The Metropolitan

Water Reclamation District

of Greater Chicago

WELCOME
TO THE MARCH EDITION
OF THE 2010
M&R SEMINAR SERIES

BEFORE WE BEGIN

- SILENCE CELL PHONES & PAGERS
- QUESTION AND ANSWER SESSION WILL FOLLOW PRESENTATION
- SEMINAR SLIDES WILL BE POSTED ON MWRD WEBSITE AT (www. MWRD.org)
- Home Page → (Public Interest) → more public interest → M&R Seminar Series → 2010 Seminar Series

Uptake of Emerging Contaminants in Plants

Kuldip Kumar, Ph.D
MWRDGC

The Chemical Sea Around Us

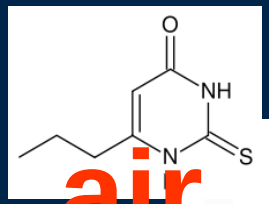
air

water

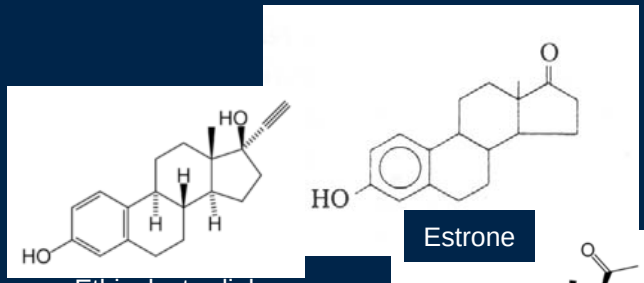
soil

food

our bodies

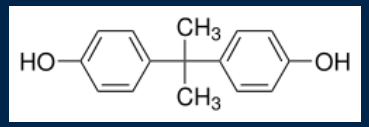


PTU

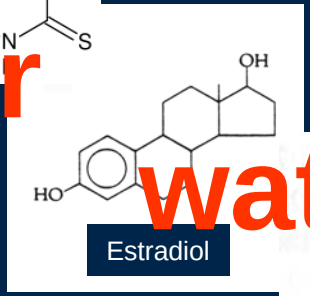


Ethinylestradiol

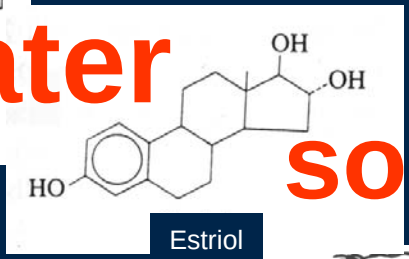
Estrone



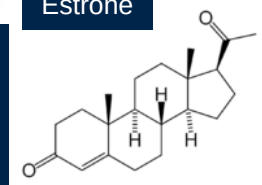
Bisphenol A



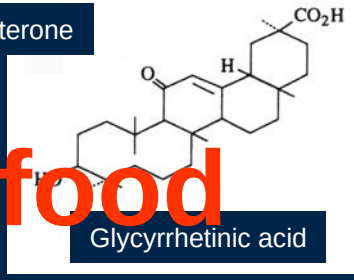
Estradiol



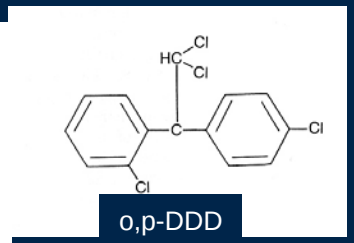
Estriol



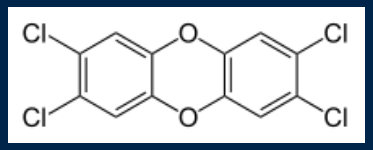
Progesterone



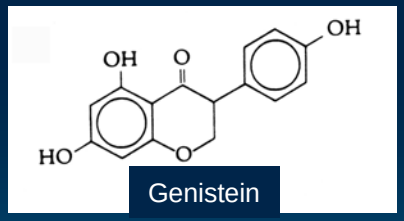
Glycyrrhetinic acid



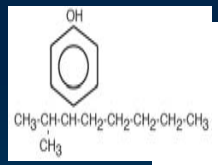
o,p-DDD



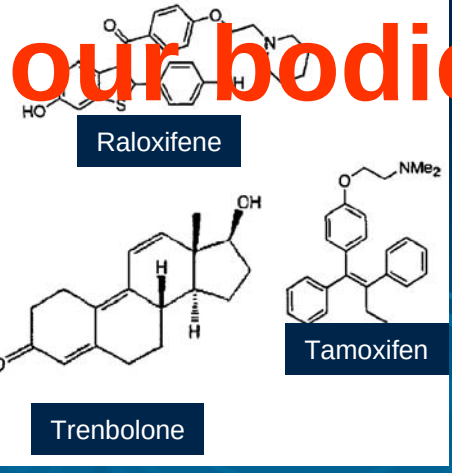
TCDD (dioxin)



Genistein



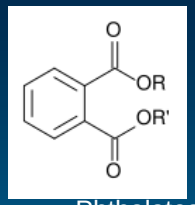
4-nonylph



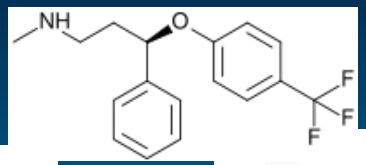
Raloxifene

Tamoxifen

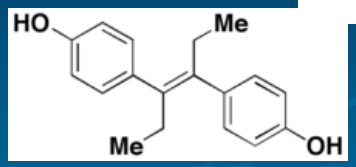
Trenbolone



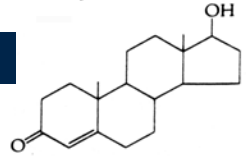
Phthalates



Fluoxetine



Diethylstilbestrol (DES)



Testosterone


Copyright: Adi Adar (2004)


Healthy ?
Exposure?
Accumulation?
Risk ?
RATfood

Risk Assessment

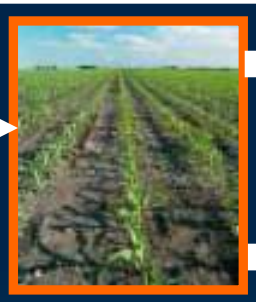
Soil Biota

Predators
Soil Biota

Air
(Dust, volatiles)

Direct Ingestion

Animals



Plants

Humans

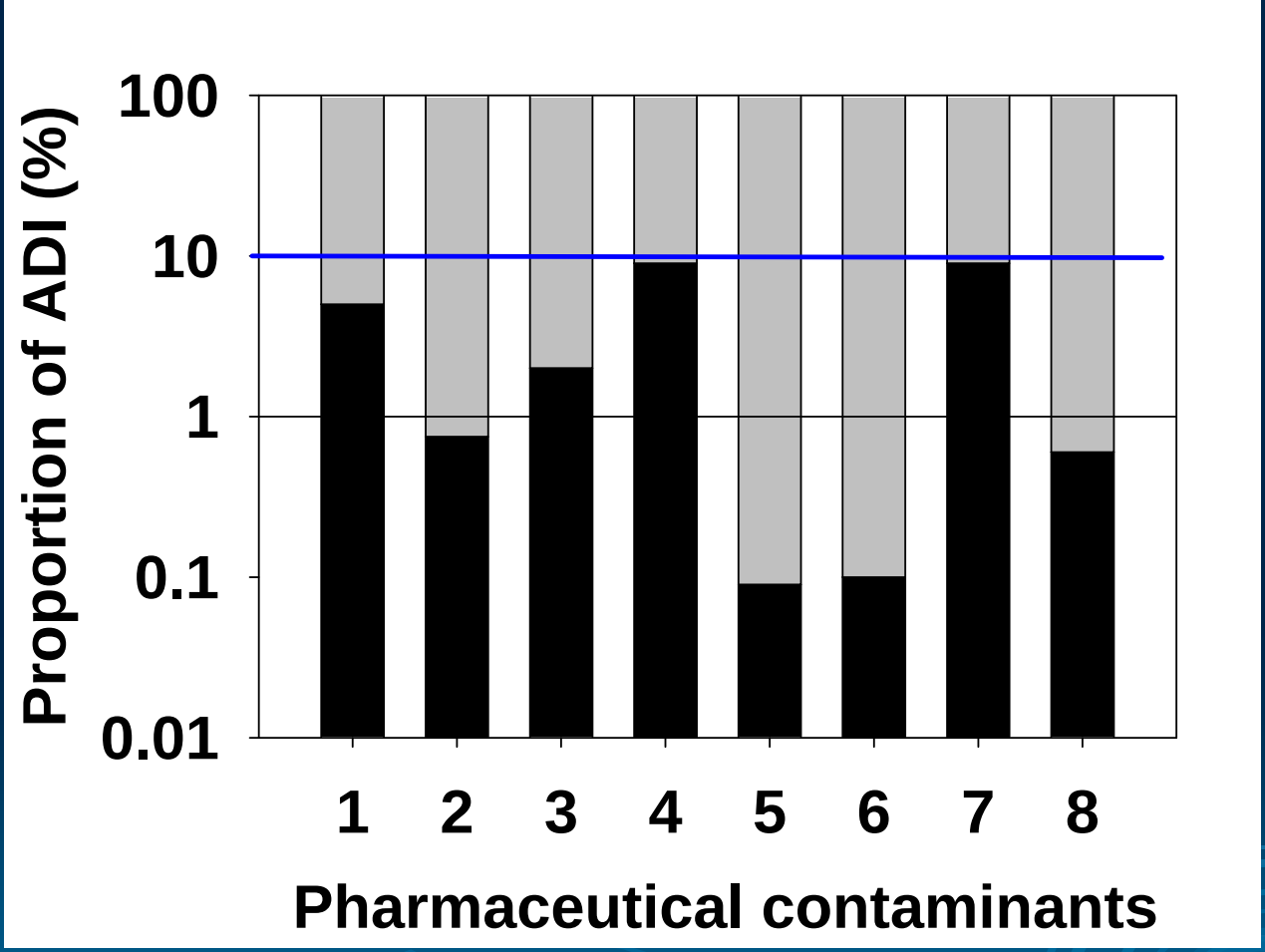
Leaching
& Runoff

Direct Ingestion

(3)

(12, 14)

Potential Contribution of Pharmaceuticals in Vegetable Material to the Acceptable Daily Intake (ADI)



What We Will Cover Today

What We Will Cover Today

Brief Review and Discussion of Current Knowledge on:

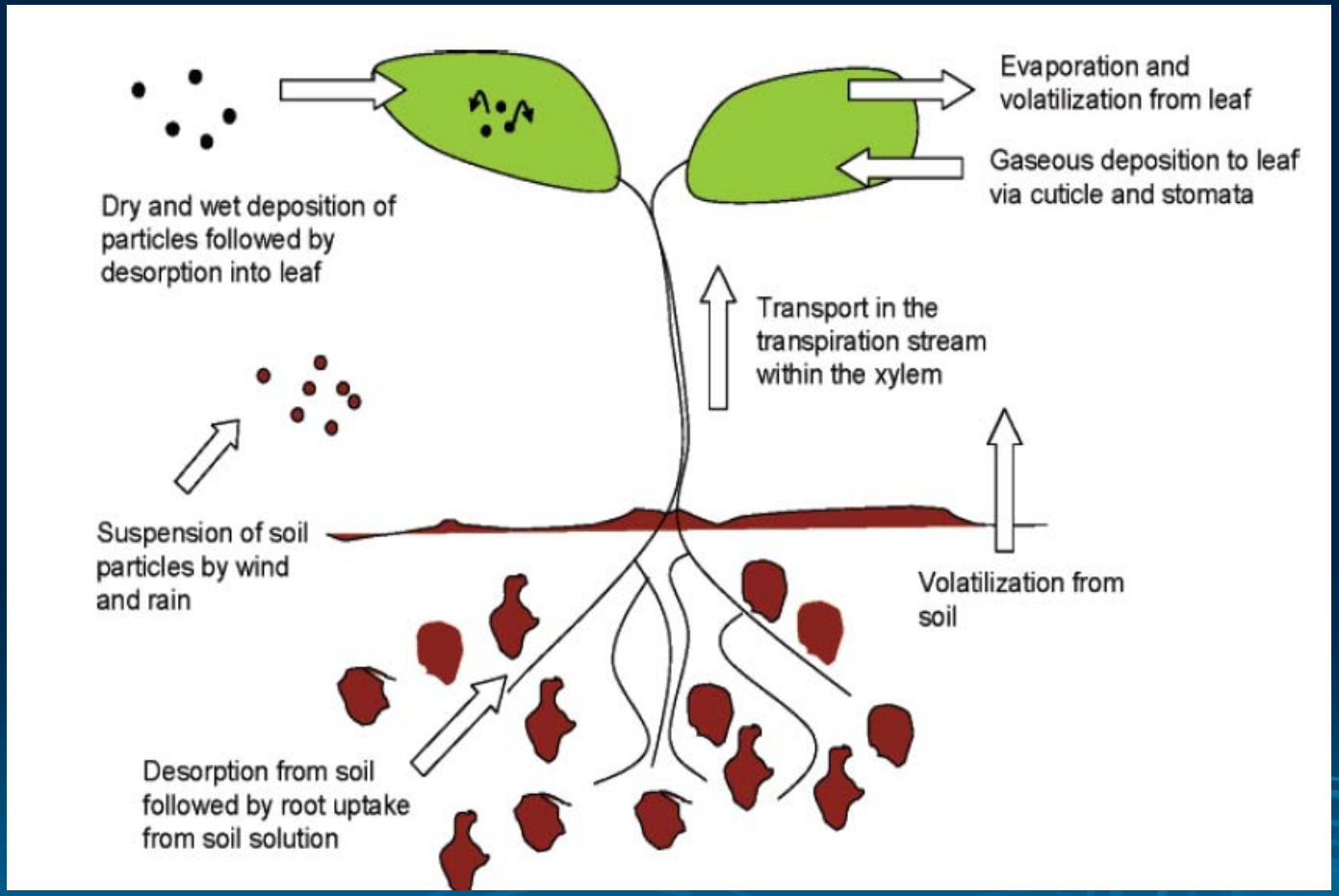
- Routes and processes of uptake of organic chemicals by plant
- The relationships between physico-chemical properties of compounds and their partitioning and transport in plant tissues
- Reported chemicals taken up by plants

Take Home Lesson – What I Want to Achieve

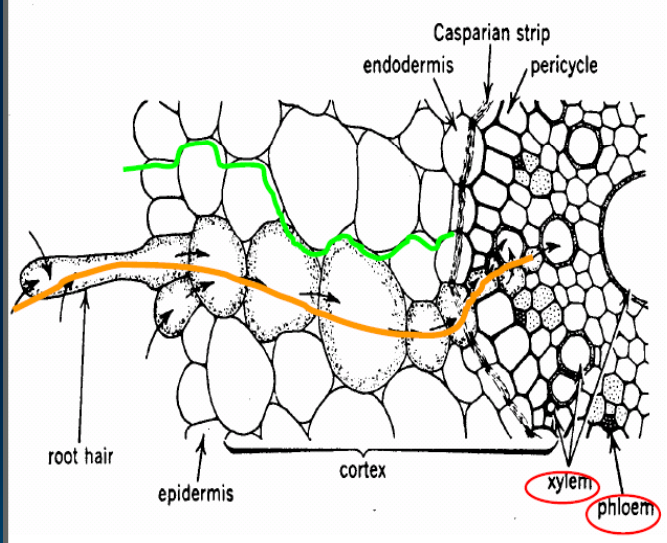
- Present a framework to predict which PPCPs have the highest uptake in plants and should be studied in detail for risk assessment.

- Which organic chemicals may or may not be suited for Phyto-remediation.

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 $K_{o/w}$

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

Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Setting

- Identifying a library with favorable physico-chemical properties that enter phase II efficacy studies
  - United States Adopted Names (USAN) ~ 8,000
  - International Non-proprietary Name (INN)
  - World Drug Index (WDI) ~ 50,000 compounds

Calculated Properties of the USAN Library

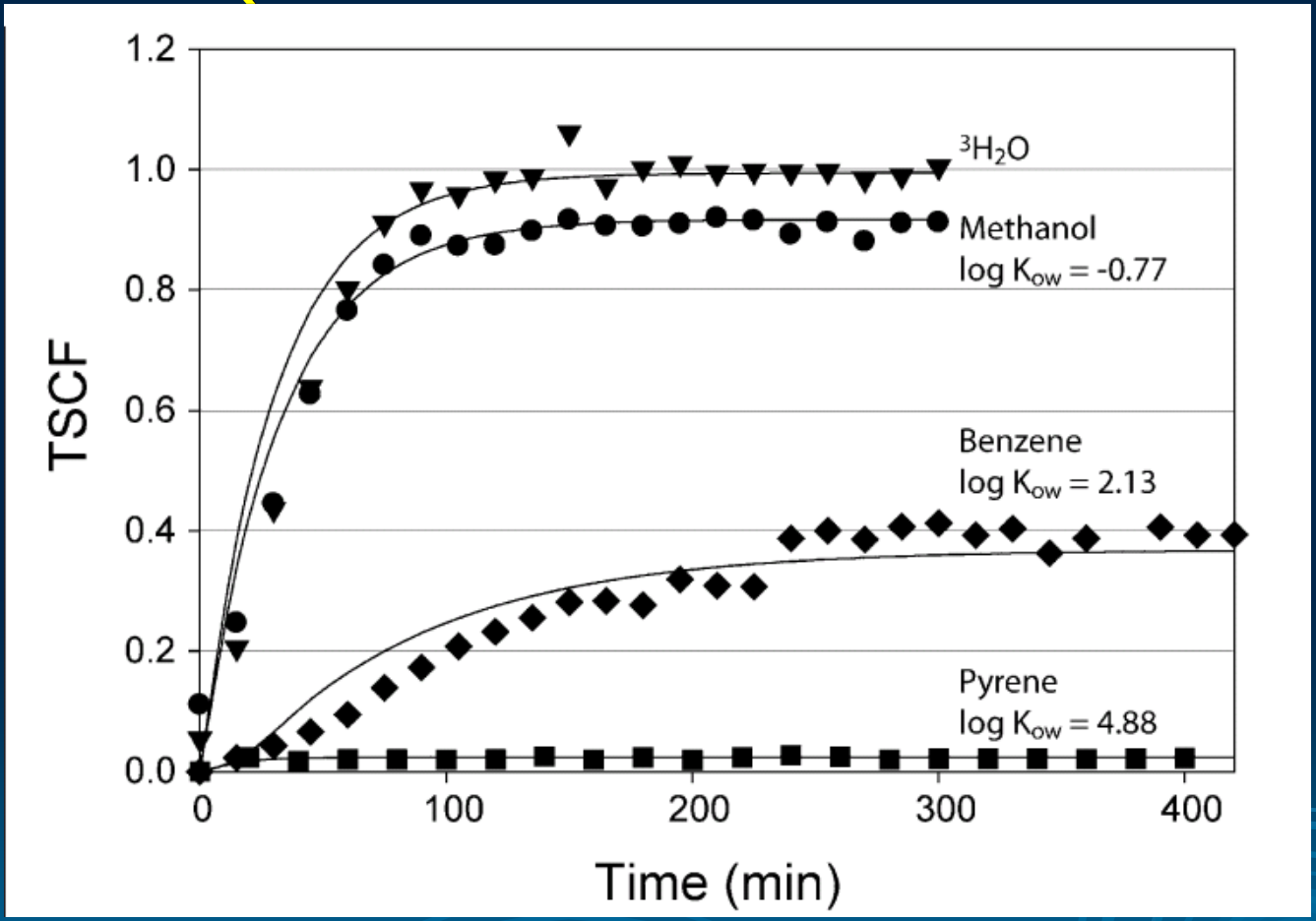
- Lipophilicity
- Molecular Weight
- H-bond donors
- H-bond acceptors

Lipophilicity: Log Kow

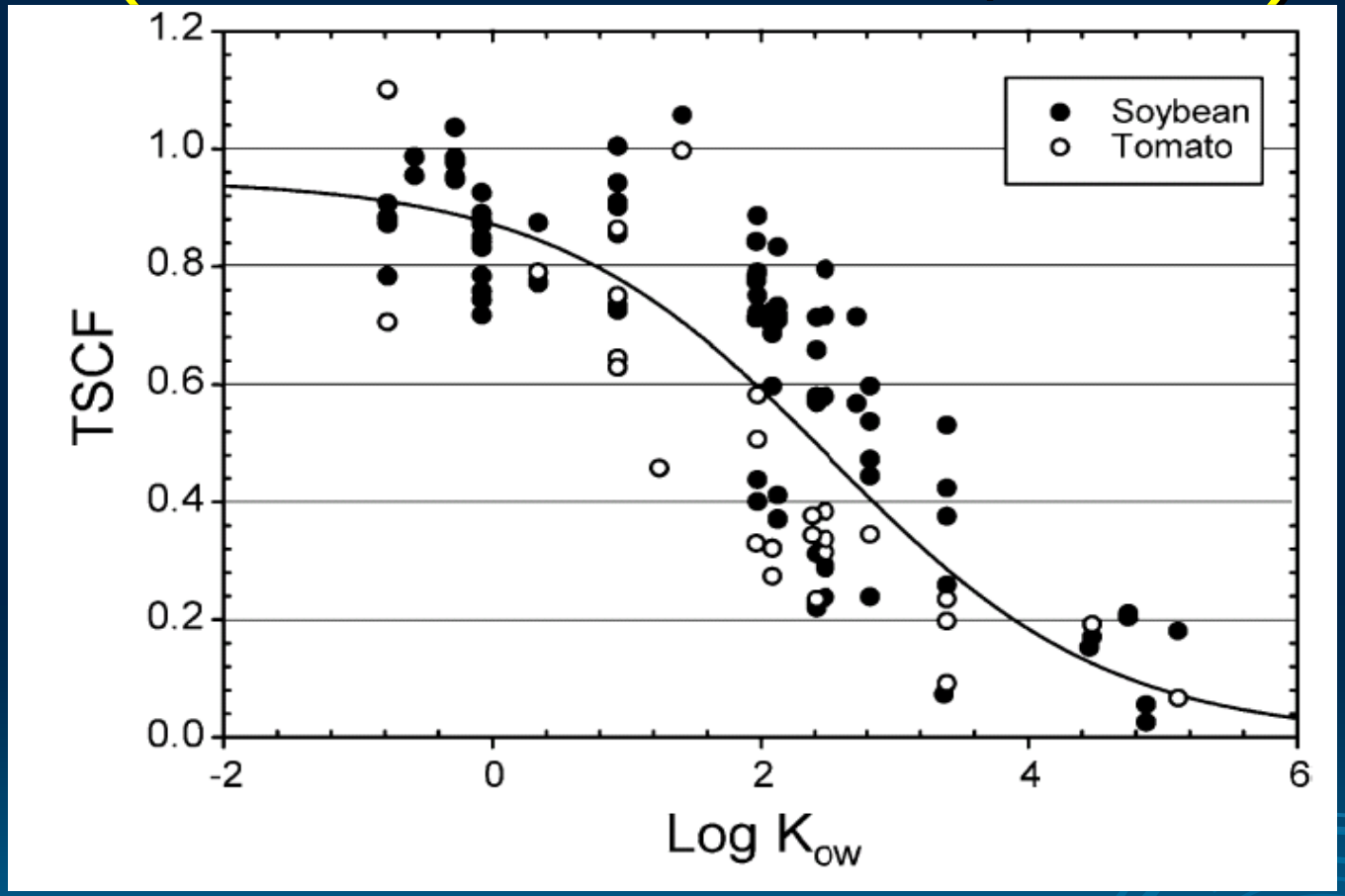
- Expressed as a ratio of octanol solubility to aqueous solubility appears in some form in almost every analysis of physico-chemical properties related to absorption.

- Only ~ 10% of USAN compounds have Log KOW > 5

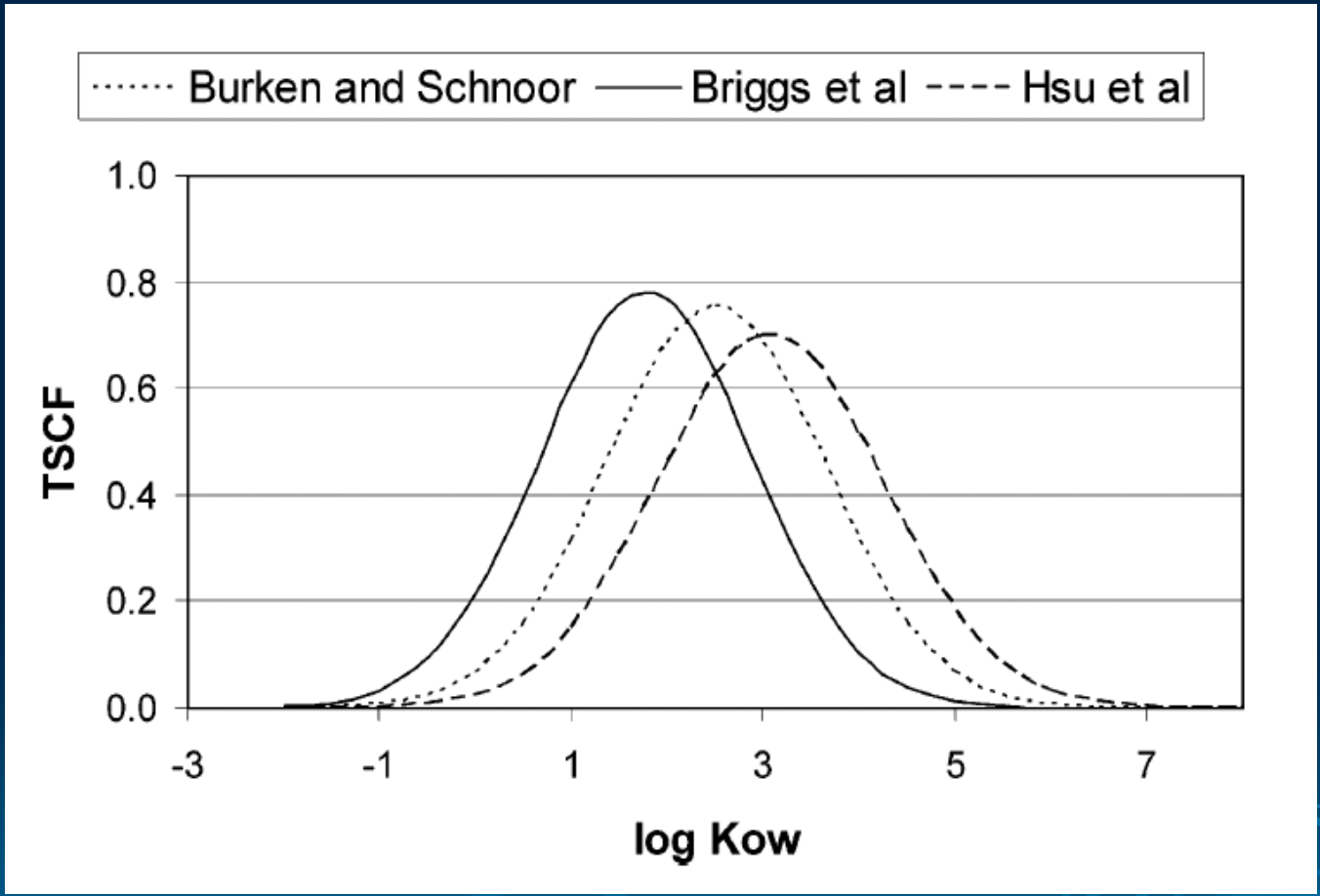
Effect of Log Kow of Chemicals on TSCF (Dettenmaier et al., 2008)



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



Variation in Prediction of TSCF with Kow



Plant CF VS Time (Topp et al., 1986)

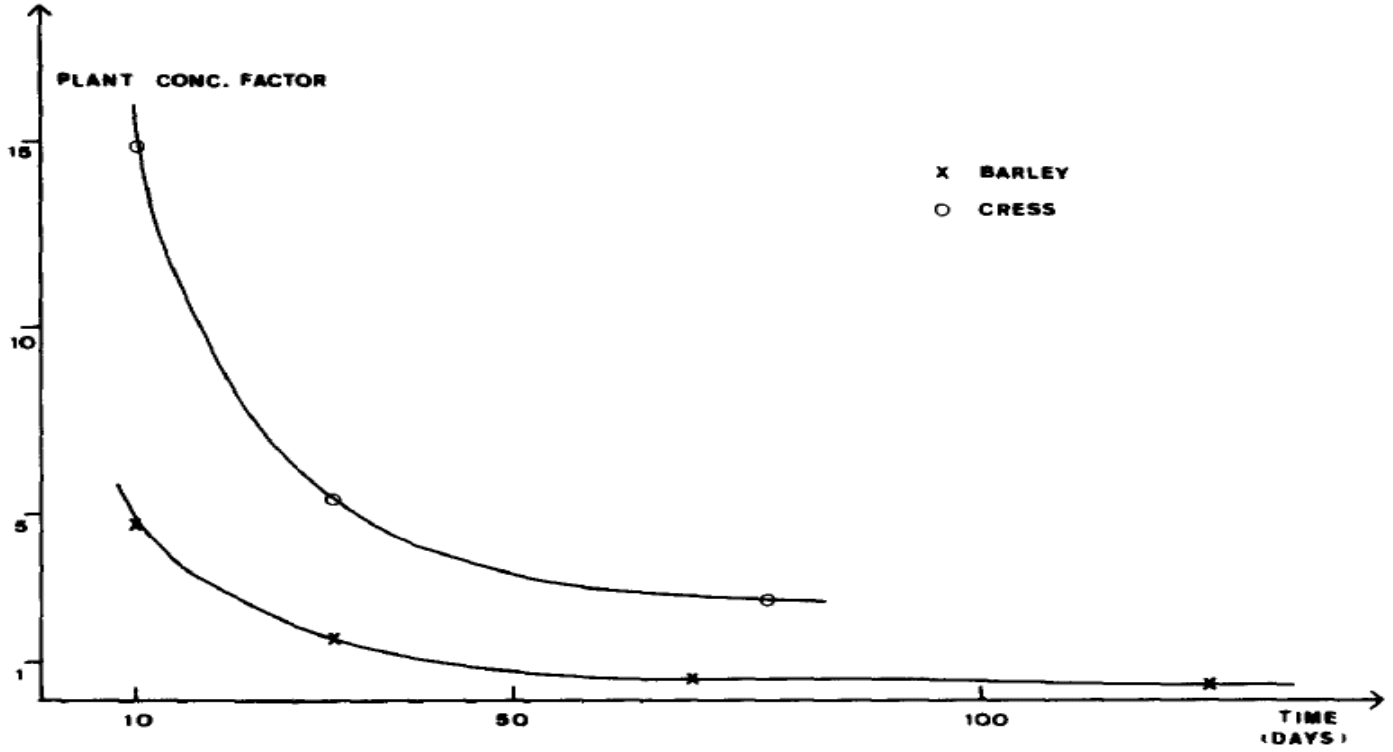
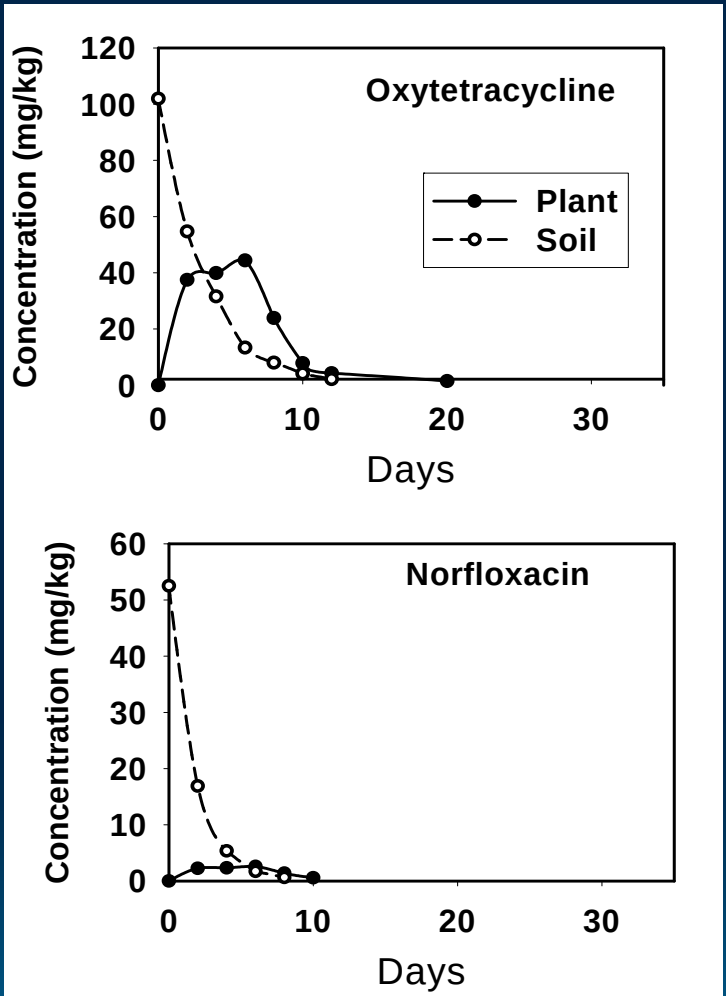


FIG. 6. Time course of uptake of hexachlorobenzene from soil by barley and cress.

$$\text{Plant conc. factor} = \frac{\text{(concentration in plant (based on dry wt)}}{\text{concentration in soil (based on air-dry wt)}}$$

Concentration in Soil and Plants with Time



Barley Root CF Vs Soil Koc (Topp et al., 1986)

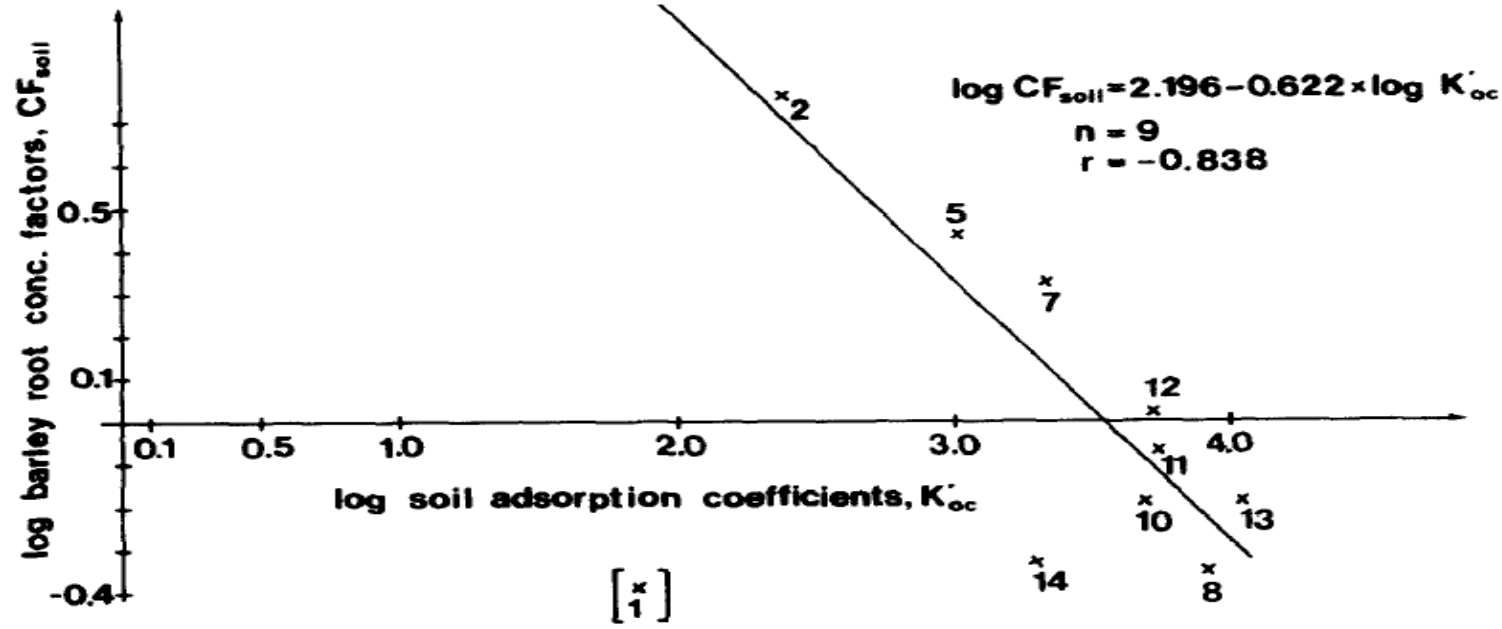
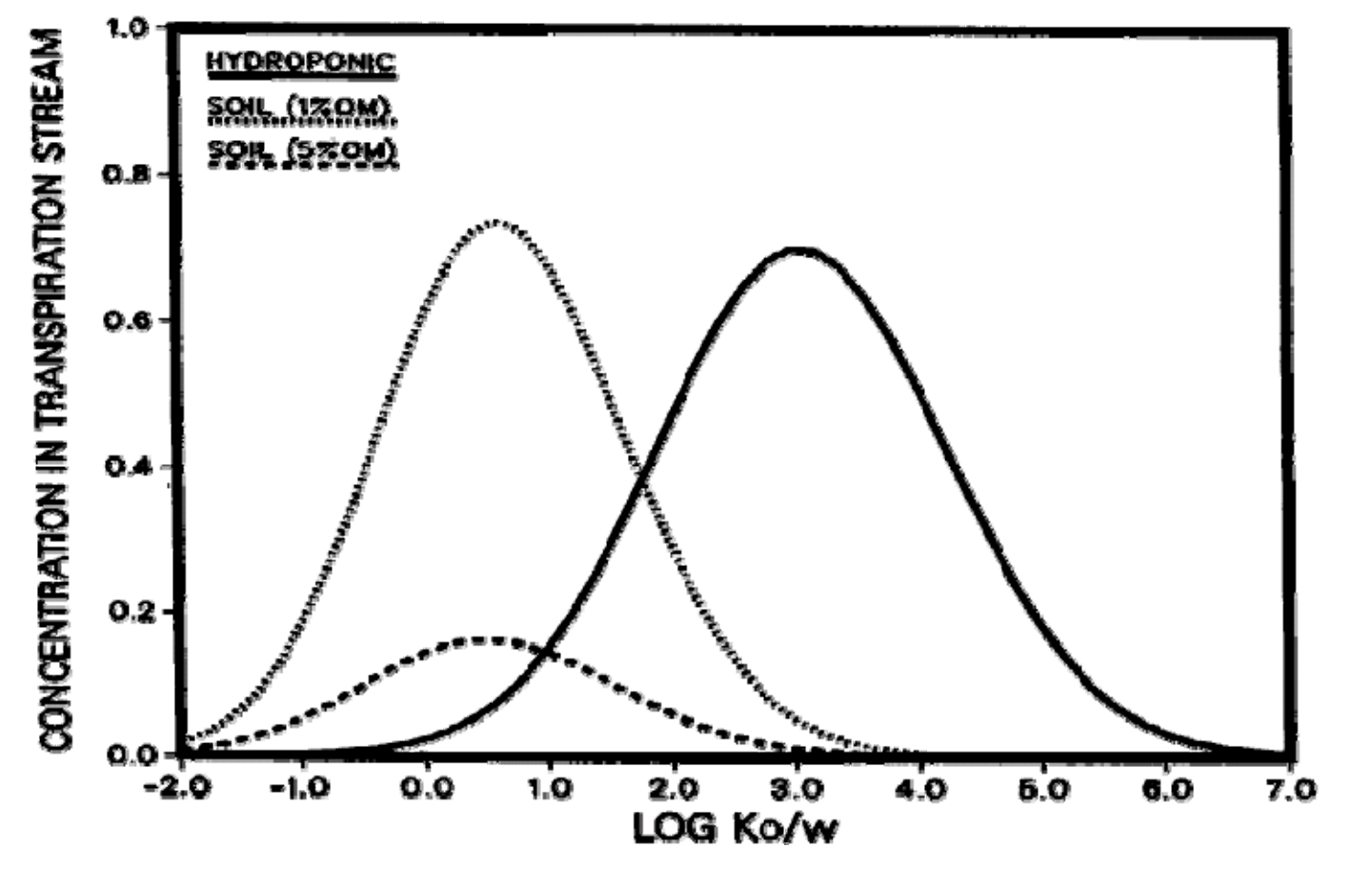


FIG. 2. Correlation of barley root concentration factors (based on soil concentrations) with soil adsorption coefficients (1 week).

$$CF_{soil} = \frac{\text{concentration in roots (based on fresh wt)}}{\text{concentration in soil (based on air-dry wt)}}$$

$$K'_{oc} = \frac{\text{g adsorbed/kg soil solids}}{\text{g dissolved/liter soil water}} \times \frac{100}{\%\ \text{organic C}}$$

Effect of SOM on the Relationship between TSCF and Log Kow (Hsu et al., 1990)



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

- USAN Data Set
  - Only 11% compounds had MW > 500
  - 8% compounds had MW > 600

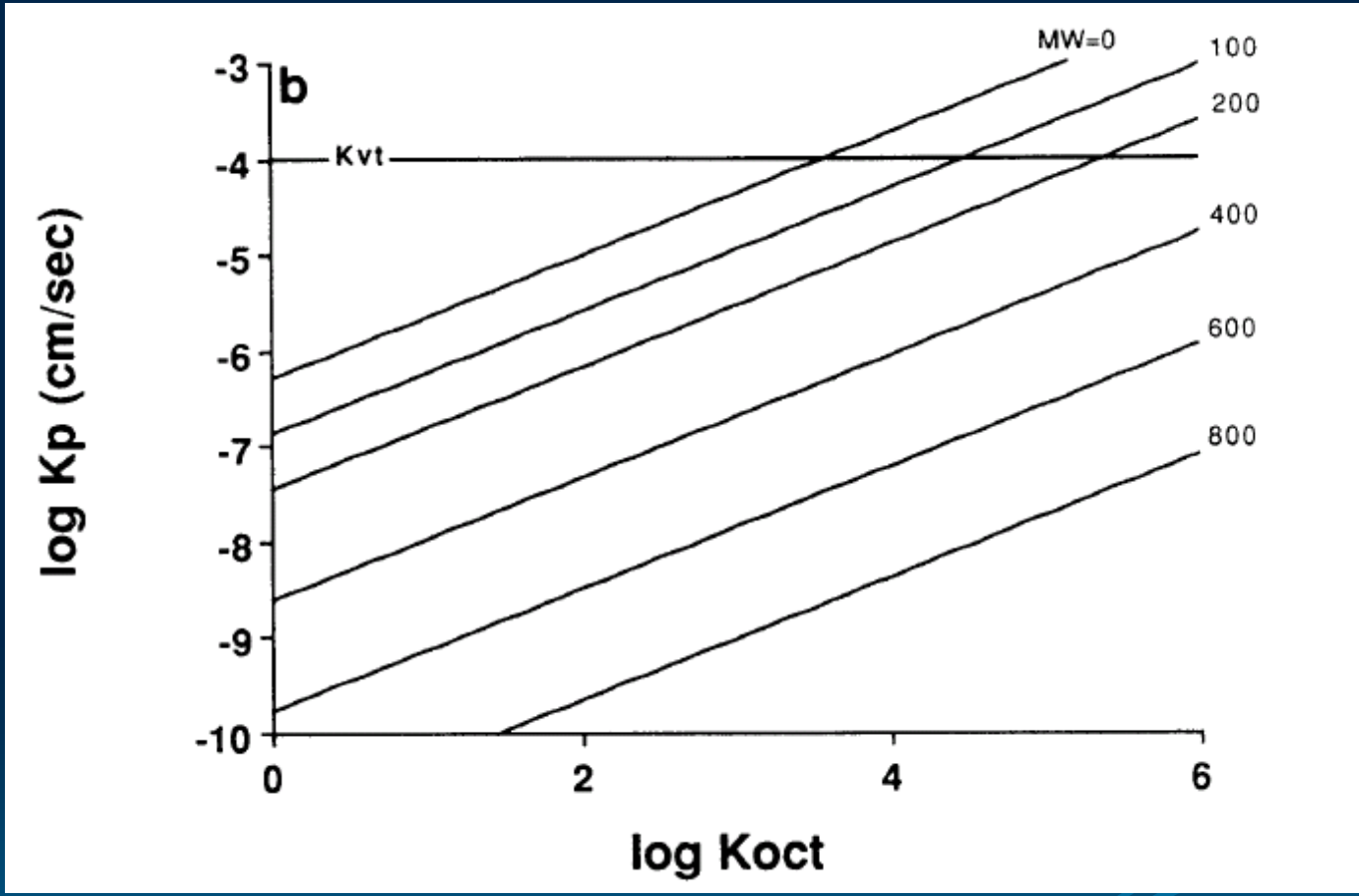
Influence of Molecular Weight

- World Drug Index (WDI) reveals that most common drugs have a MW range 300-400

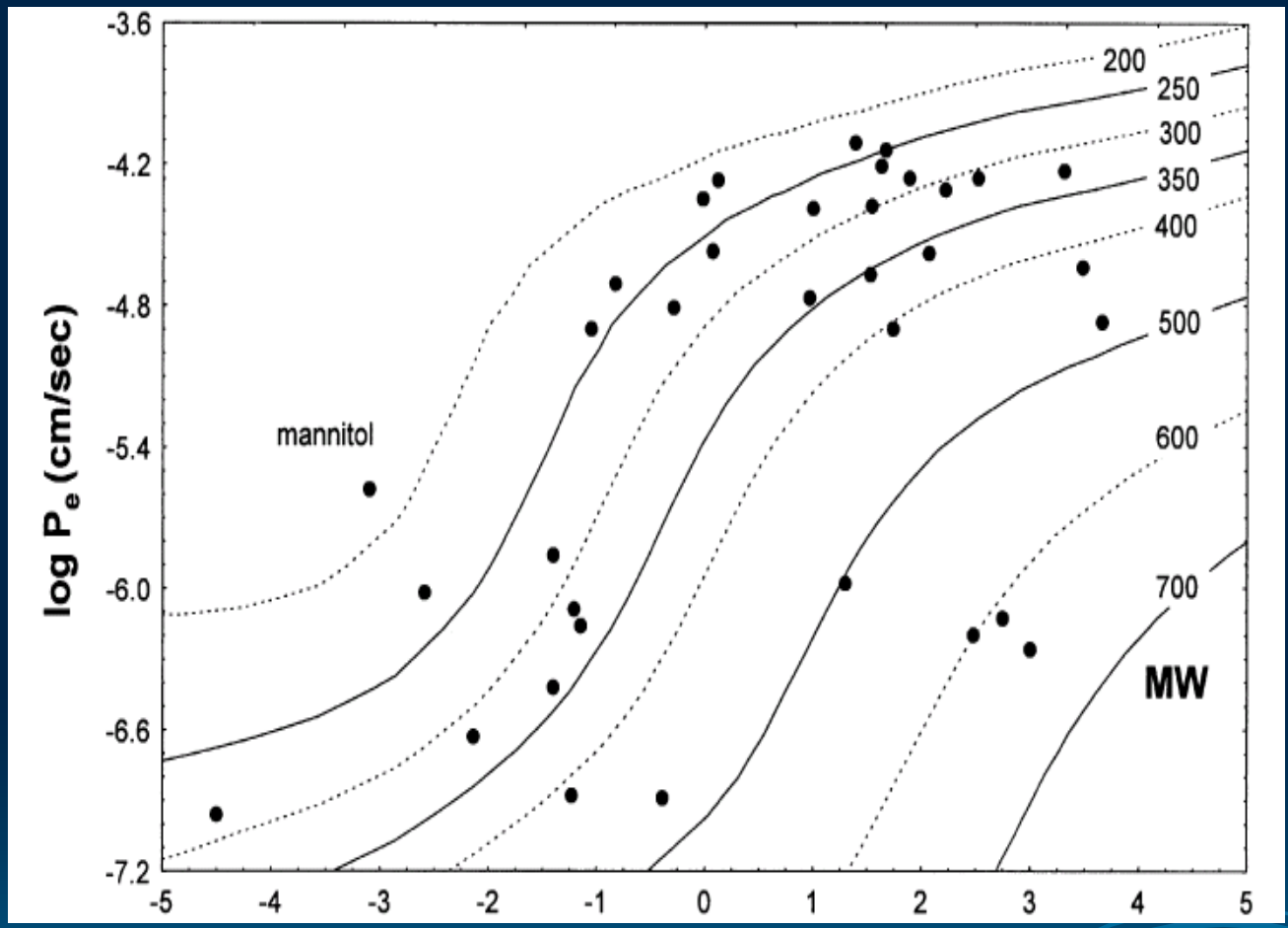
Tentatively 4 MW ranges have been defined:

1) MW < 200 Pore Diffusion (Restricted or non-Restricted)
2) MW ~ 200, a sieving effect becomes perceptible
3) MW 350+150 can readily diffuse through membranes
4) MW > 500-600 Restricted Membrane Diffusion

Permeability vs Log Kow (Potts and Guy, 1992)



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



Log Kow

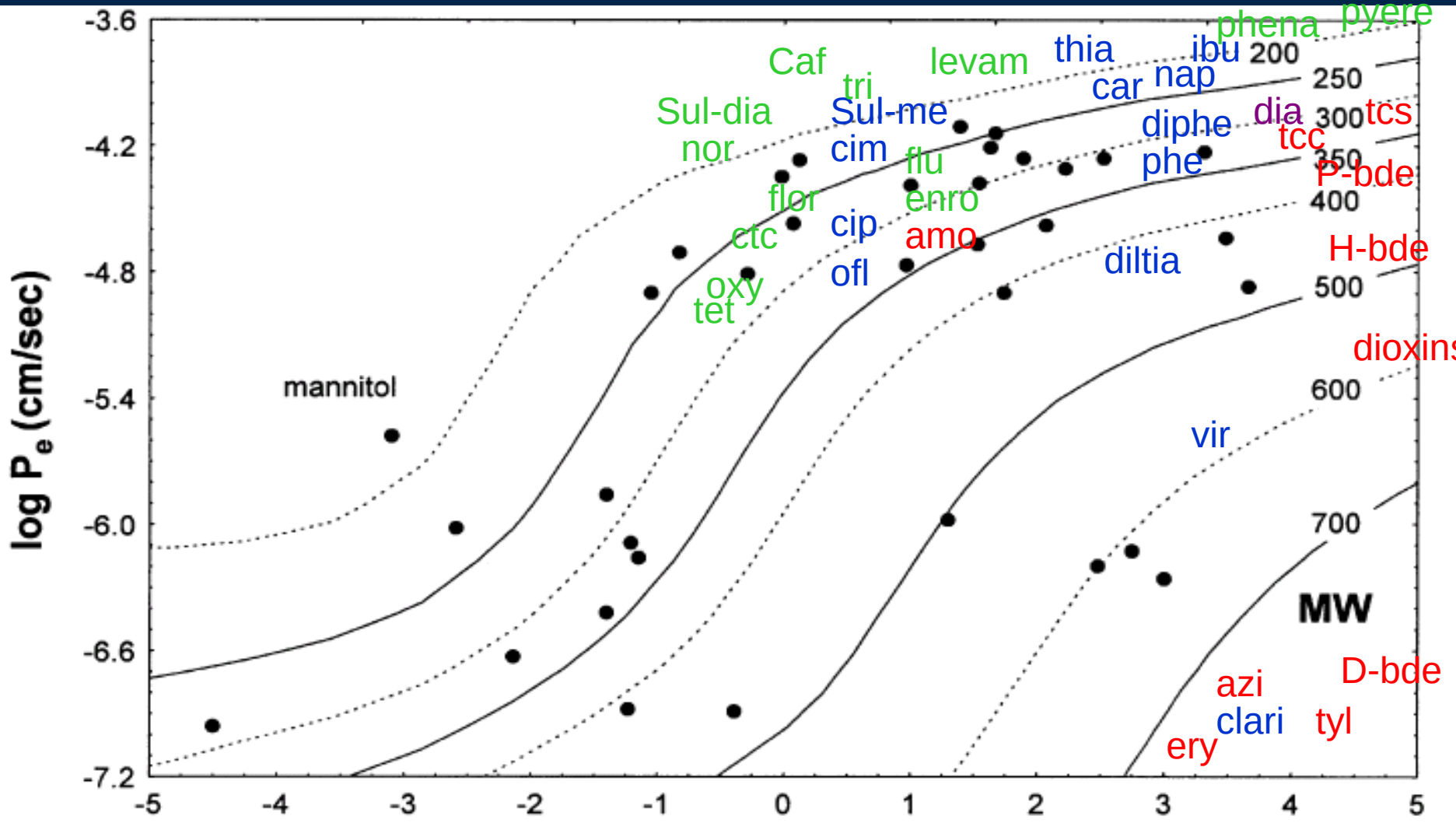
Highlights of 2006-2007 TNSSS

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

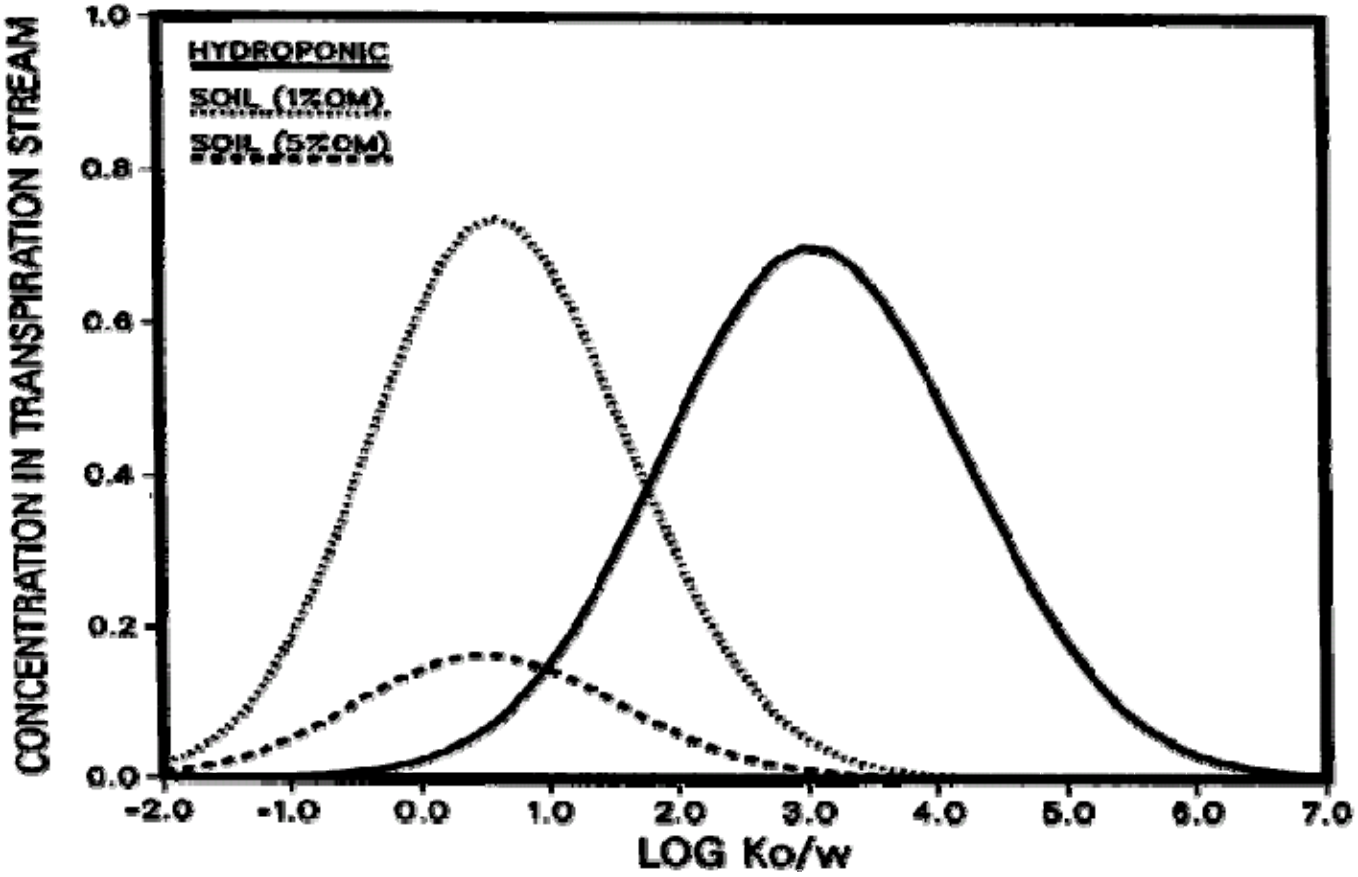
Highlights of 2006-2007 TNSSS

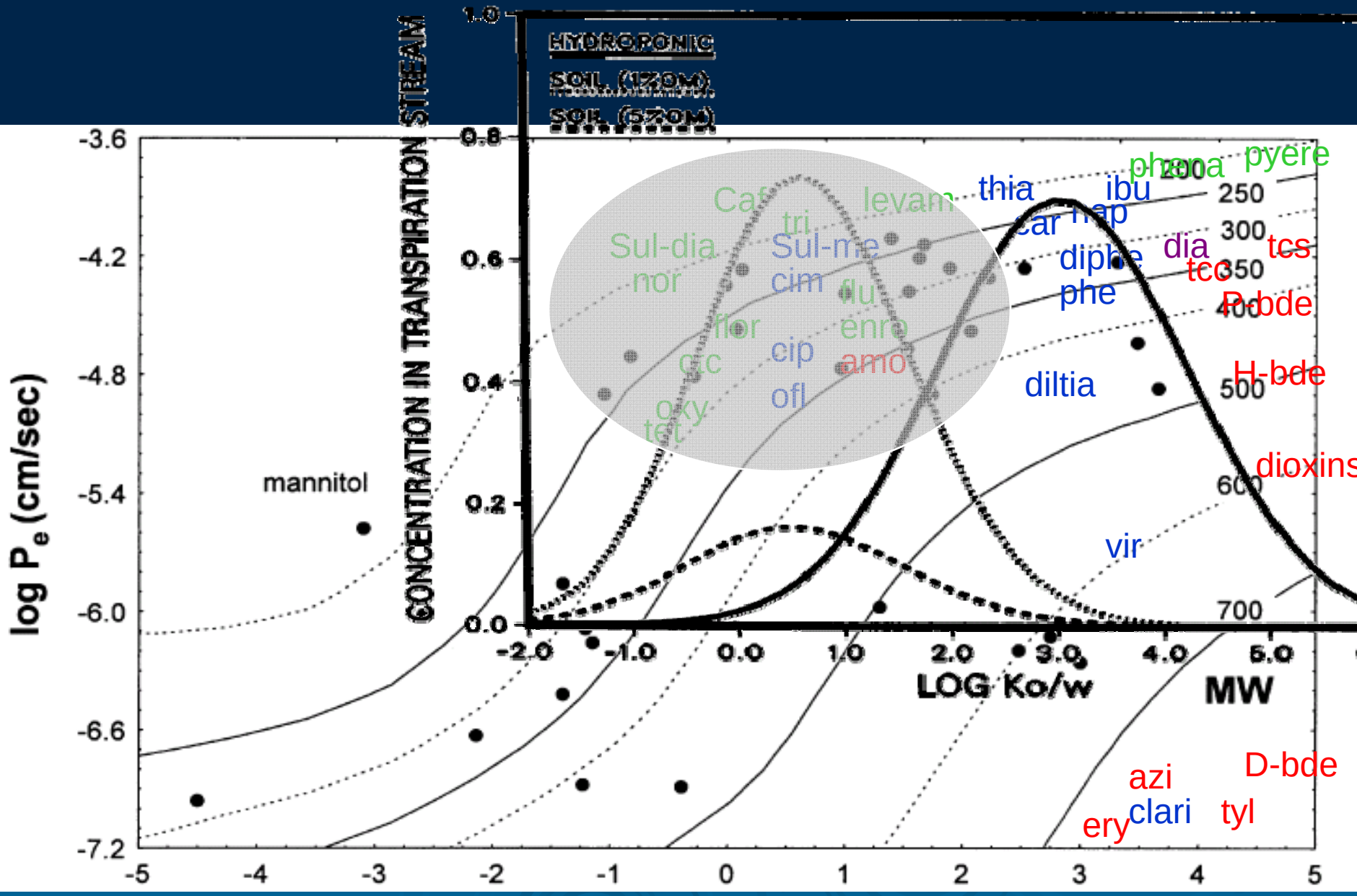
Steroids/hormones	Use	# Detects (out of 84)	Conc Range µg/kg
Estrone	Estrogen	60	27-965
Androsterone	Testosterone	50	21-1,030
Andostenedione	Testosterone	32	108-1,520
Flame retardants			
Tri & Tetra BDEs	Reduce flammability	84	77-5,126
Penta-BDEs		84	23-5,250
Hexa-BDEs		84	21-1,010
Deca-BDEs		83	150-17,000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

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



Effect of SOM on the relationship between TSCF and Log Kow (Hsu et al., 1990)




HYDROPONIC
SOIL (12OM)
SOIL (6%OM)
CONCENTRATION IN TRANSPIRATION STREAM
log P_e (cm/sec)
LOG Ko/w
MW
mannitol
Caf
levam
tri
Sul-dia
Sul-me
nor
cim
flu
flor
enro
cip
cfc
amo
ofl
oxy
tet
thia
ibu
car
nap
phena
pyere
dia
tcs
diphe
tcc
phe
P-bde
H-bde
diltia
dioxins
vir
azi
D-bde
clari
tyl
ery

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
- In USAN library there is a sharp cutoff in the number of compounds containing more than 5 OHs and NHs. Only 8% have more than 5.

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.
- USAN library: Sharp cutoff in profiles with only 12% of compounds having more than 10 Ns and Os.

The ‘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.

Desirable Range Exceedences Combinations of 2 of 4 Parameters in USAN Library

- Sum of N and O + Sum of NH and OH – 10%
- Sum of N and O + MW – 7%
- Sum of NH and MW – 4%
- Sum of MW + Log KOW – 1%

If 2 parameters are out of range, a ‘poor absorption or permeability is possible’

New Chemical Entities (NCEs)

- Derwent World Drug Database – 133 NCEs

Rule of 5

Average Log KOW – 1.80

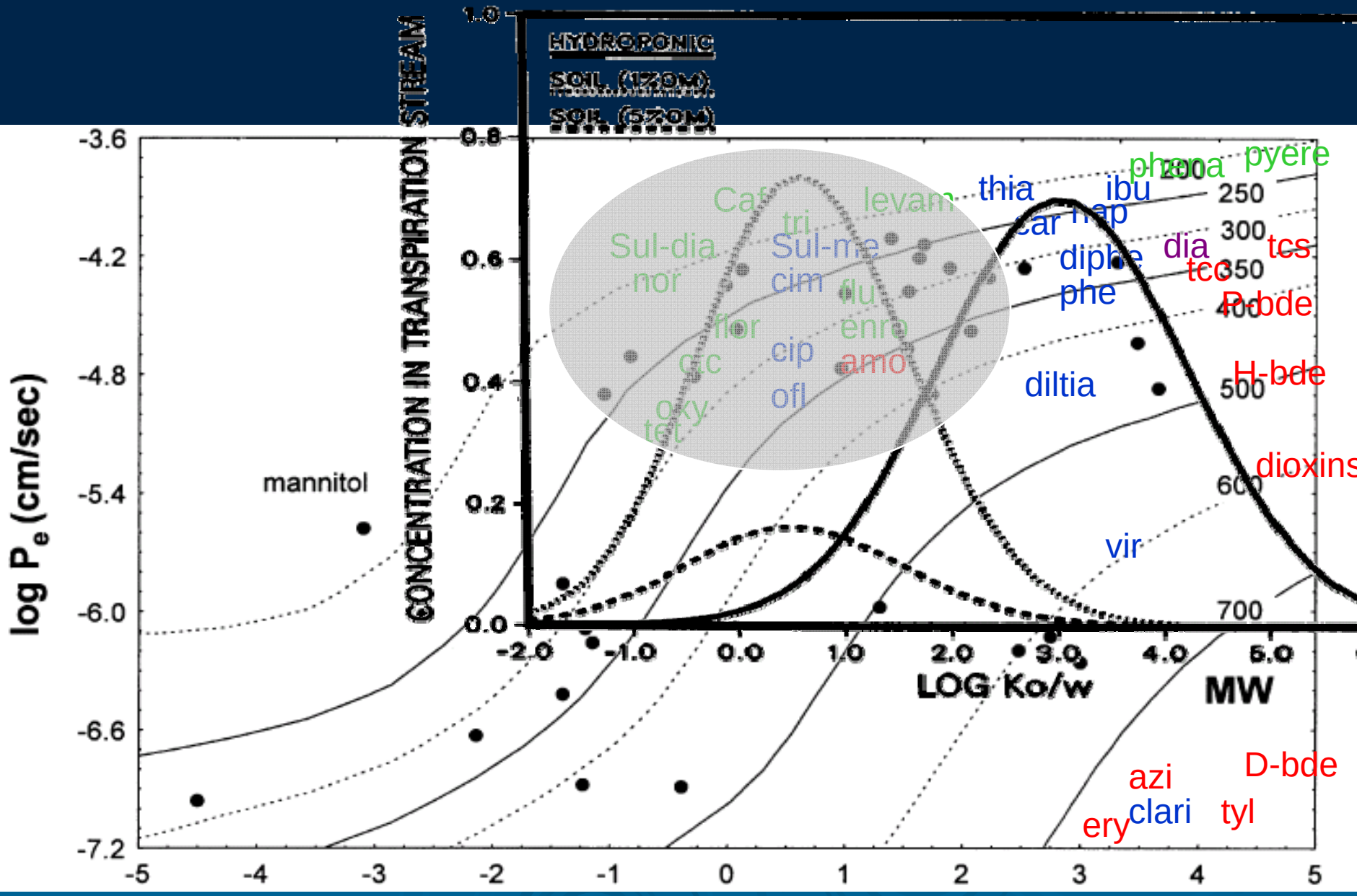
Average H-bond donors – 2.53

Average MW – 408

Average Sum of Ns and Os – 6.53

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	3.53	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


HYDROPONIC
SOIL (120M)
SOIL (670M)
CONCENTRATION IN TRANSPIRATION STREAM
log P_e (cm/sec)
LOG Ko/w
MW
mannitol
Caf
levam
tri
Sul-dia
Sul-me
nor
cim
flu
flor
enro
cip
cfc
amo
ofl
oxy
tet
thia
ibu
car
nap
phena
pyere
dia
diphe
tcs
tcc
phe
P-bde
H-bde
diltia
dioxins
vir
azi
D-bde
clari
tyl
ery

Log Kow

Conclusions

- ‘Rule of 5’ should be the first step in deciding which compounds will not 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 <450
  - The Log KOW is <3
  - <6 H-bond acceptors (expressed as sums of Ns and Os);

  Should only be studied in field plant uptake studies for risk assessment.