Concepts of non-linear pharmacokinetics and KMD

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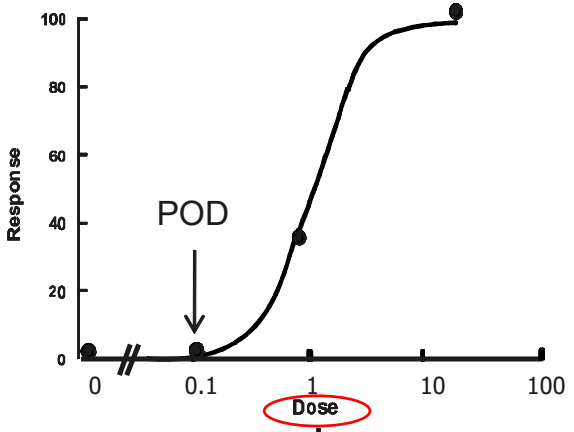
Disclosure Statement

- Member of several science advisory boards (public and private sector) [non-remunerated] (e.g. ILSI, HESI, Owlstone Medical, Cosmetics Europe LRSS, Swiss Centre for Applied Human Toxicology, MSU Center for Research on Ingredient Safety, A*STAR Food and Chemical Safety Programme Singapore)
- Member/chair of several national and international scientific advisory committees (UK COT, UK COMEAP, JMPR, JECFA, TobReg, ISO TC126 WG10 Intense Smoking Regime)
- I have no financial interests in the subject matter of the session

Risk characterization

Hazard ID
Hazard characterisation



Exposure assessment

Uncertainty factor

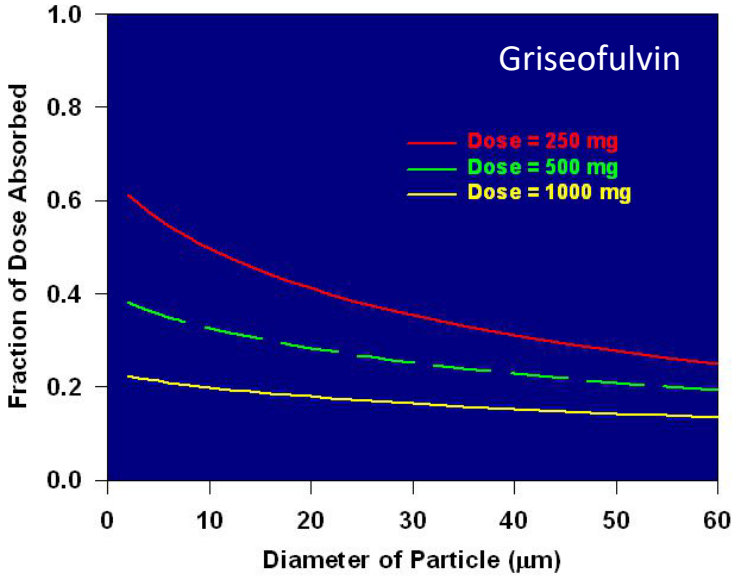
HBGV (e.g. ADI)
HBGV = POD/UF

Risk characterisation
(Exposure cf HBGV)

MOE = POD/Exposure

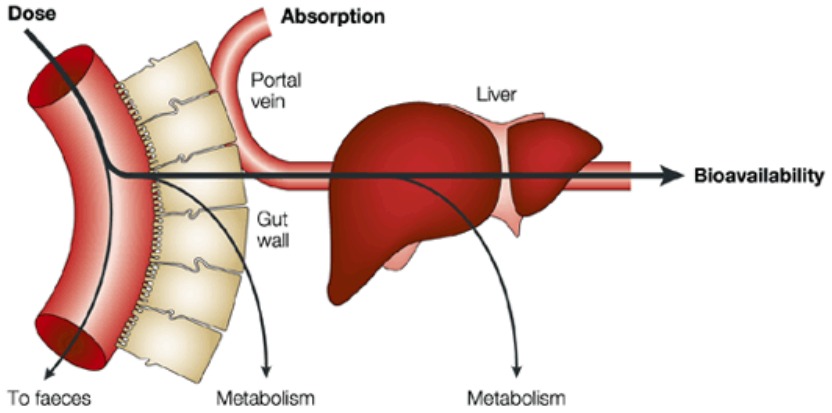
Bioavailability

Solubility

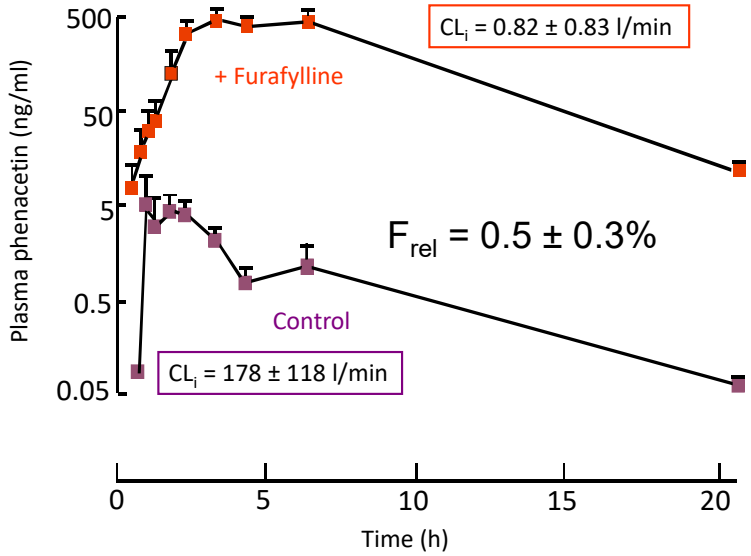


Yu, 1999

Permeation & pre-systemic metabolism



Nature Reviews | Drug Discovery



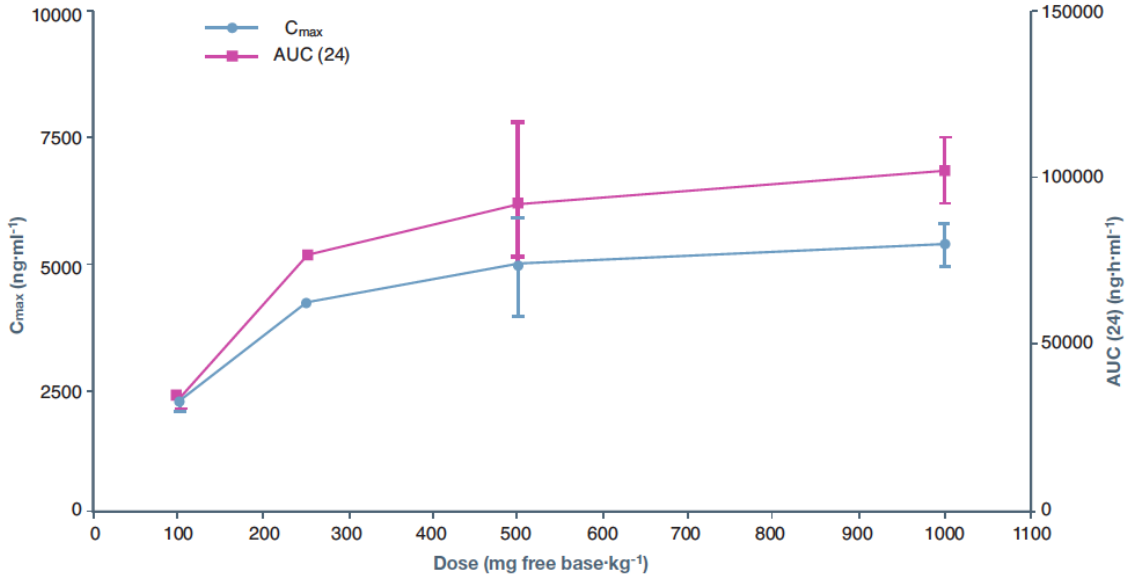
External dose → Bioaccessible dose → Bioavailable dose

Dose-dependency of systemic exposure

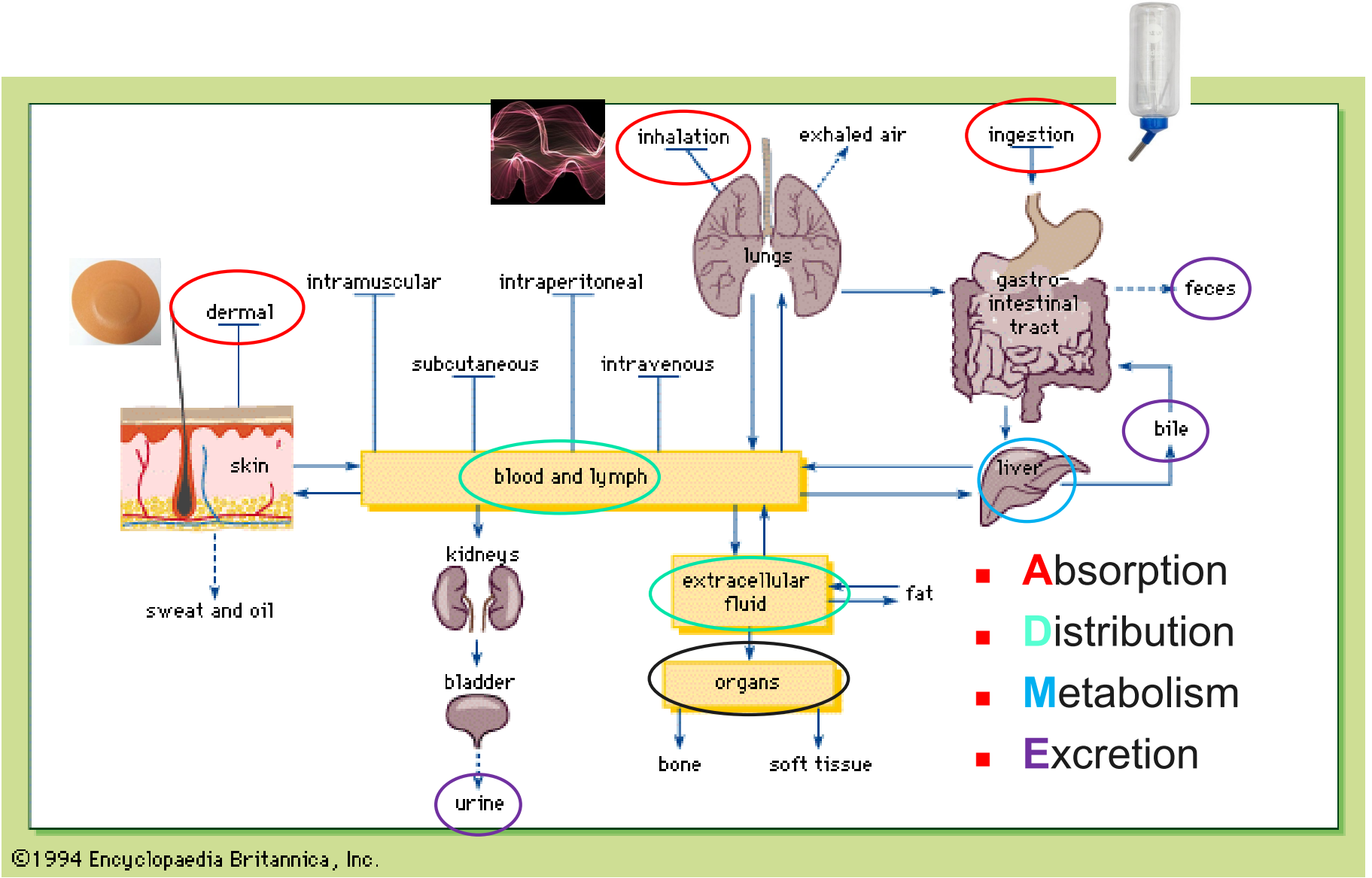
Fractional absorption independent of dose

Species	Durat.	Dose (mg/kg)	Plasma concentration (μg/ml)		AUC(0-24) (μg·h/ml)	
			Male	Female	Male	Female
Rat	2 Week	**Gavage**				
		500	13.5	9.92	120	102
		1250	27.6	25.2	332	334
		2500	47.4	40.7	626	602
		Diet				
		500	11.5	10.7	199	181
		1250	25.9	19.0	491	336
		2500	50.7	32.4	921	606

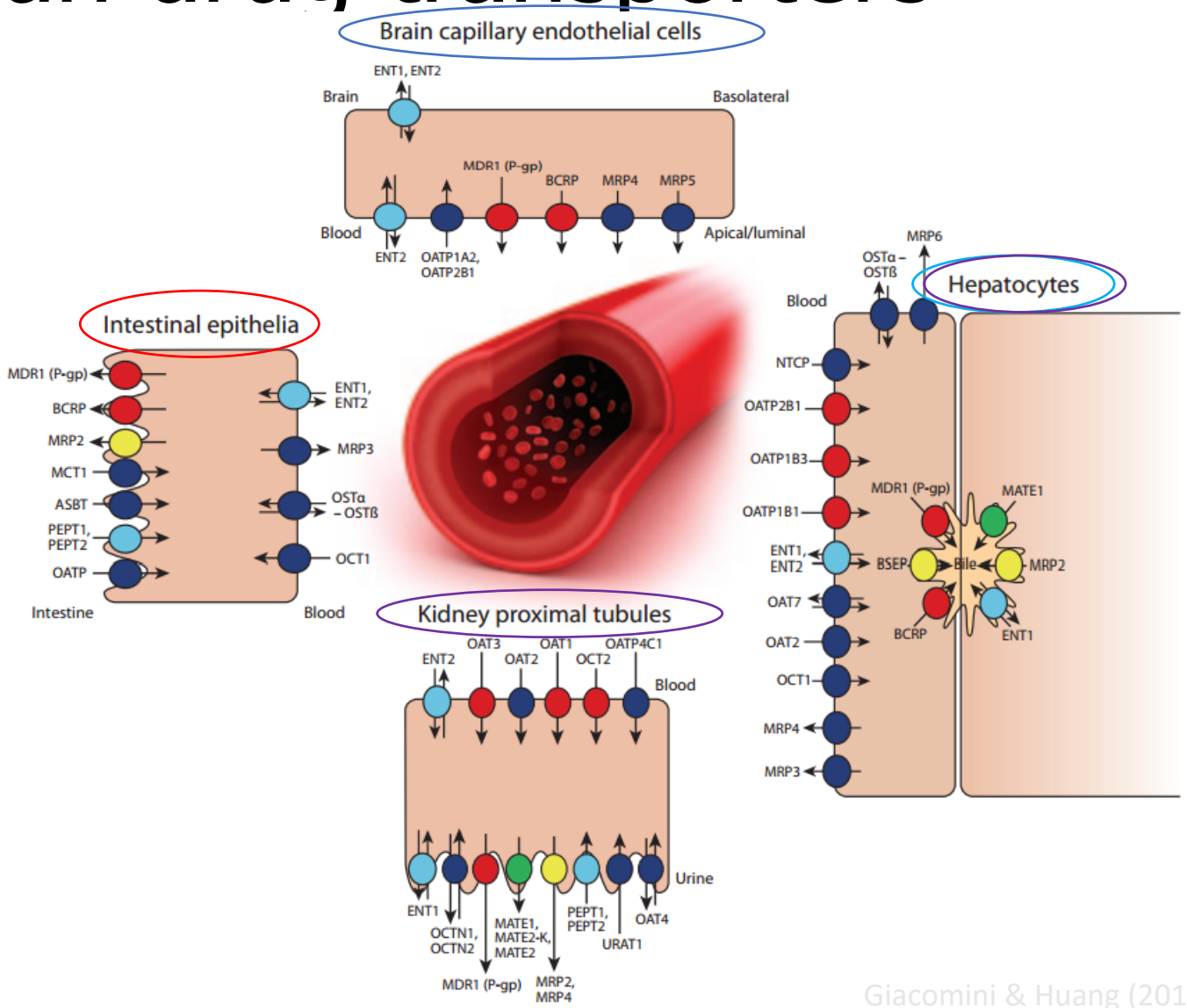
Fractional absorption dependent on dose

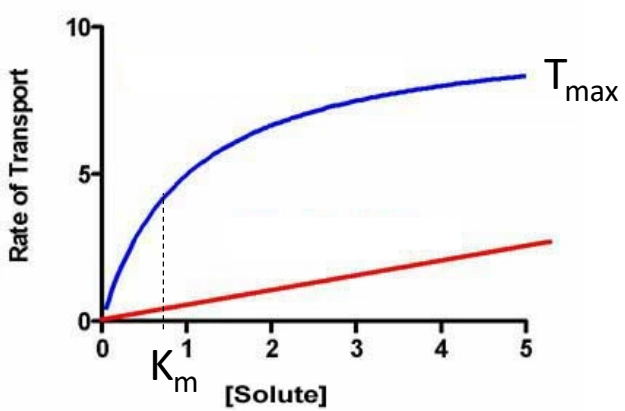


Absorption, distribution, metabolism, excretion (ADME) determine exposure



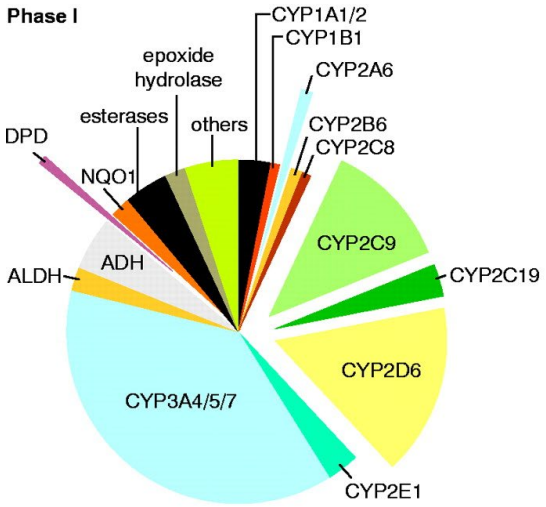
Human drug transporters

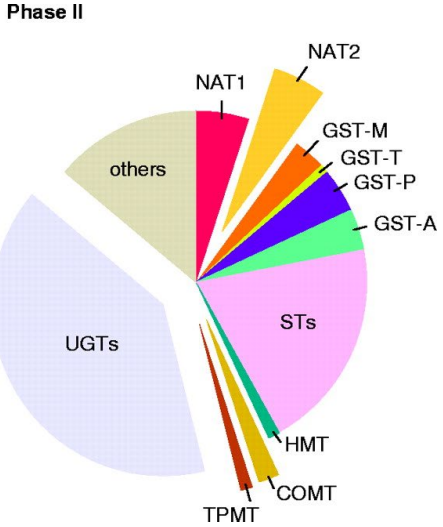


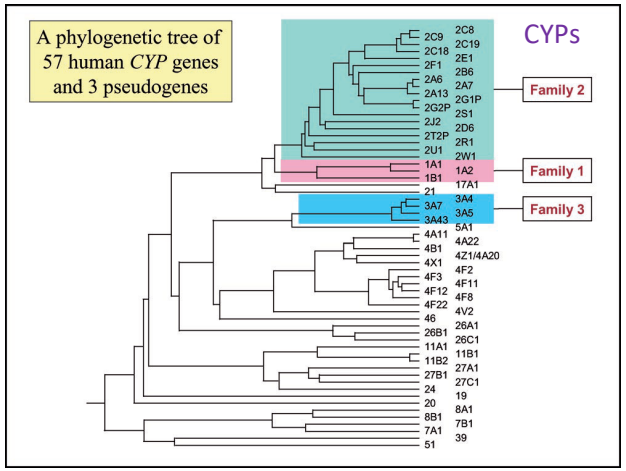


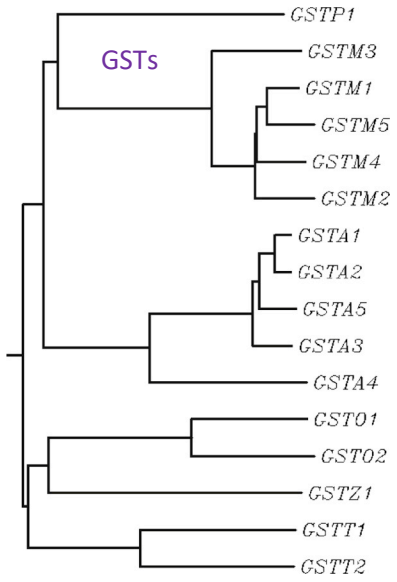
Giacomini & Huang (2013)

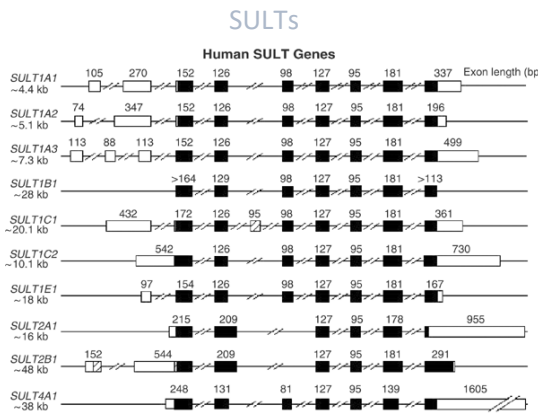
Xenobiotic biotransformation

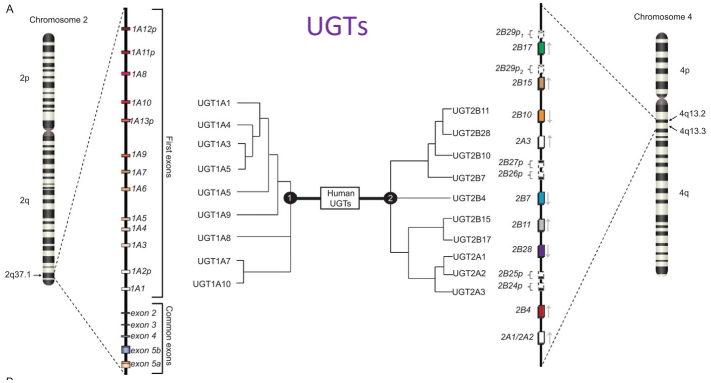




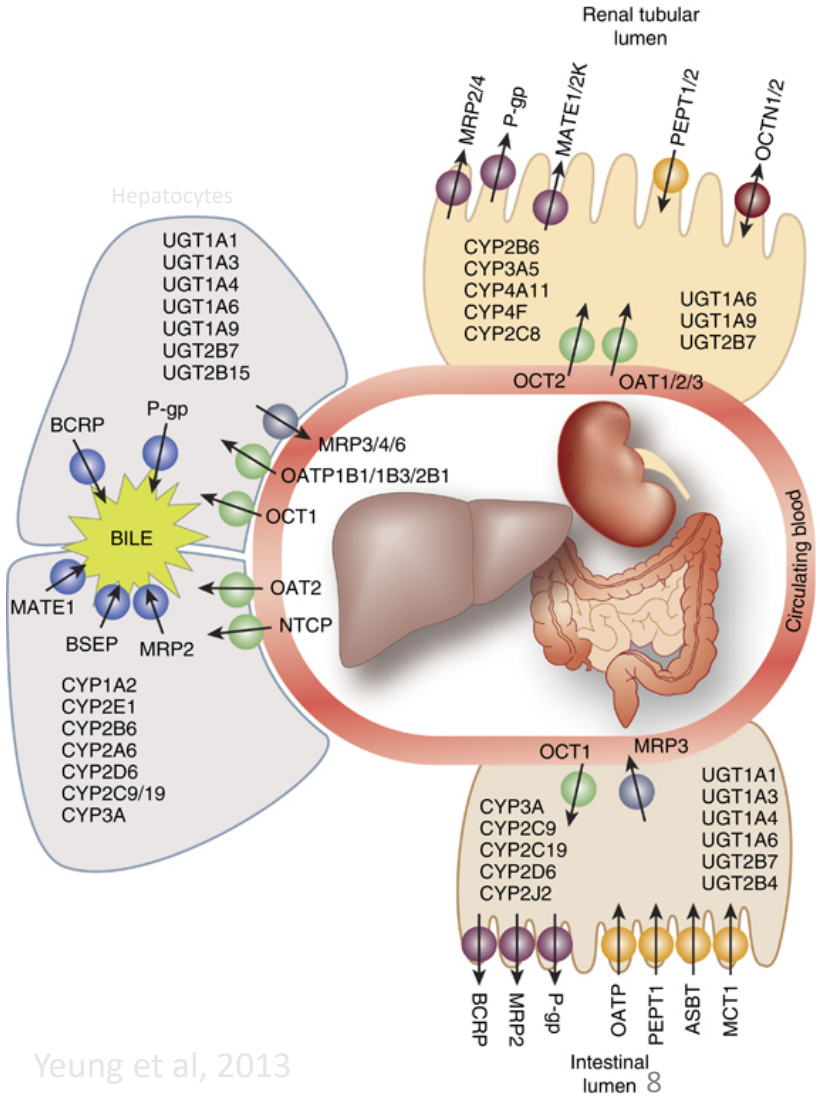








- Specificity
- Maximum rate (V_{max})
- Affinity (K_m)



Yeung et al, 2013

Kinetics of metabolism

$$Rate\ of\ metabolism = \frac{V_{max} \times C}{K_m + C}$$

When C << K_m

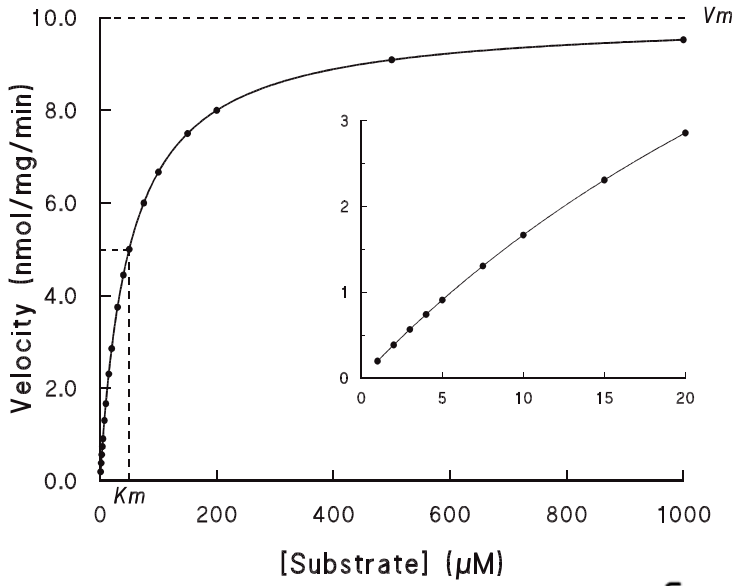
$$Rate\ of\ metabolism \approx \frac{V_{max} \times C}{K_m}$$

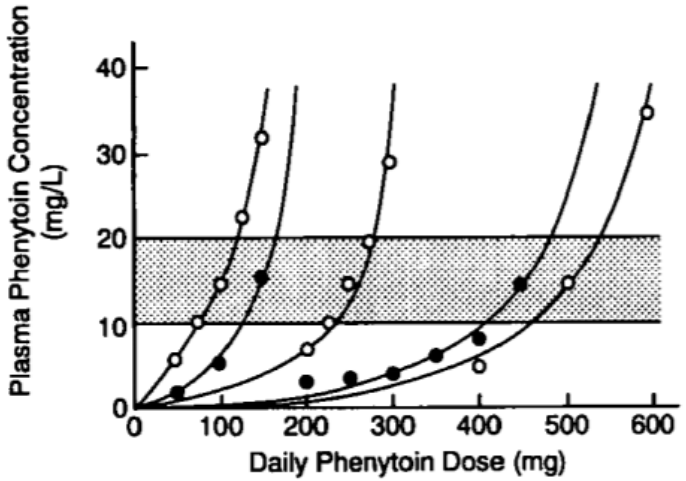
$$i.e.\ Rate\ of\ metabolism \propto C$$

When C > K_m

$$Rate\ of\ metabolism \approx \frac{V_{max} \times C}{C}$$

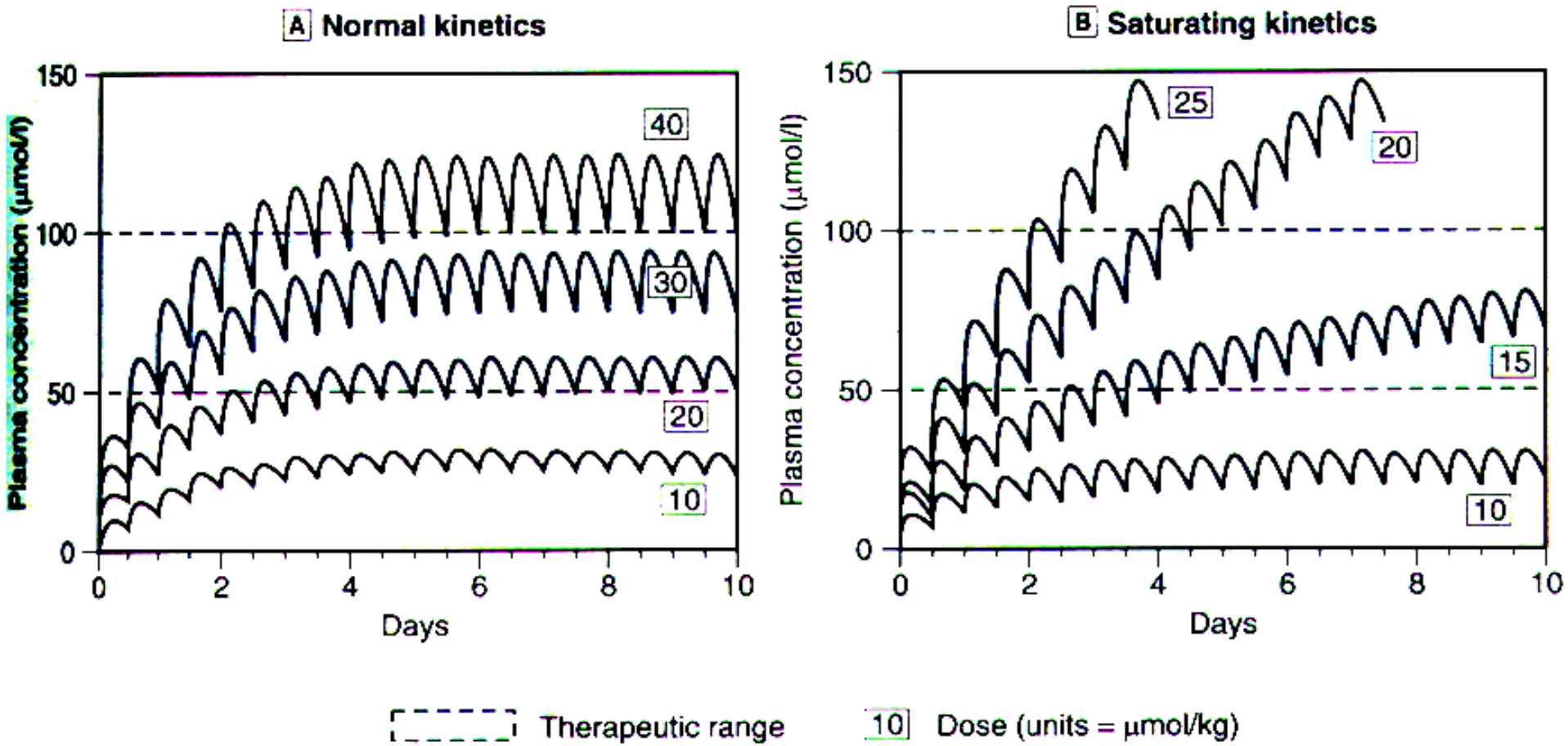
$$i.e.\ Rate\ of\ metabolism\ \rightarrow V_{max}$$



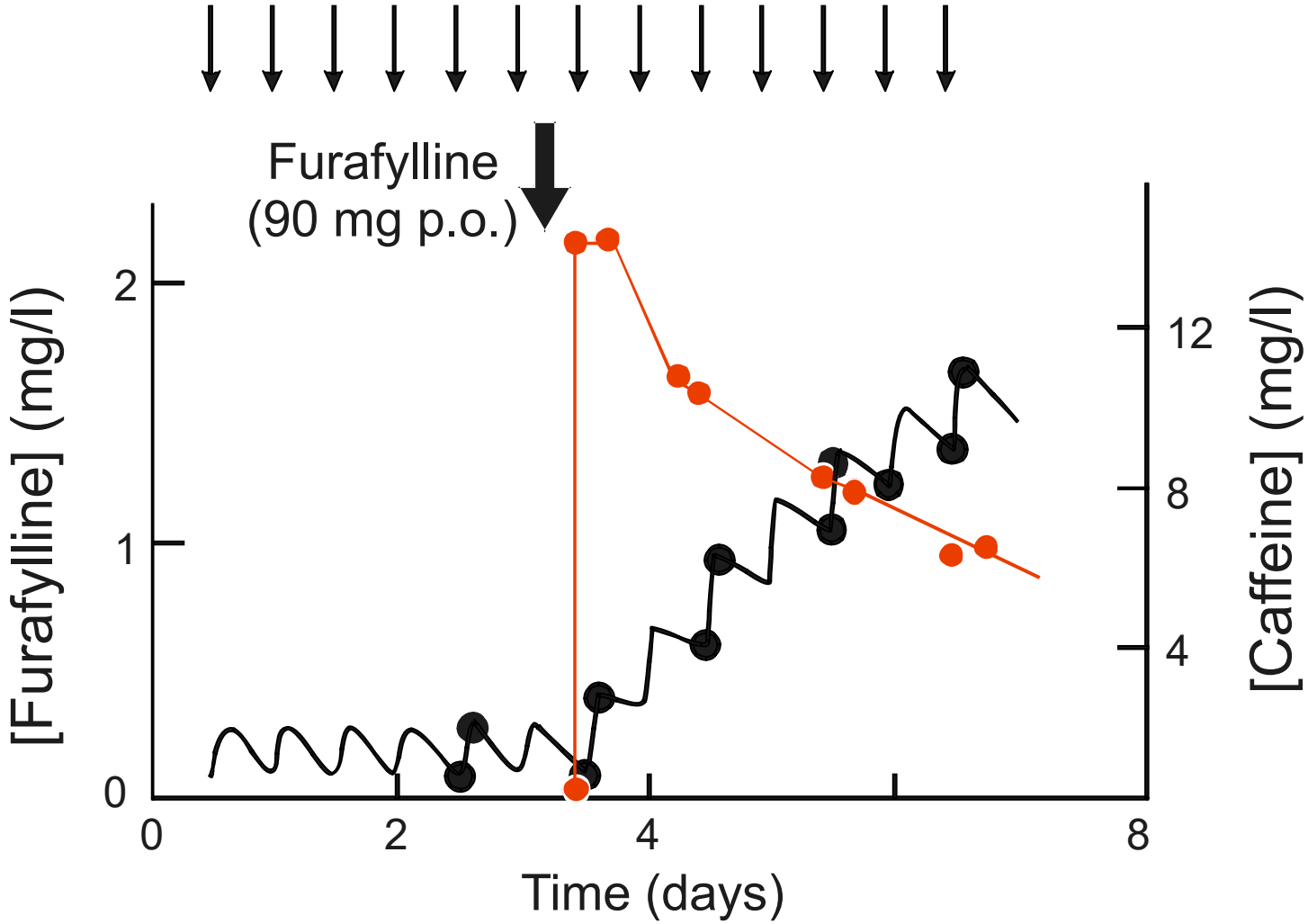


From Winter & Tozer, 1986

Normal *vs.* saturating kinetics

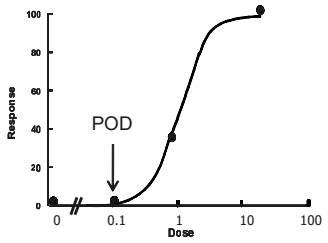


Effects of furafylline on caffeine kinetics



Point of departure

Hazard ID
Hazard characterisation



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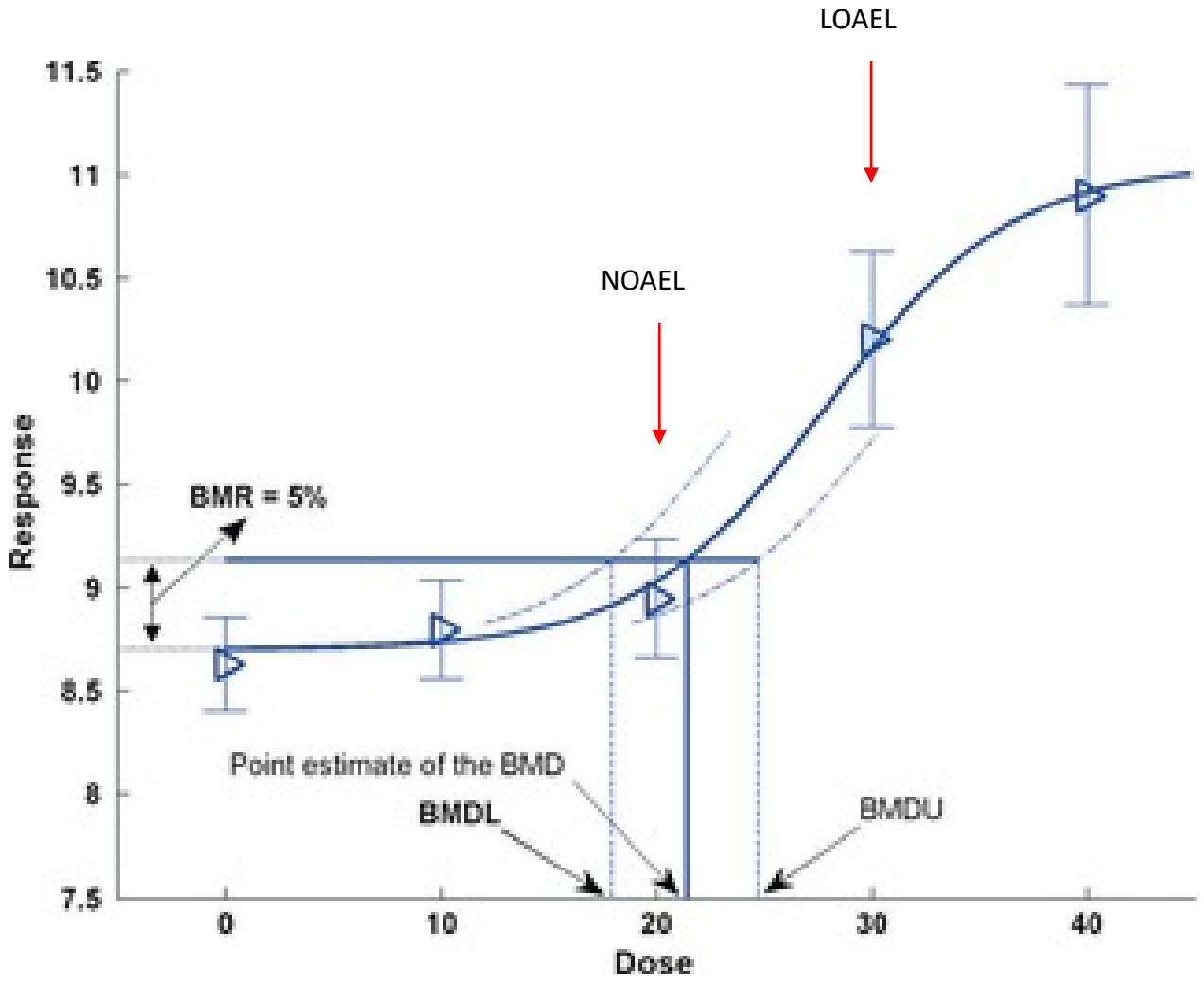
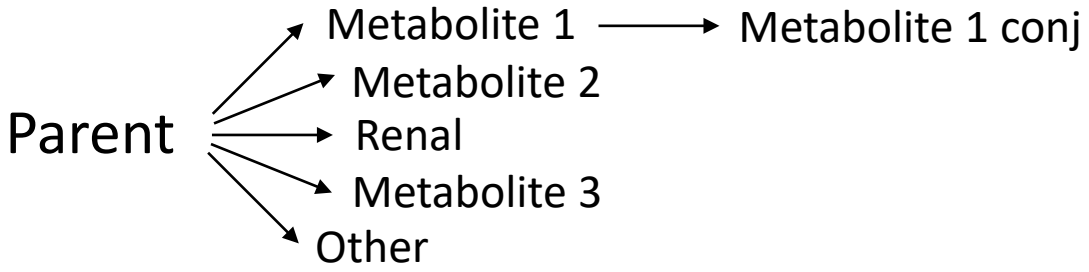
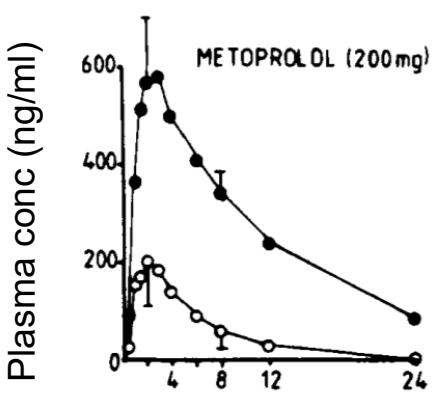


Major and minor routes of elimination



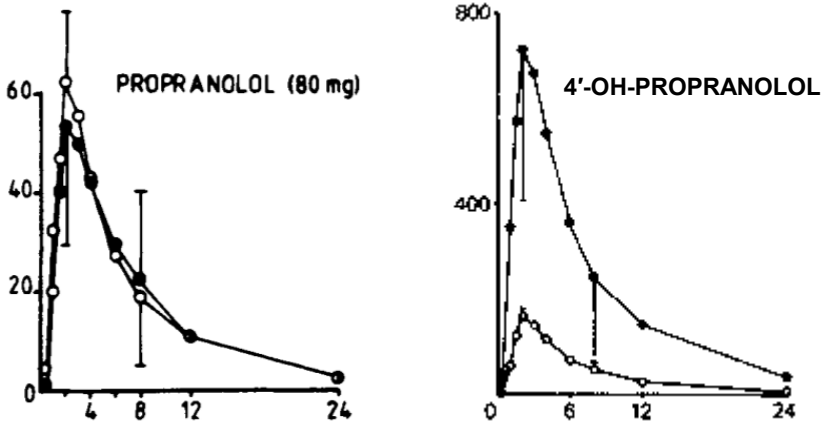
Propranolol and metoprolol are both cleared > 90% by CYP-dependent oxidation

$$Cl = Cl_R + Cl_{m1} + Cl_{m2} + Cl_{m3} + Cl_{other}$$



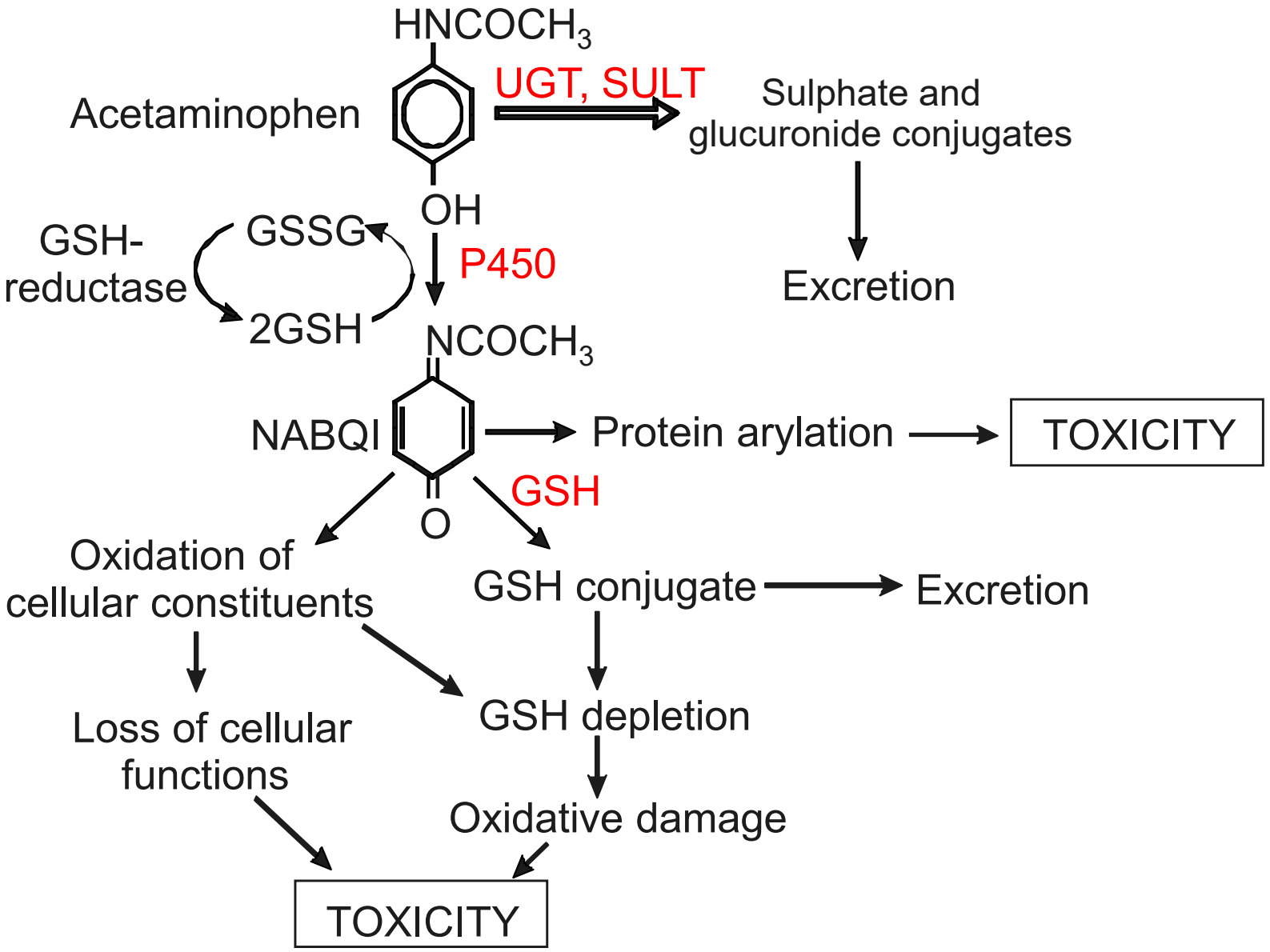
Urinary metoprolol and metabolites (% dose)

	M	*HM*	*H117-04*
EMs	4.0 ± 2.6	7.4 ± 3.1	57.6 ± 13.6
PMs	10.6 ± 3.9	0.06 ± 0.04	45.5 ± 13.1
P, (EMs *vs* PMs)	< 0.001	< 0.001	< 0.005

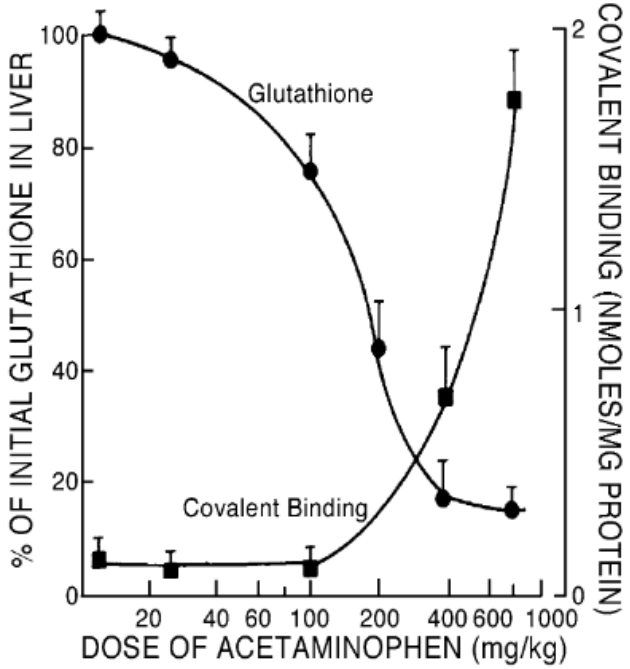


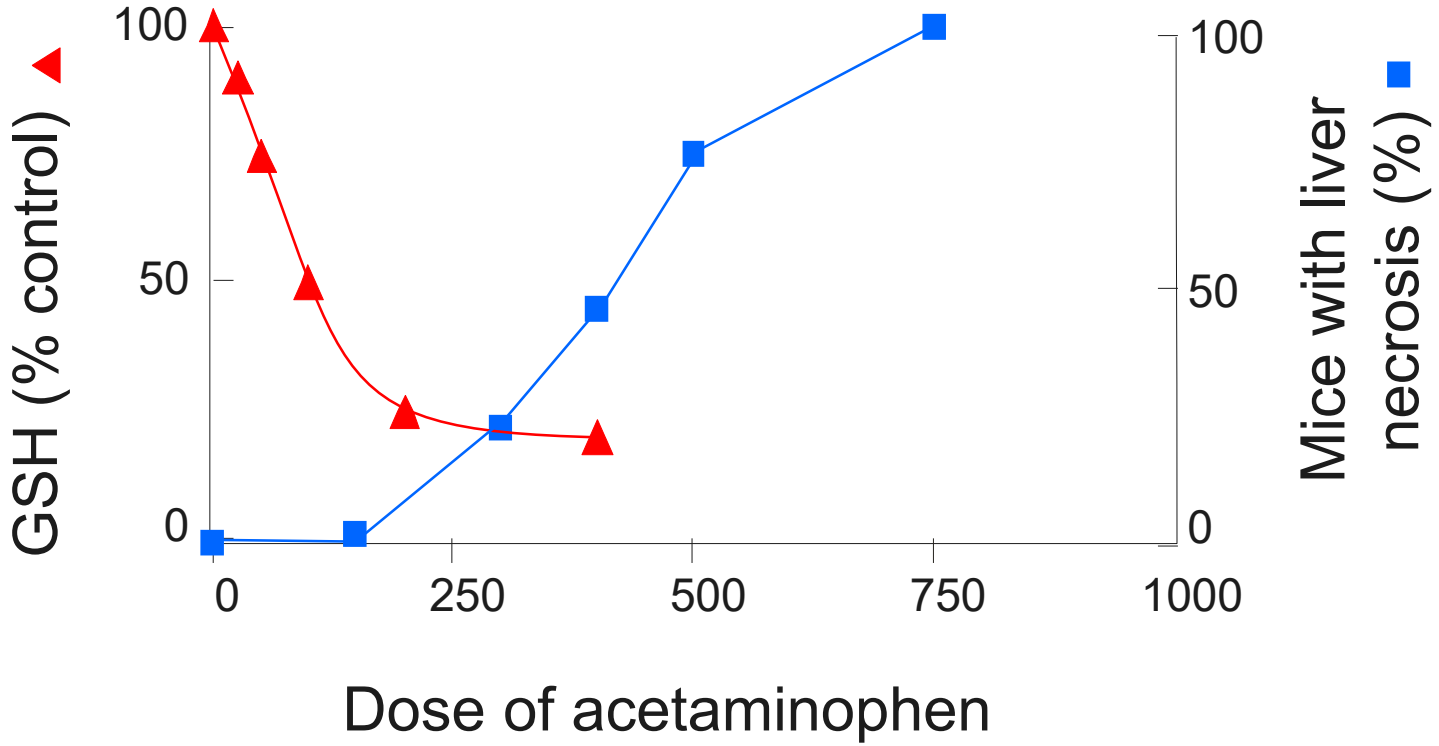
Data from Tucker, Lennard, Wood et al

Acetaminophen hepatotoxicity



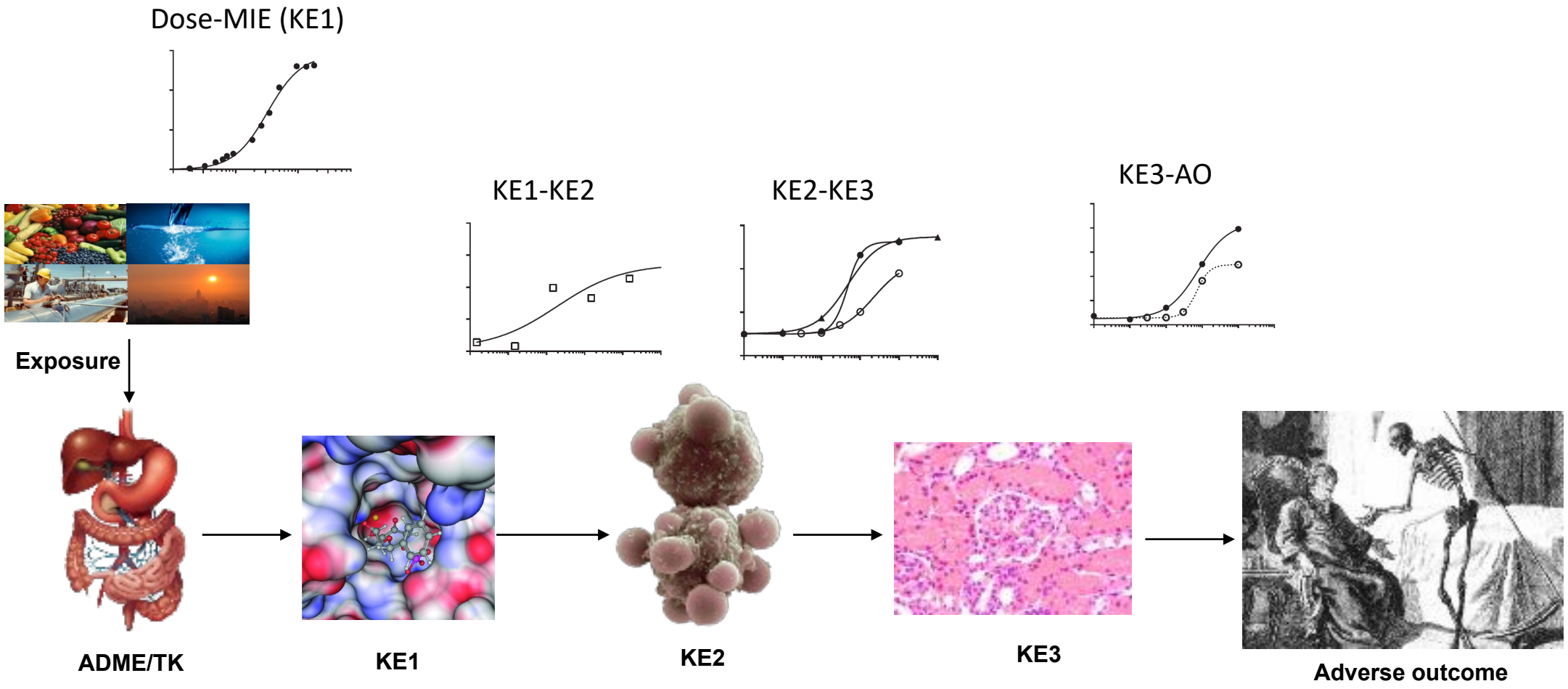
GSH depletion and acetaminophen toxicity





Data of Gillette, Mitchell, et al

Quantitative Adverse Outcome Pathway (AOP)



Adverse Outcome Pathway

Conclusions

- The maximum dose used in toxicity testing is often many orders of magnitude greater than worst-case human exposure
- Limited solubility and/or saturation of processes of absorption, distribution, metabolism and excretion can lead to marked non-linearity between dose and plasma/active-site concentration
- This confounds interpretation of dose-effect relationships and extrapolation to human relevant exposures; hence, substantial over- or under-estimation of risk to exposed populations is possible
- Kinetic considerations are therefore essential in both study design and data interpretation