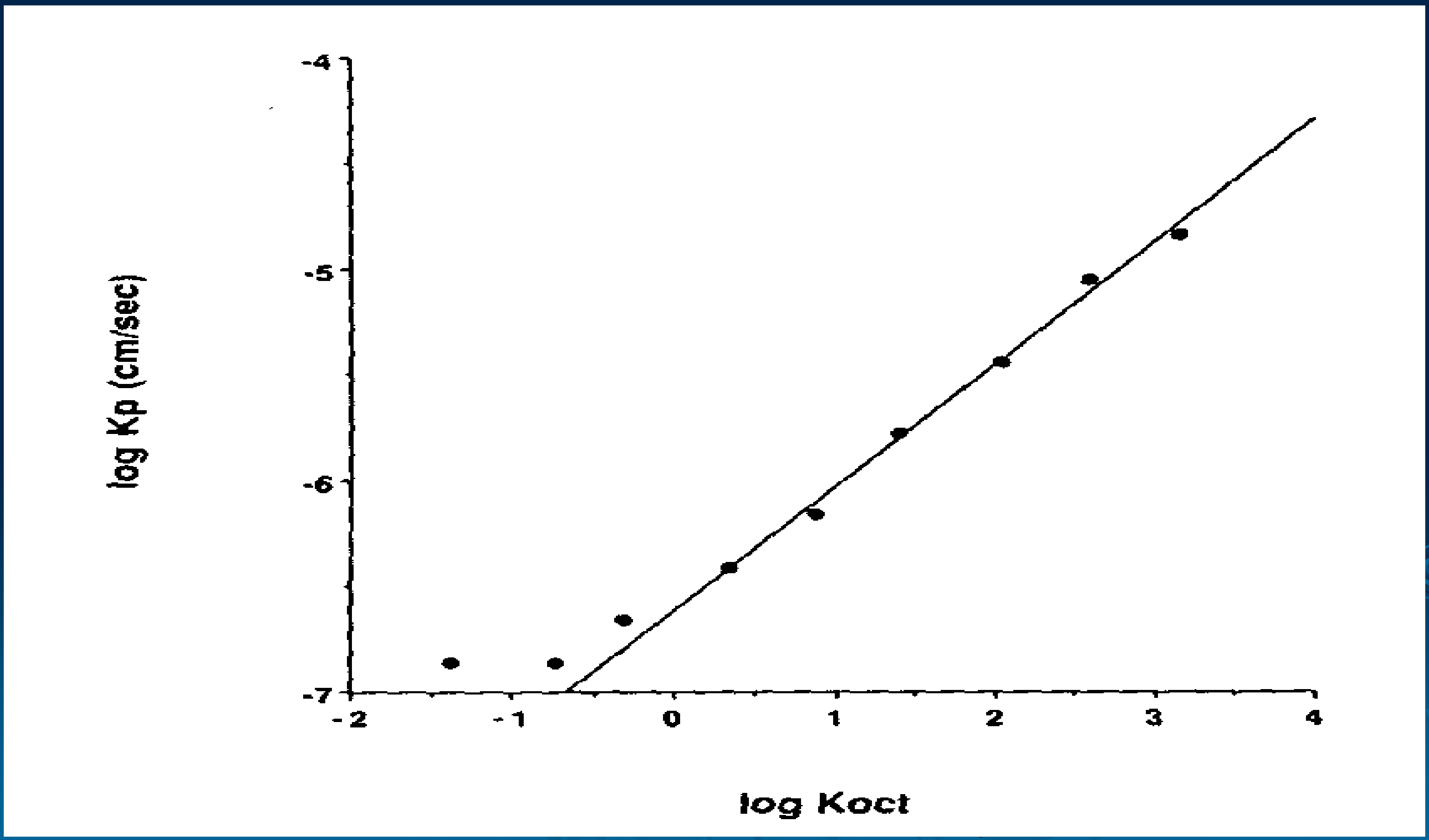
TSCF vs Log Kow (Dettenmaier et al., 2008)



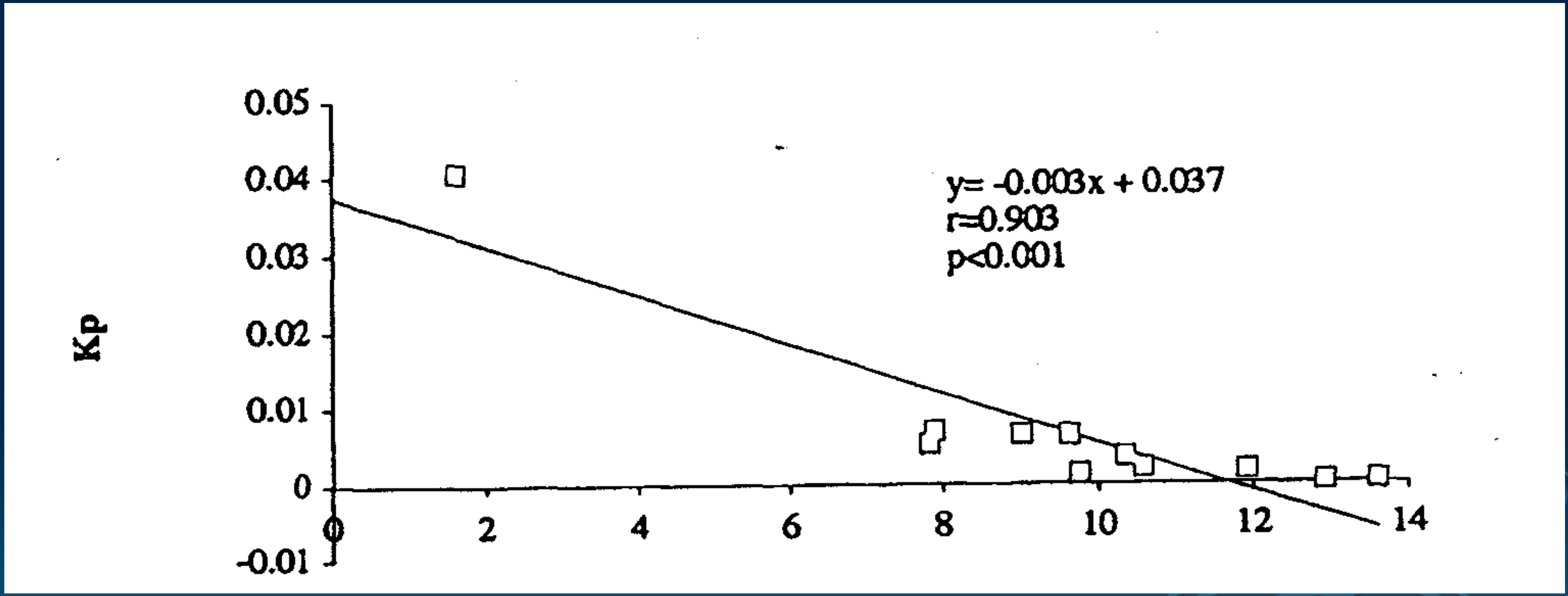
Variation in Prediction of TSCF with Kow

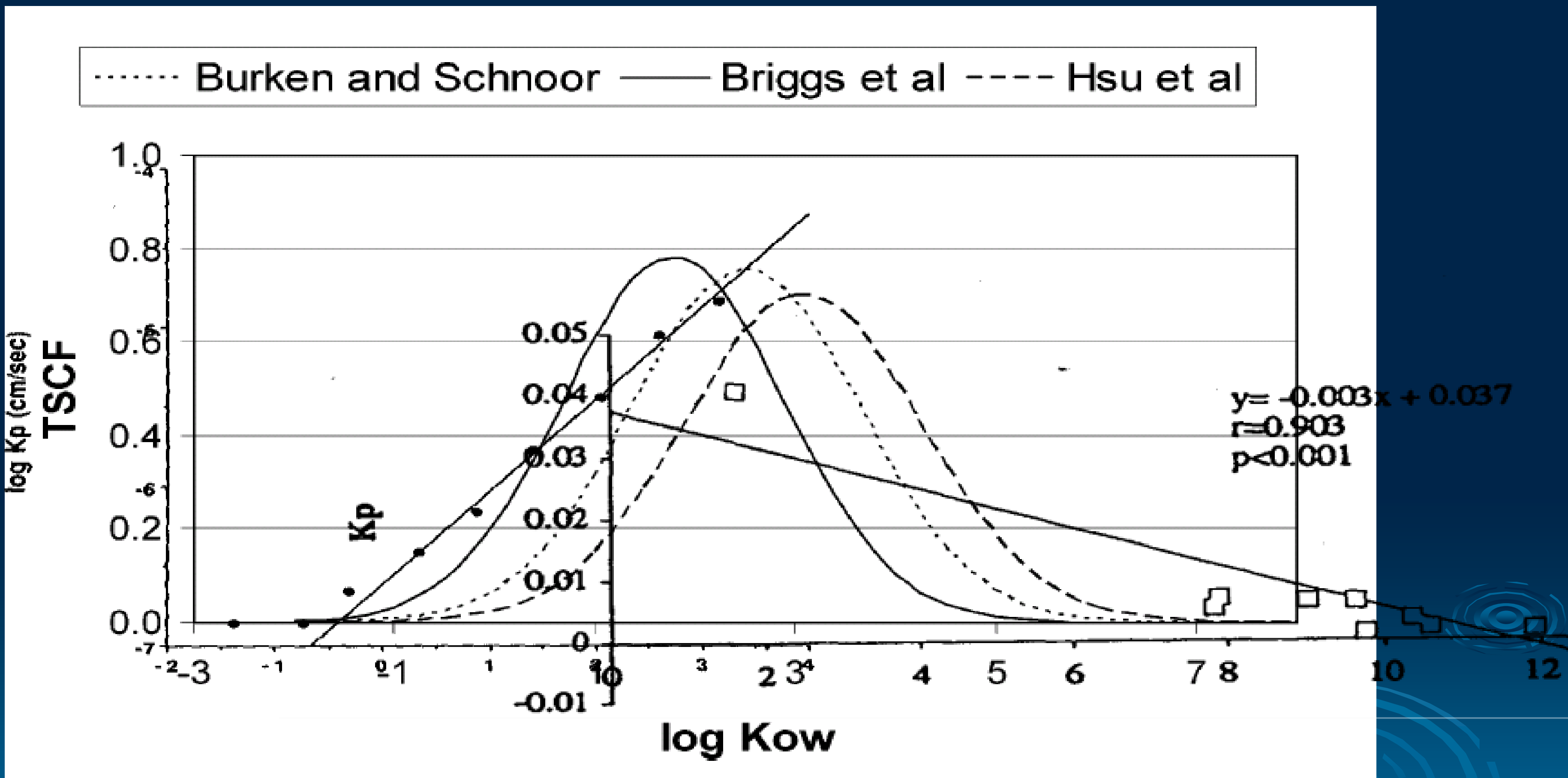


Permeability of Epidermis vs Log Kow (Potts and Guy, 1992)



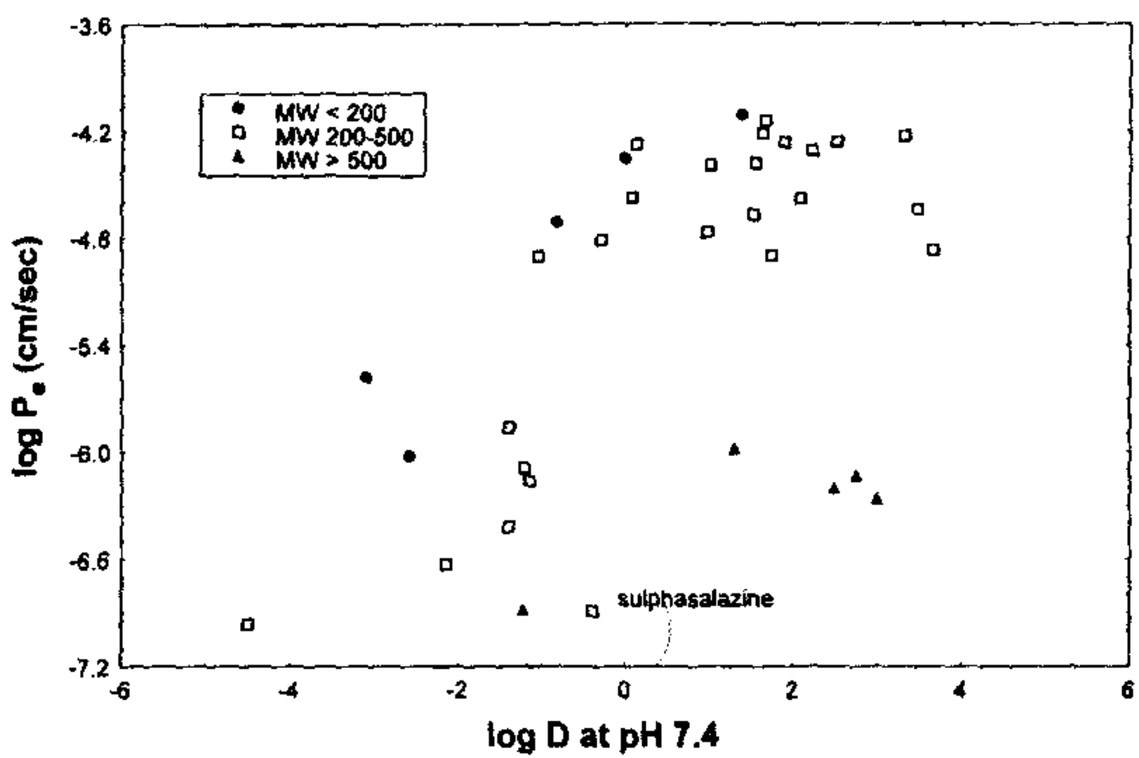
Permeability through Monkey's Skin vs. Log Kow (Sartorelli et al., 1998)





Burken and Schnoor
Briggs et al
Hsu et al
TSCF
log Kp (cm/sec)
Kp
log Kow
1.0
0.8
0.6
0.4
0.2
0.0
0.05
0.04
0.03
0.02
0.01
0
-0.01
y= -0.003x + 0.037
r=0.903
p<0.001

Permeability through Caco-2 Cell Membranes vs. Log Kow (Camenisch et al., 1998)

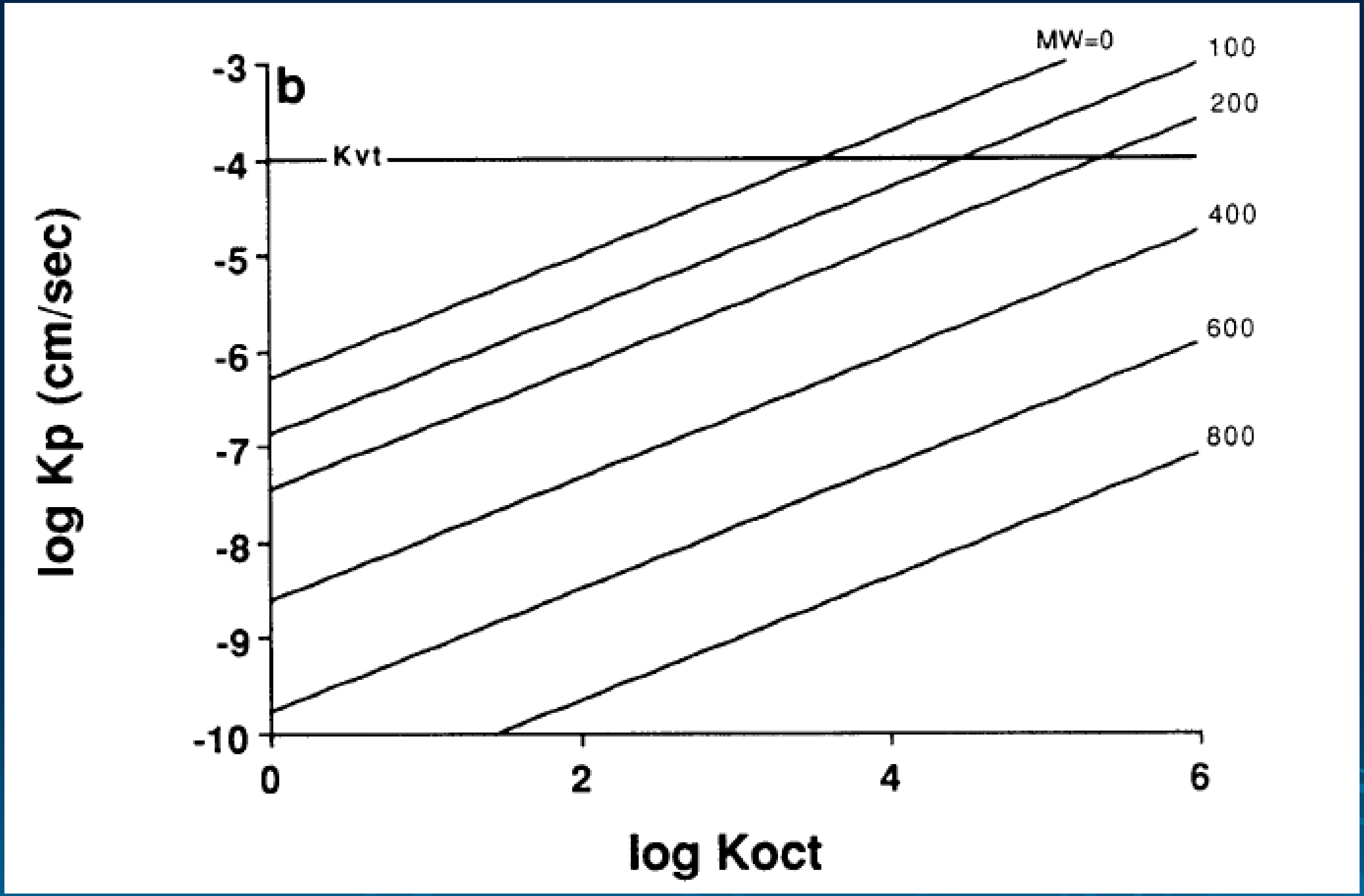


(a)

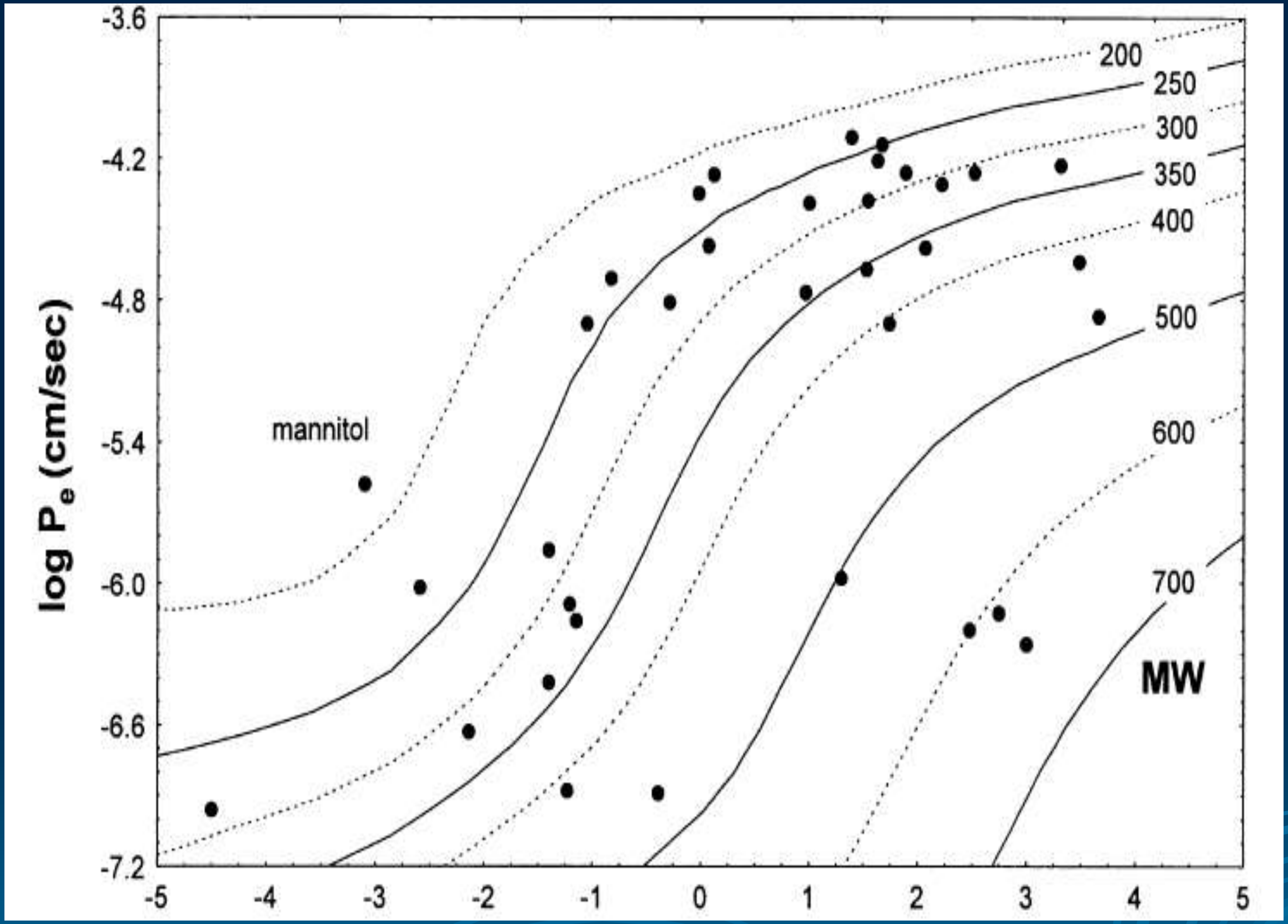
Molecular Weight (MW)

- Obvious choice because of the literature relating poorer intestinal and blood brain barrier permeability to increasing MW
- Rapid decline in permeation time as a function of MW in lipid bi-layers as opposed to aqueous media

Permeability vs Log Kow (Potts and Guy, 1992)



Effect of MW on permeability through Caco-2 monolayers (Camenisch et al., 1998)



Log Kow

H-bond Donors

- An excessive number of H-bond donor groups impair permeability across a membrane bi-layer, it is the smaller number of donors that the literature links with better permeability.

- Expressed as log of the ratio of octanol to hydrocarbon partitioning

- Simply adding the number of NH bonds and OH bonds in a good index of H-bond donor characteristic

H-bond Acceptors

- Too many H-bond acceptor groups also hinder permeability across a membrane bi-layer.

- The sum of Ns and Os is a rough measure of H-bond acceptor ability.

Lipinski's 'Rule of 5'

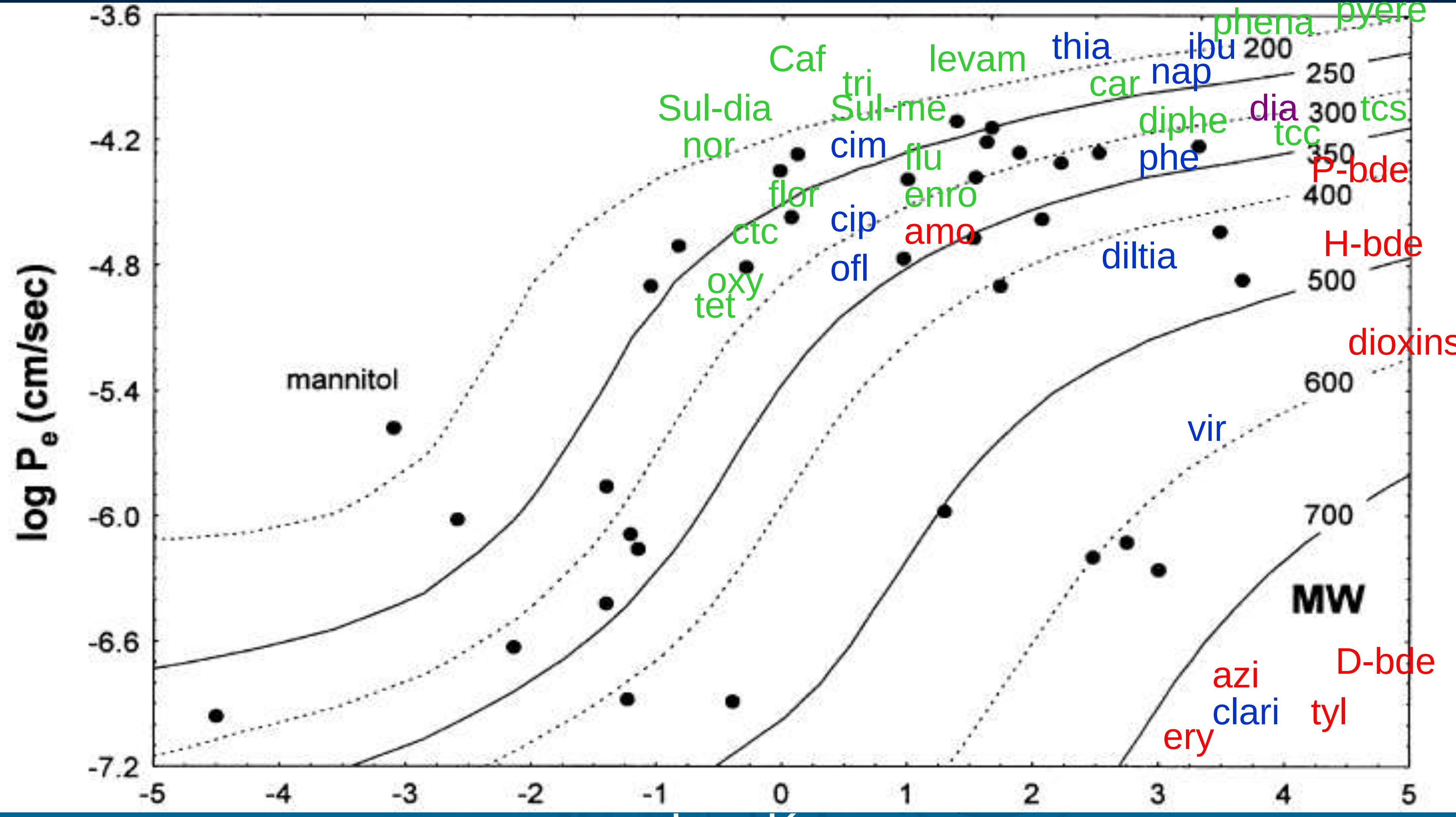
- The 'rule of 5' states that: Poor absorption or permeation are likely when:
  - There are more than 5 H-bonds donors (expressed as the sum of OHs and NHs);
  - THE MW is > 500
  - The Log KOW is > 5
  - There are more than 10 H-bond acceptors (expressed as sums of Ns and Os);

Note: Compound classes that are substrates for biological transporters are exceptions to the rule.

Partial List of Drugs in Absorption and Permeability Studies

Drug	Log KOW	OH+NH	MW	N+O	Alert (poor absorption)
Aspirin	1.70	1	180.16	4	No
Azithromycin	0.14	5	749.00	14	YES
Caffeine	0.20	0	194.19	6	No
Carbamazepine	2.90	2	236.28	3	No
Chloramphenicol	1.23	3	323.14	7	No
Cyclosporine	-0.32	5	1202.6	23	YES
Diazepam	3.36	0	284.75	3	No
Erythromycin	-0.14	5	733.95	14	YES
Ibuprofen	3.23	1	206.29	2	No
Methotrexate	1.60	7	454.45	13	YES
Testosterone	3.70	1	288.43	2	No
Vinblastine	2.96	3	811.00	13	YES

Effect of MWT on permeability through Caco-2 monolayers (Camenisch et al., 1998)



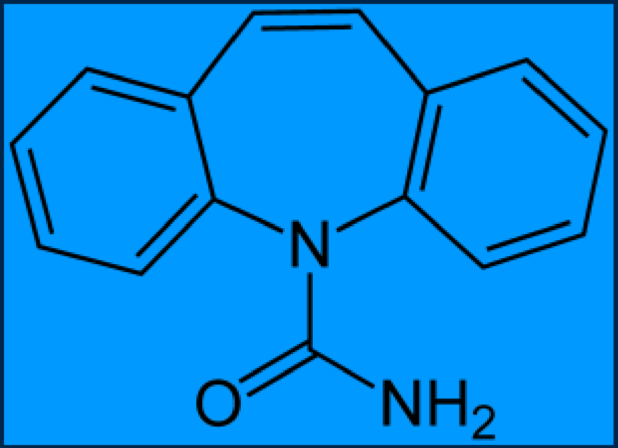
Log Kow

Kumar’s ‘Rule of 3’

- Log Kow < 3.0
- Molecular Weight < 300
- H-Bond Donors (OH+NH) < 3
- H-Bond Acceptors (N+O) < 6

Carbamazepine
Follows Rule of 3

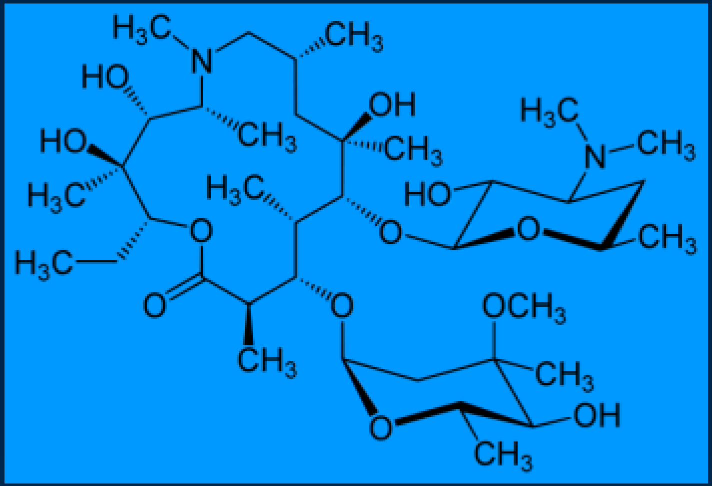
$C_{15}H_{12}N_2O$



- Log Kow 2.90
- Molecular Weight 236
- H-Bond Donors (OH+NH) 2
- H-Bond Acceptors (N+O) 3

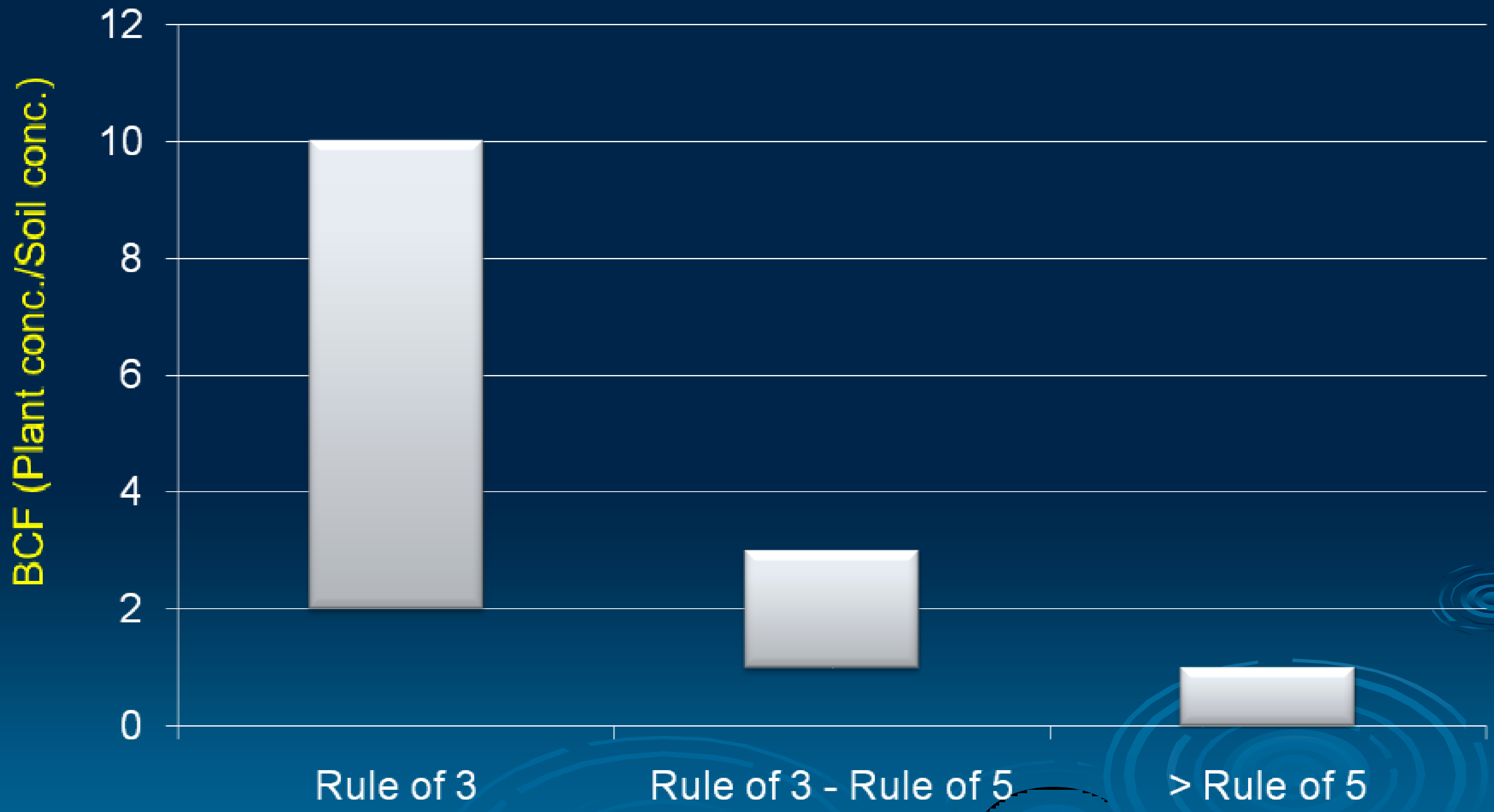
Azithromycin
Rule of 5 Alert for Poor Permeability

$C_{38}H_{72}N_2O_{12}$



- Log Kow 0.14
- Molecular Weight 749
- H-Bond Donors (OH+NH) 5
- H-Bond Acceptors (N+O) 14

BCF vs Kumar's Rule of 3



Conclusions

- ‘Rule of 5’ should be the first step in deciding which compounds will be taken up by plants.
- Compounds following **‘Kumar’s Rule of 3’** i.e
  - < 3 H-bonds donors (expressed as the sum of OHs and NHs);
  - THE MW is <300
  - The Log KOW is <3
  - <6 H-bond acceptors (expressed as sums of Ns and Os);

should be prioritized in field plant uptake studies for risk assessment for crops receiving manure or biosolids as fertilizer or wastewater for irrigation.

FUTURE WORK

Develop a ‘Risk Assessment Tool” for various ecotox endpoints like bioaccumulation in plants, aquatic organisms etc.