

Pharmacokinetics and Disposition of UDM Comparison of Various Sources for Drug Testing: Urine, Blood, Hair, Saliva

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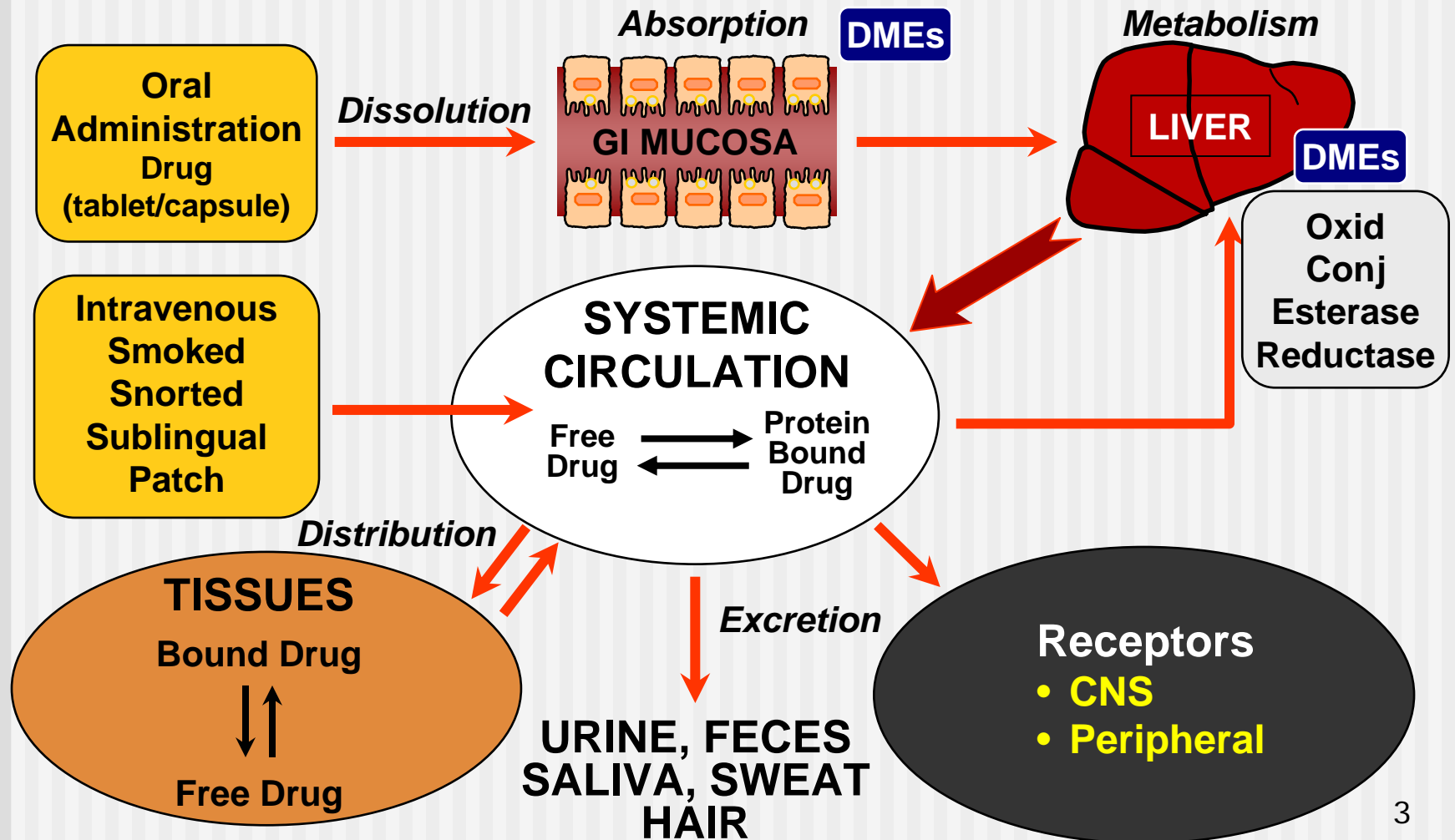
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Outline:

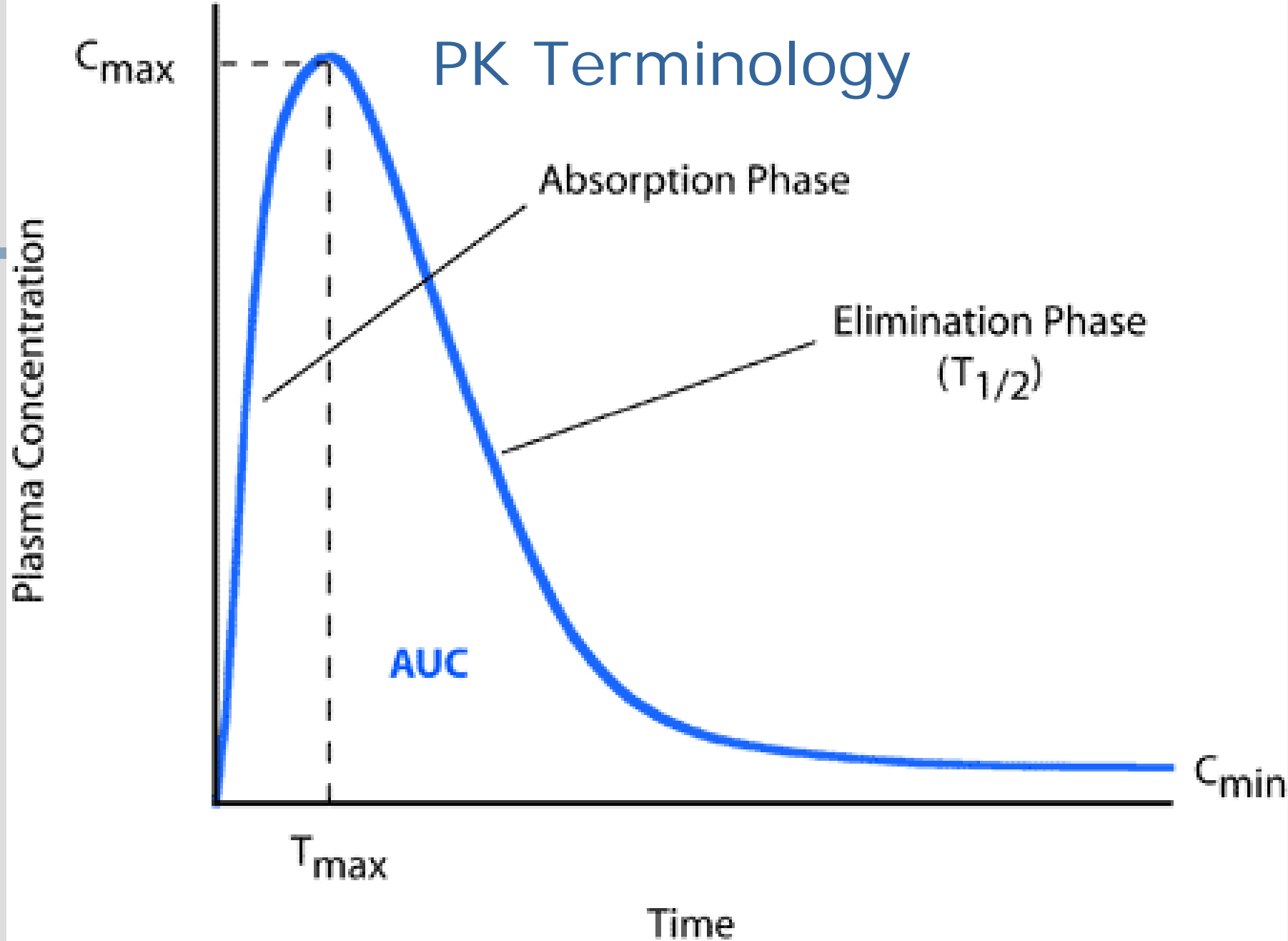
Pharmacokinetics and Disposition of UDM Comparison of Various Sources for Drug Testing: Urine, Blood, Hair, Saliva

- Pharmacokinetics
 - Concepts & terminology
- Drug disposition
 - Blood, saliva, urine, hair
 - Profiles & specimen comparisons
- Metabolism
- Interpretational challenges

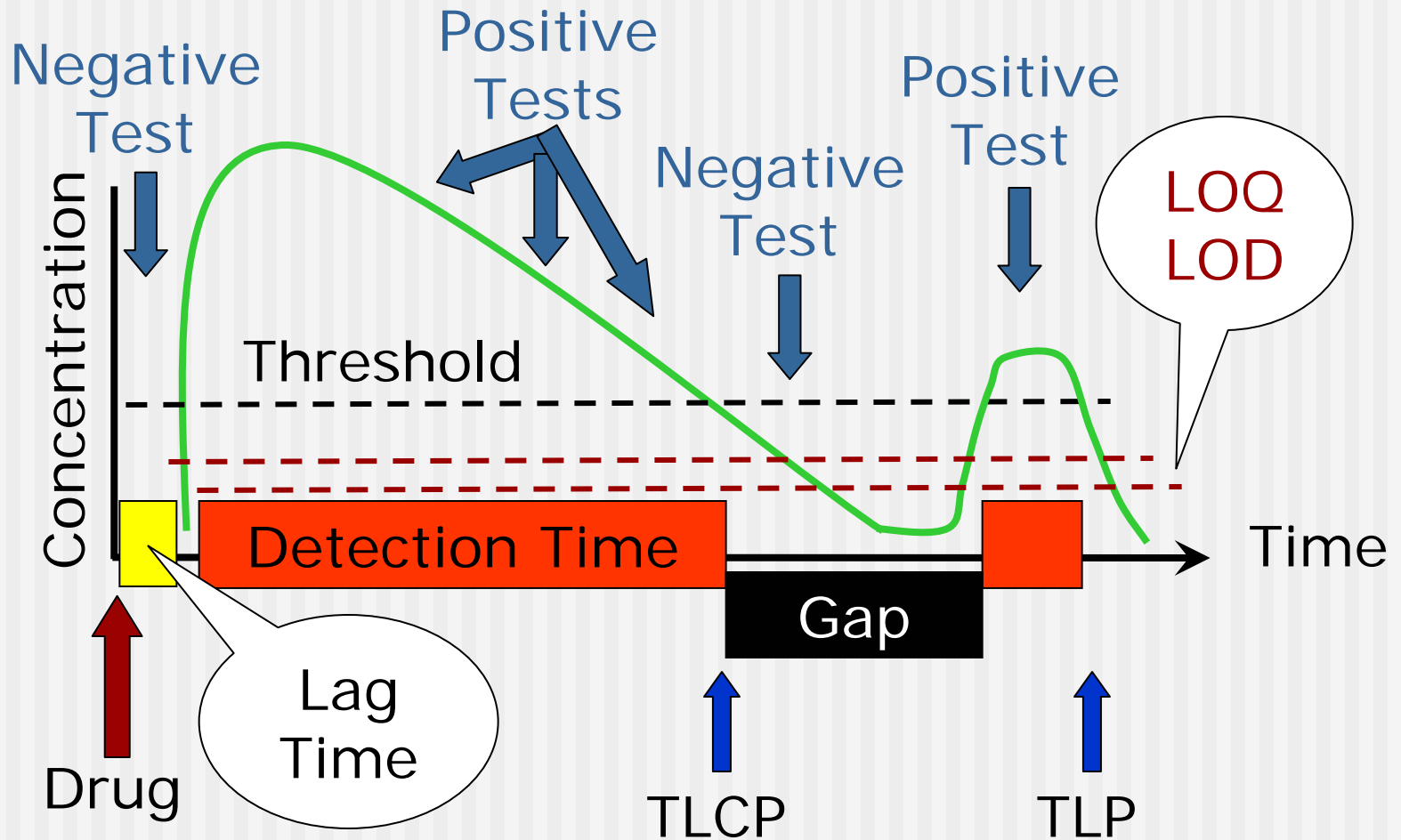
Factors Affecting Drug Concentrations at Site of Action



PK Terminology



Testing Terms & Concepts



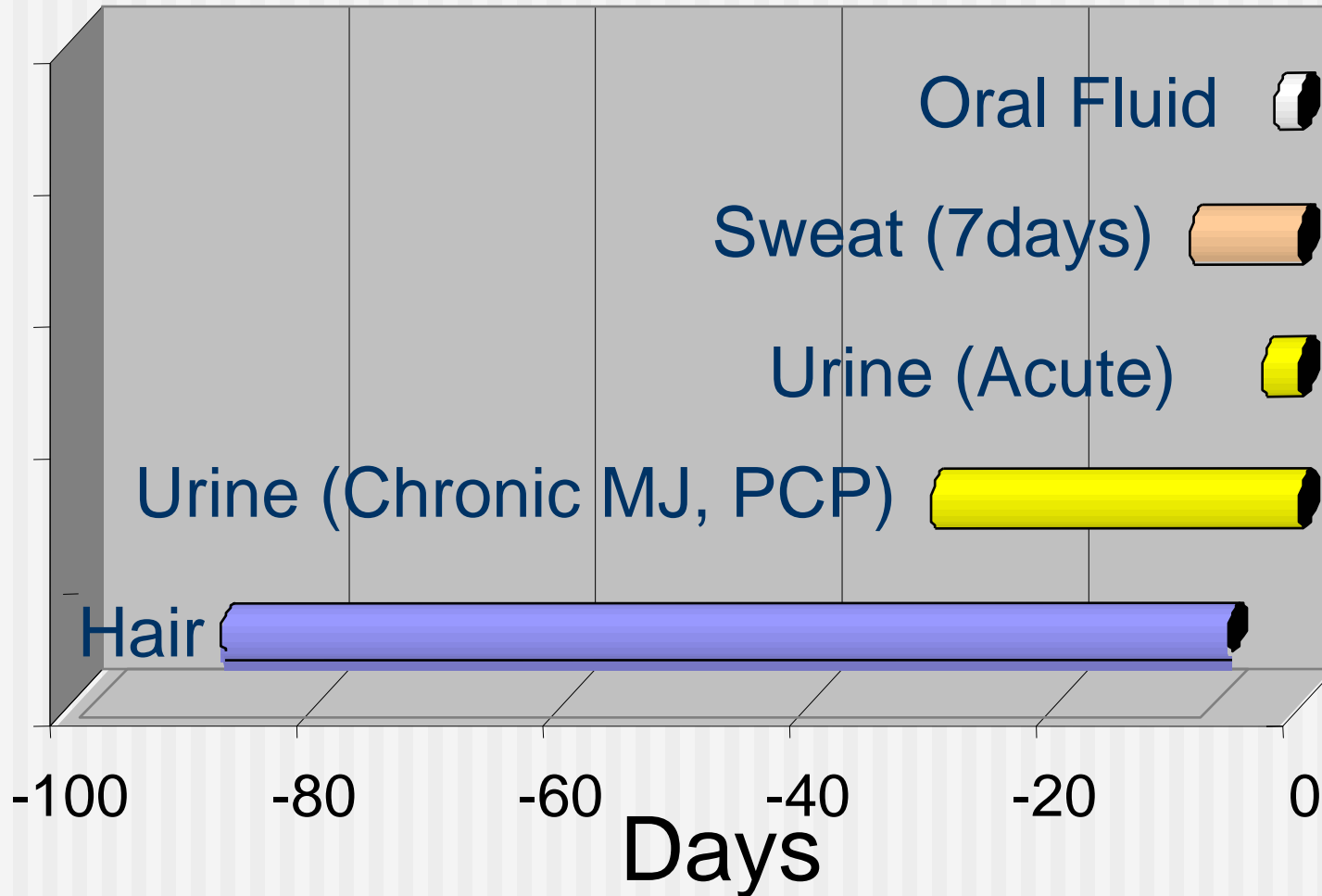
Specimens and Drugs

- Urine (aqueous)
 - Water soluble metabolites
- Blood/plasma (aqueous, protein)
 - Drug & metabolite
- Oral fluid "Saliva" (aqueous, mucus)
 - Drug & metabolite
- Hair (dry, protein-complex)
 - Drug > metabolite

Drug Testing with Blood, Saliva, & Hair

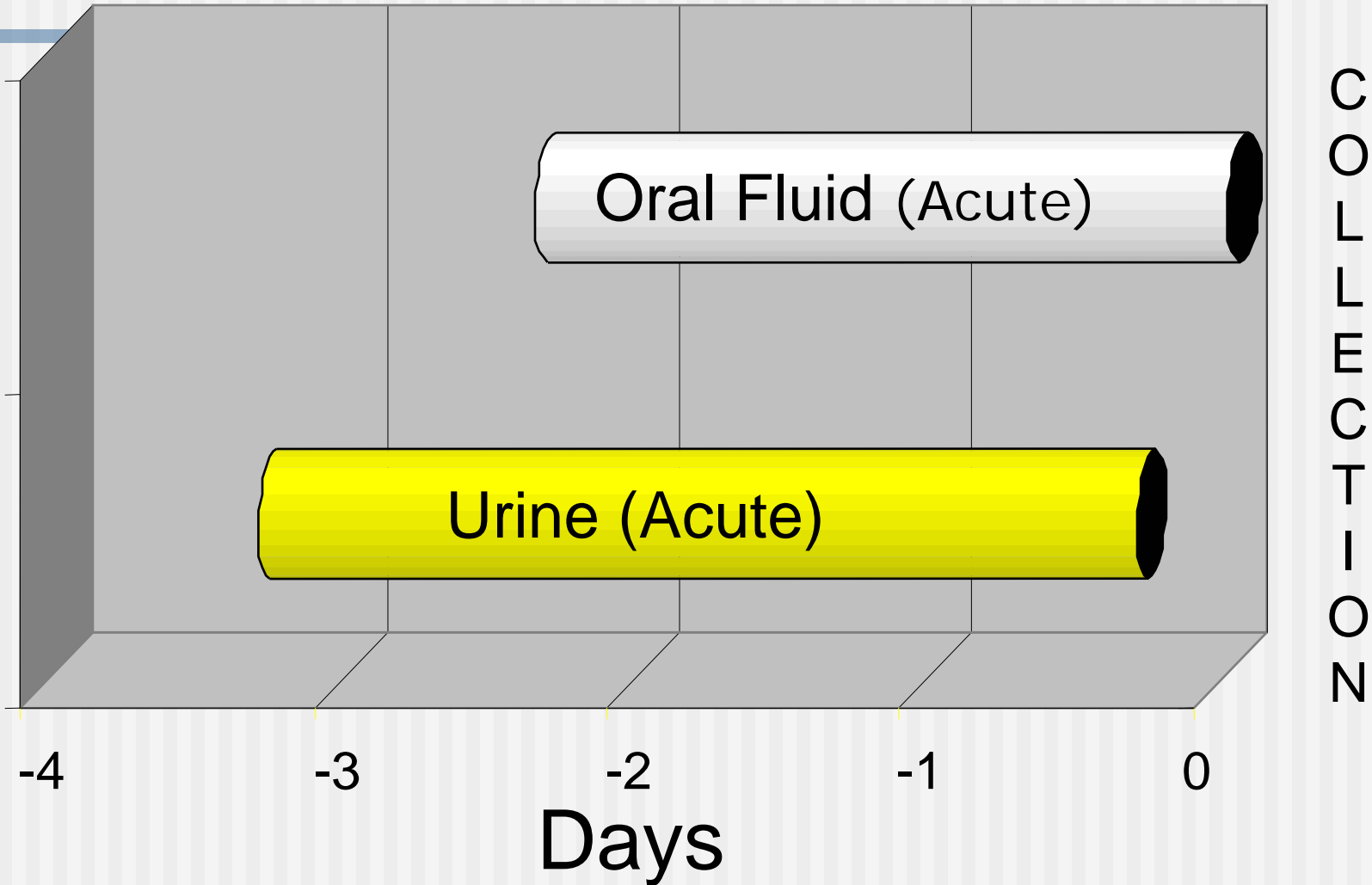
- Higher sensitivity required
- Specimen differences
 - Different time-courses
 - Each specimen contains a different historical record
 - Some are similar; some are not
 - Unique strengths and weaknesses
 - Blood: best for interpretation of impairment
 - Saliva: similar to blood; detects recent use; noninvasive
 - Hair: best for detection of heavy long term use
- *Test results do not have to agree!*

Specimen Detection Windows



NO-TI-C-T-I-O-N

Urine v. Oral Fluid Detection Times

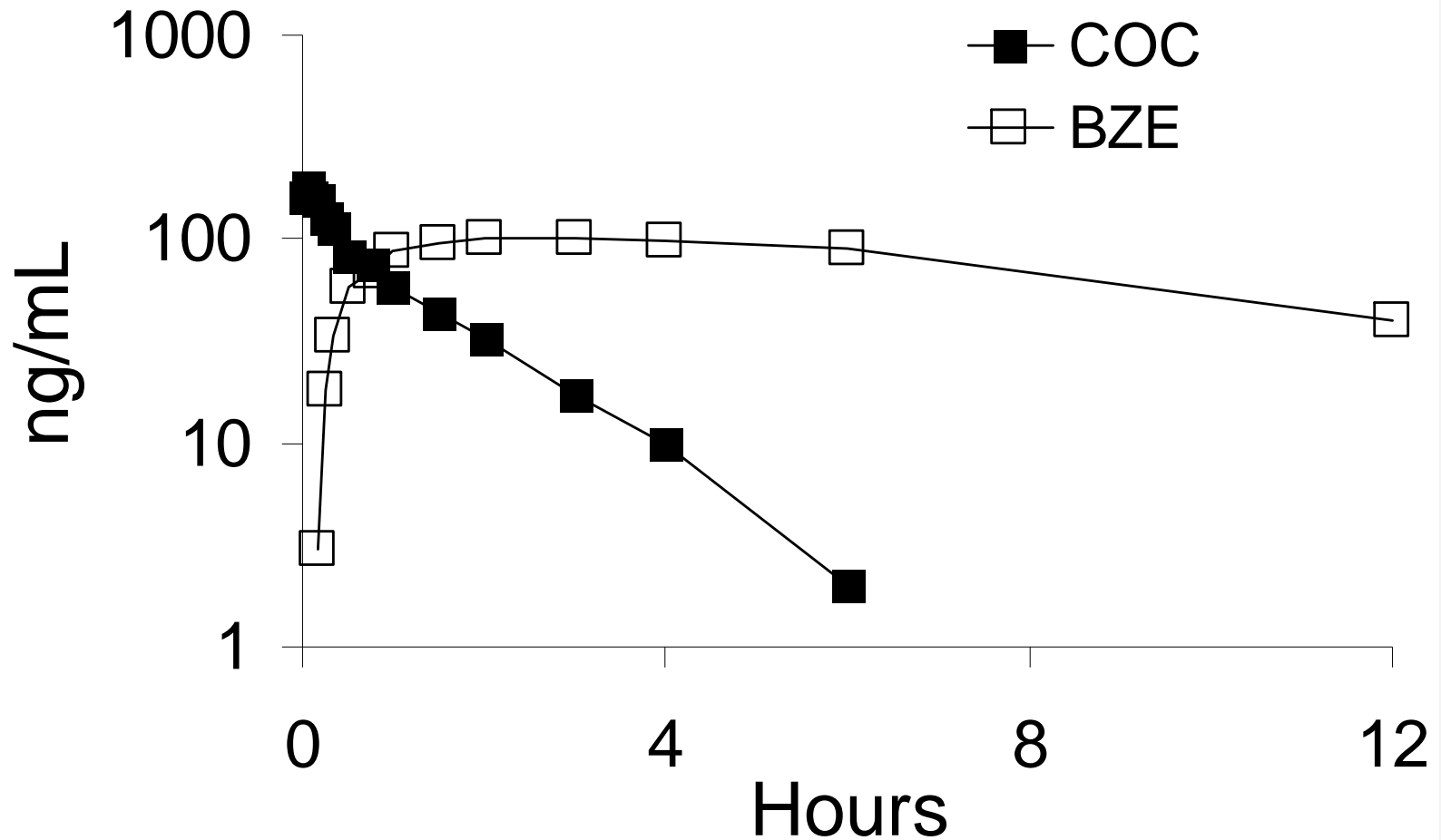




Now, lets take
a look at a few
specimen
profiles....

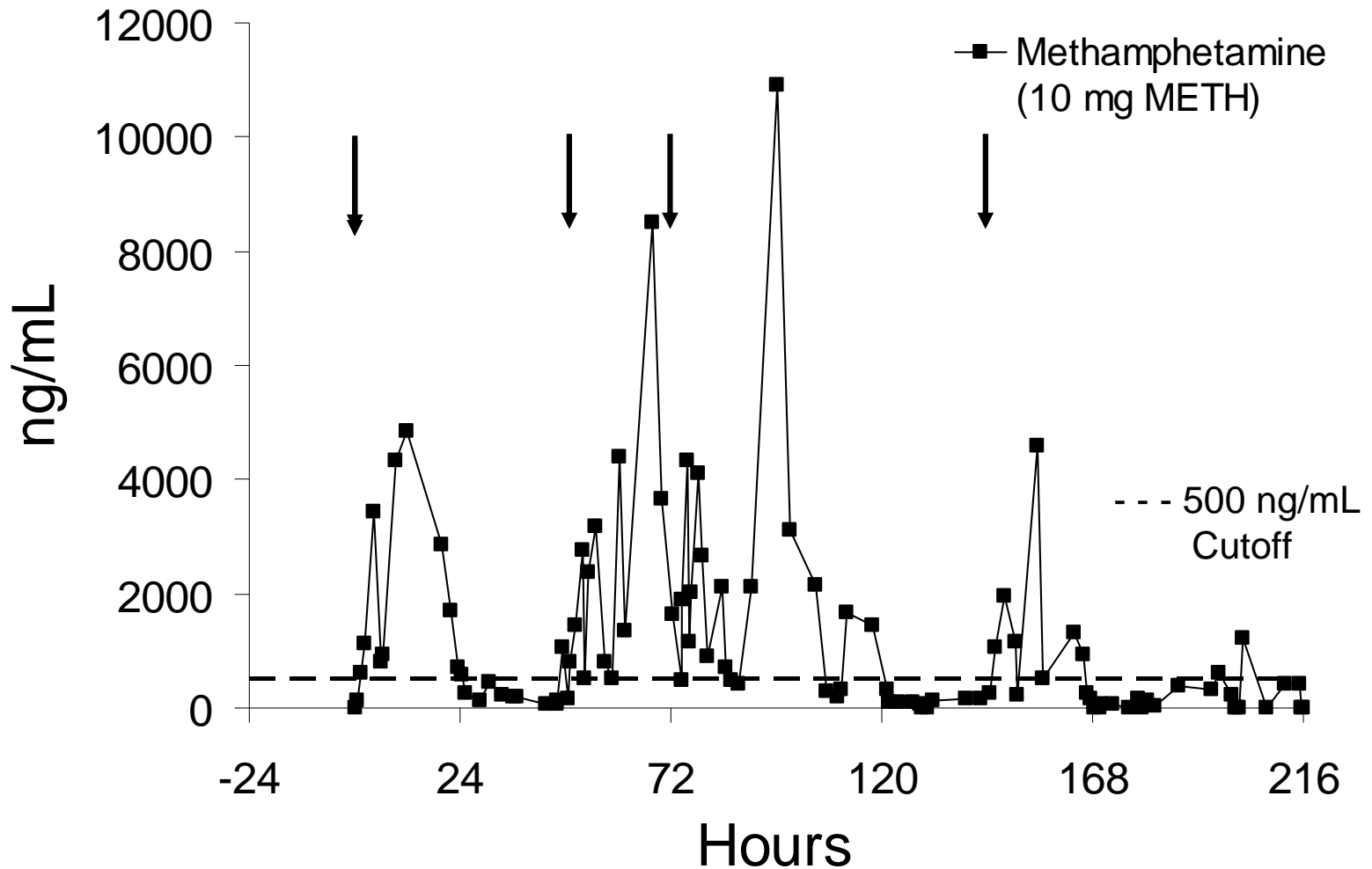
Cocaine & BZE in Plasma

(25 mg Cocaine HCl, IV) (Source: Cone et al, JAT 1995)



Methamphetamine in Urine

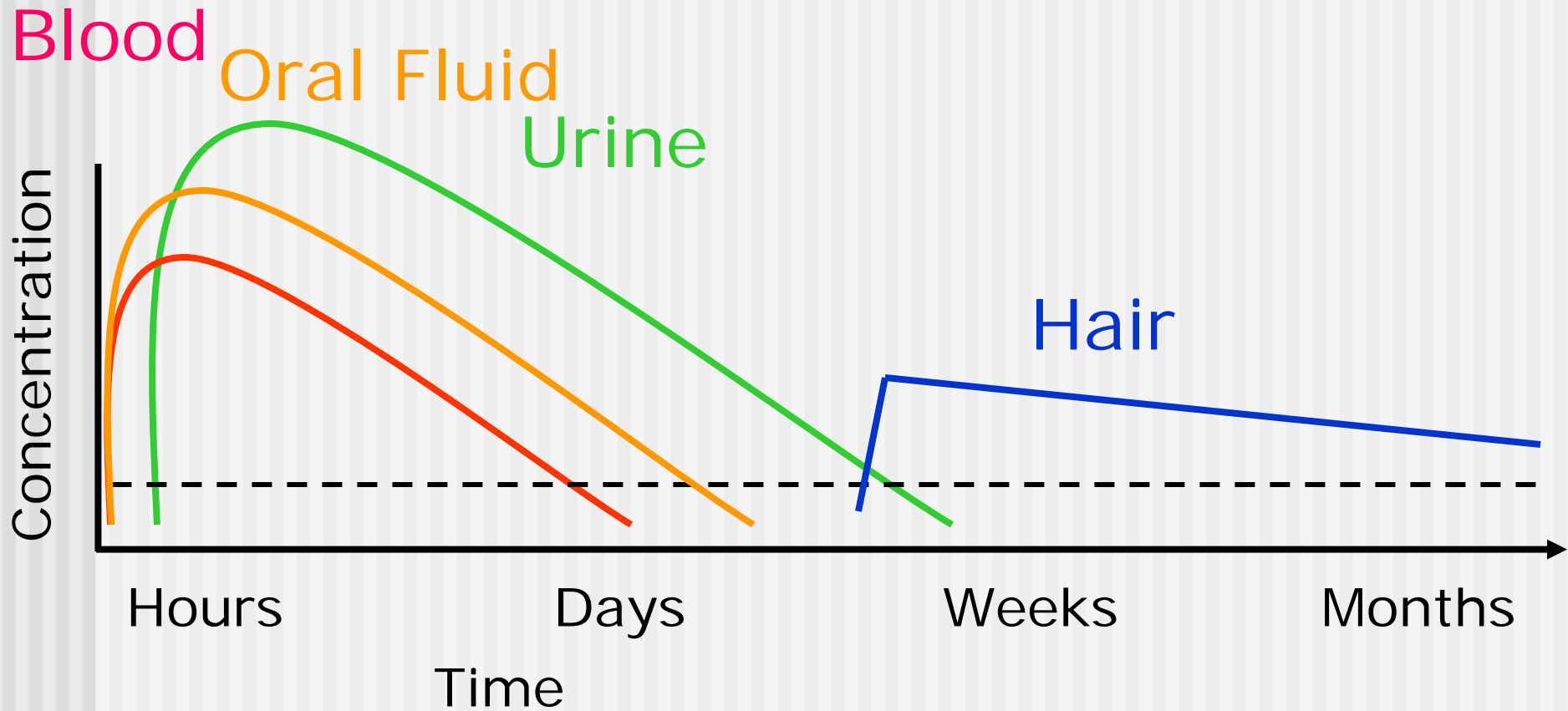
(10 mg, oral) (Source: Huestis & Cone, NYAS, 2007)



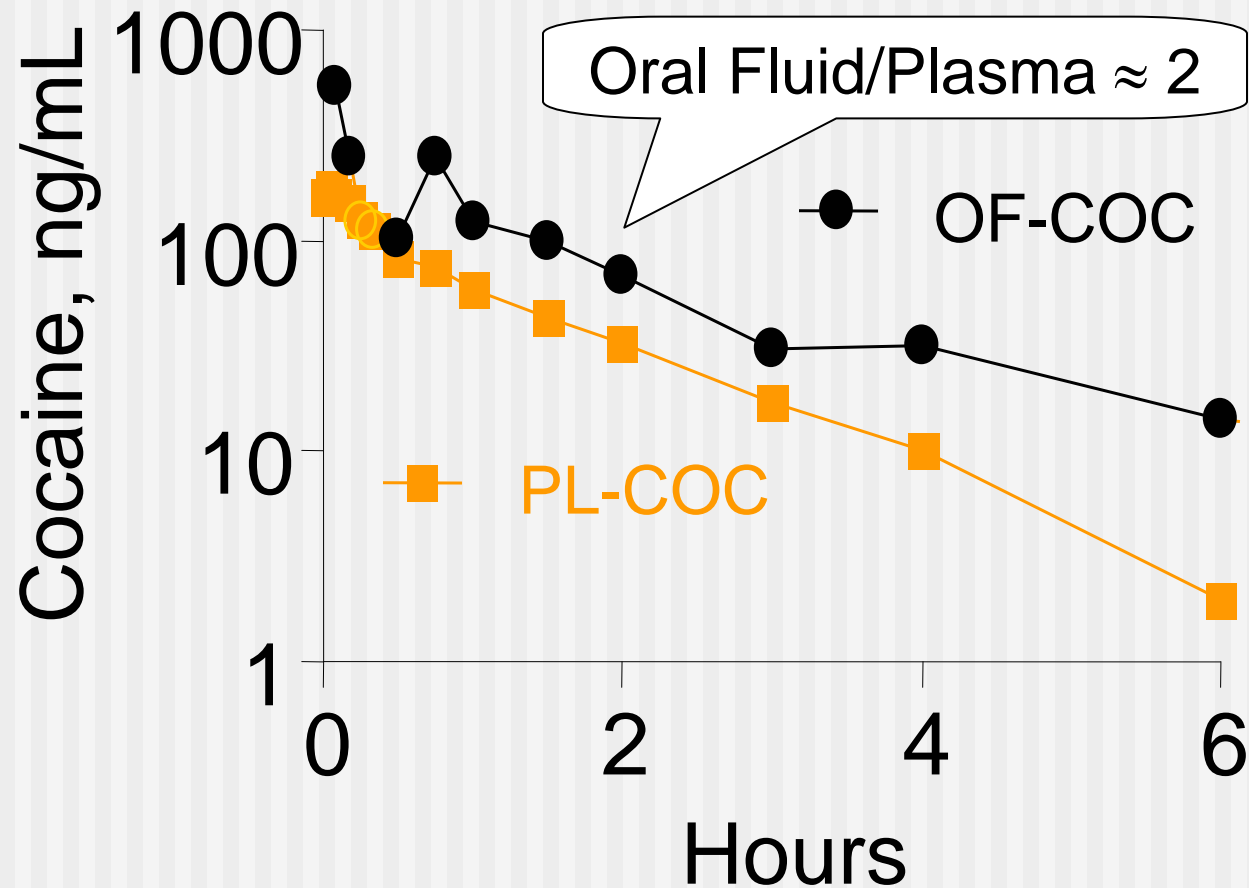
Different specimens are not mirror images of each other!



Drug Testing Profiles

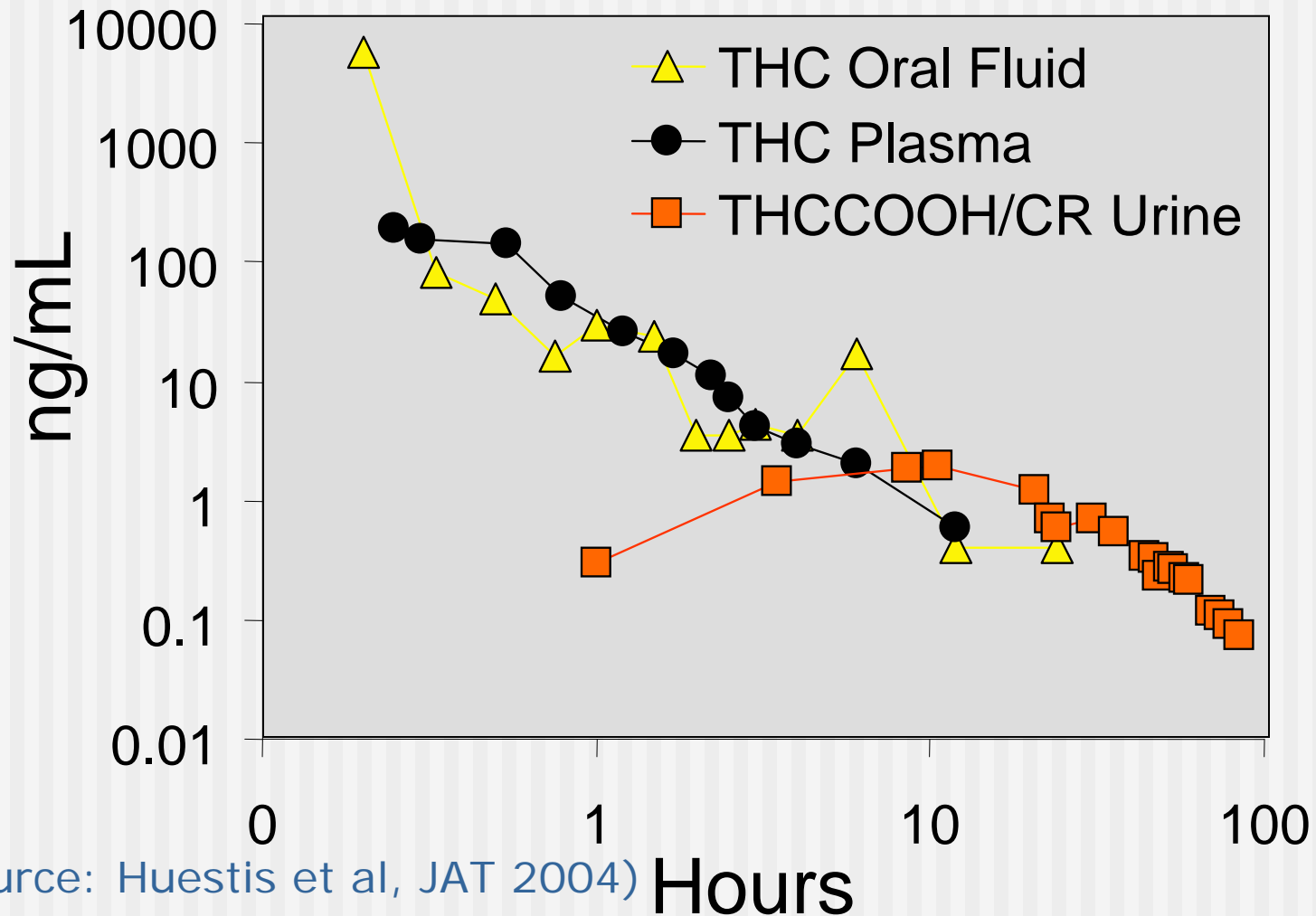


Relationship of Oral Fluid to Blood (Cocaine, 25 mg, IV) (Source: Cone et al, JAT 1995)



Oral Fluid, Plasma & Urine

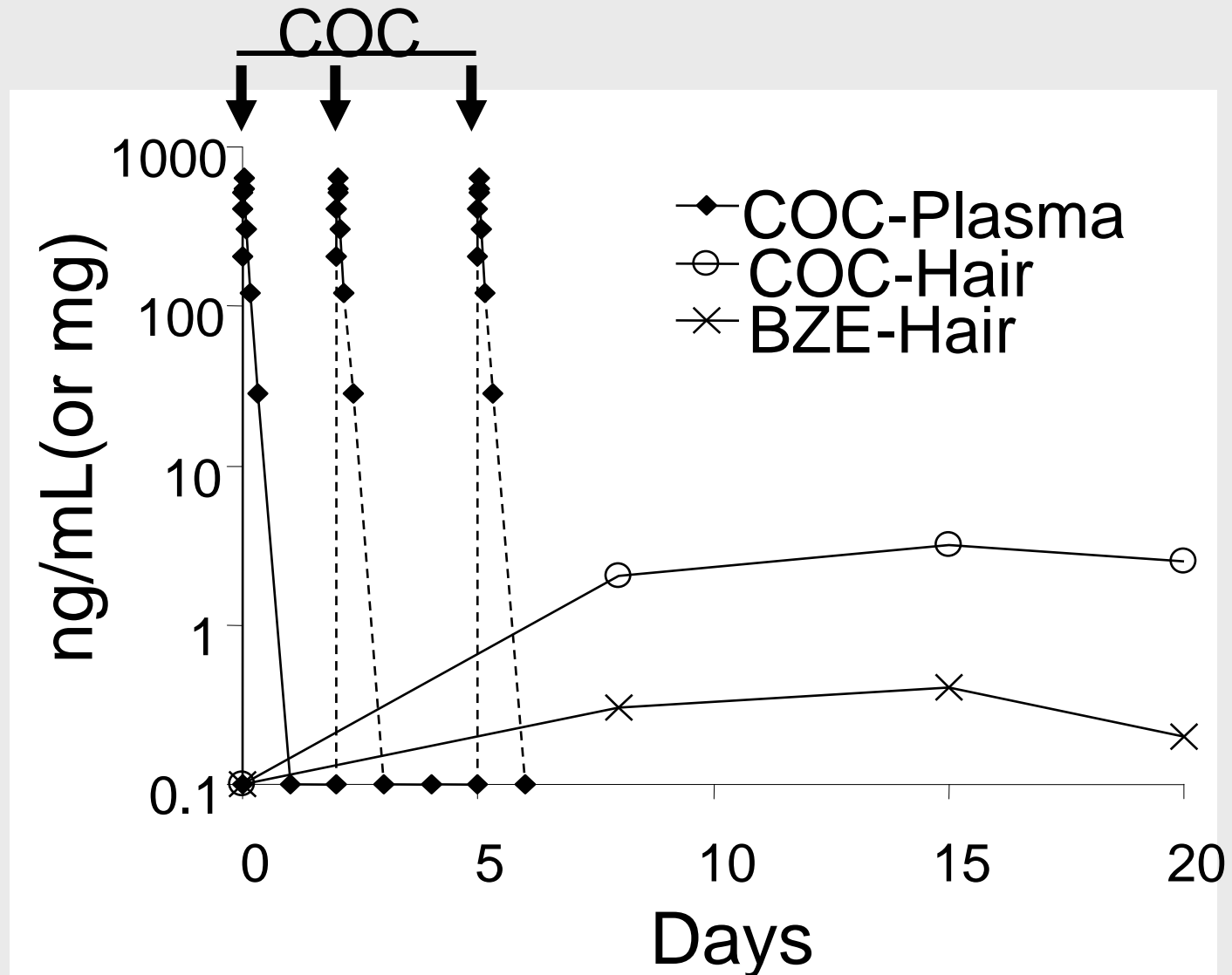
(Smoked Cannabis: Subject G; 3.55% THC; GC-MS)



(Source: Huestis et al, JAT 2004)

Hours

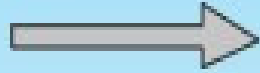
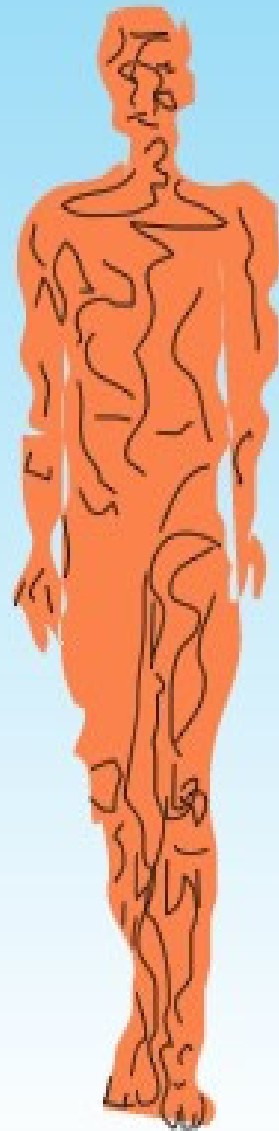
Cocaine Disposition in Plasma & Hair



(what goes in)

(what goes out)

oxygen
830 g



carbon dioxide
1.140 g

water
3.300 g



evaporated water
(sweat and breath)
1.820 g

dry food
630g



urine
1.500 g

chemical energy
2.800 kcal

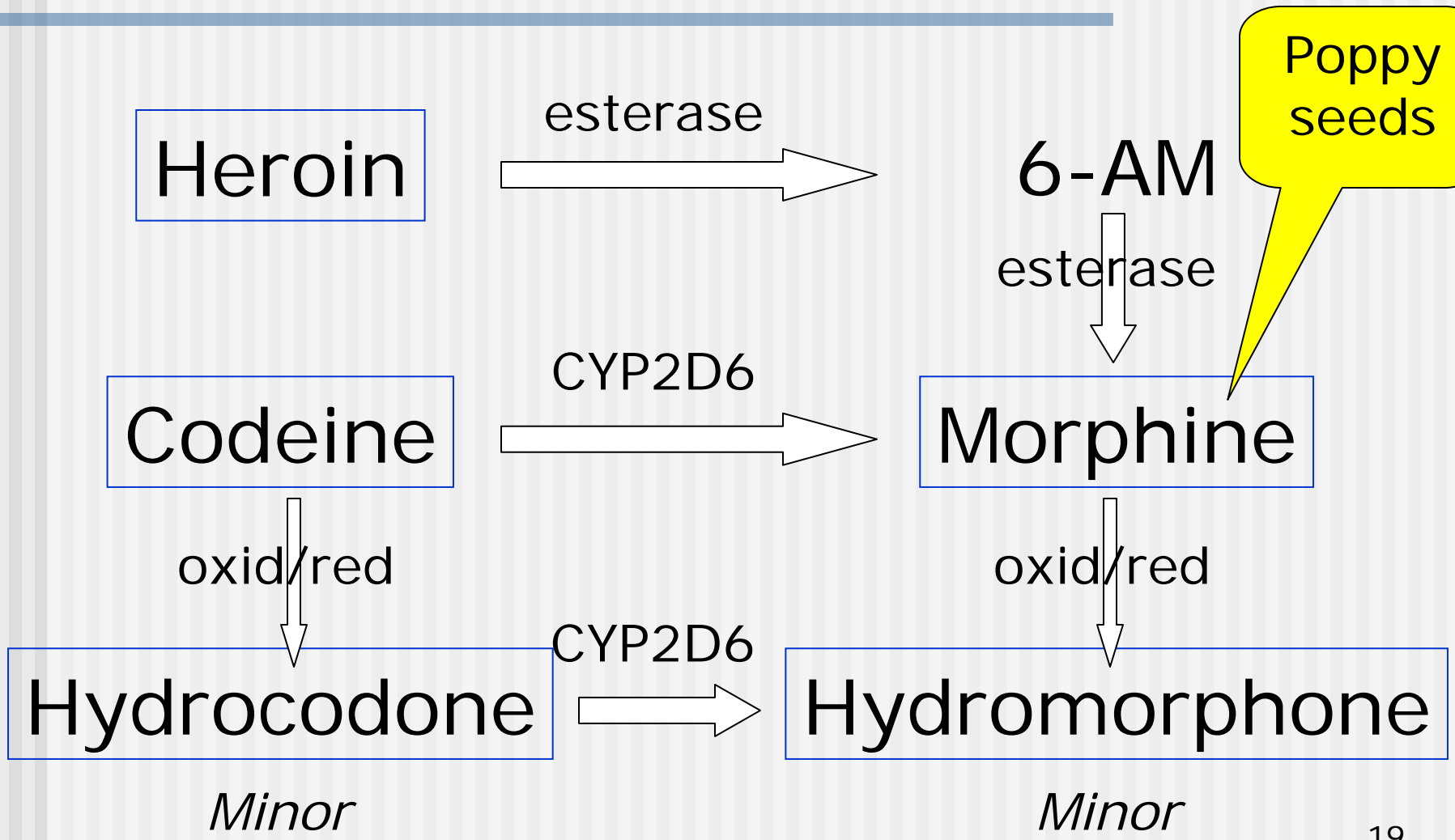


faeces
300 g



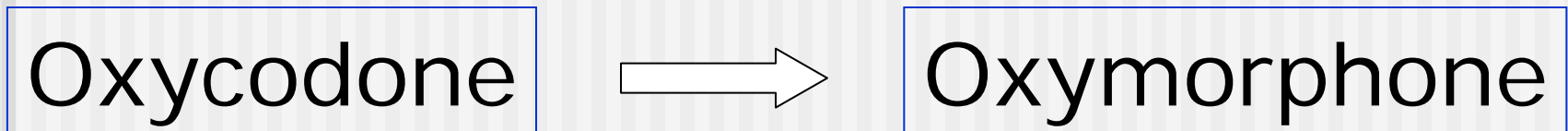
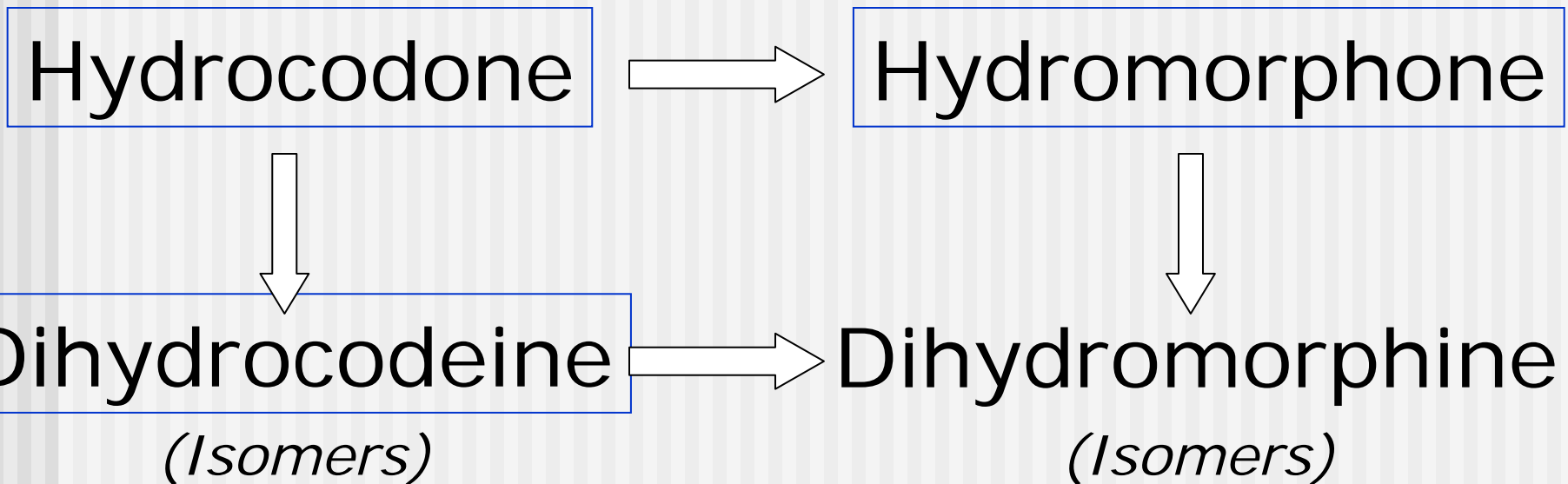
heat
2.800 kcal

Metabolism: Heroin/Codeine/Morphine



Metabolism:

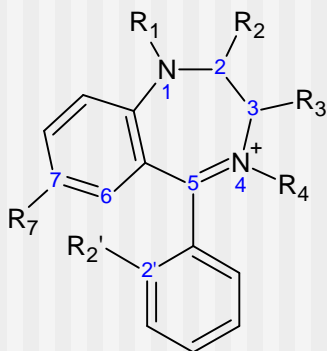
Hydrocodone/Hydromorphone
Oxycodone/Oxymorphone



Benzodiazepine Types

5-Aryl-1,4-benzodiazepines

“azepam”

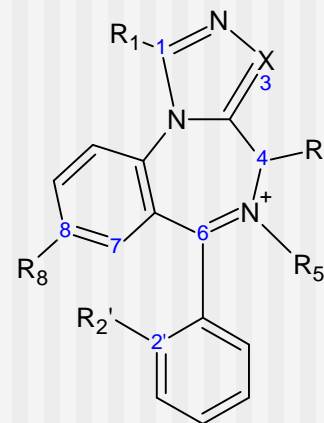


- Chlordiazepoxide
- Clonazepam
- Clorazepate
- Diazepam
- Flurazepam

- Halazepam
- Lorazepam
- Oxazepam
- Quazepam
- Temazepam

1,2-Triazolo-benzodiazepines

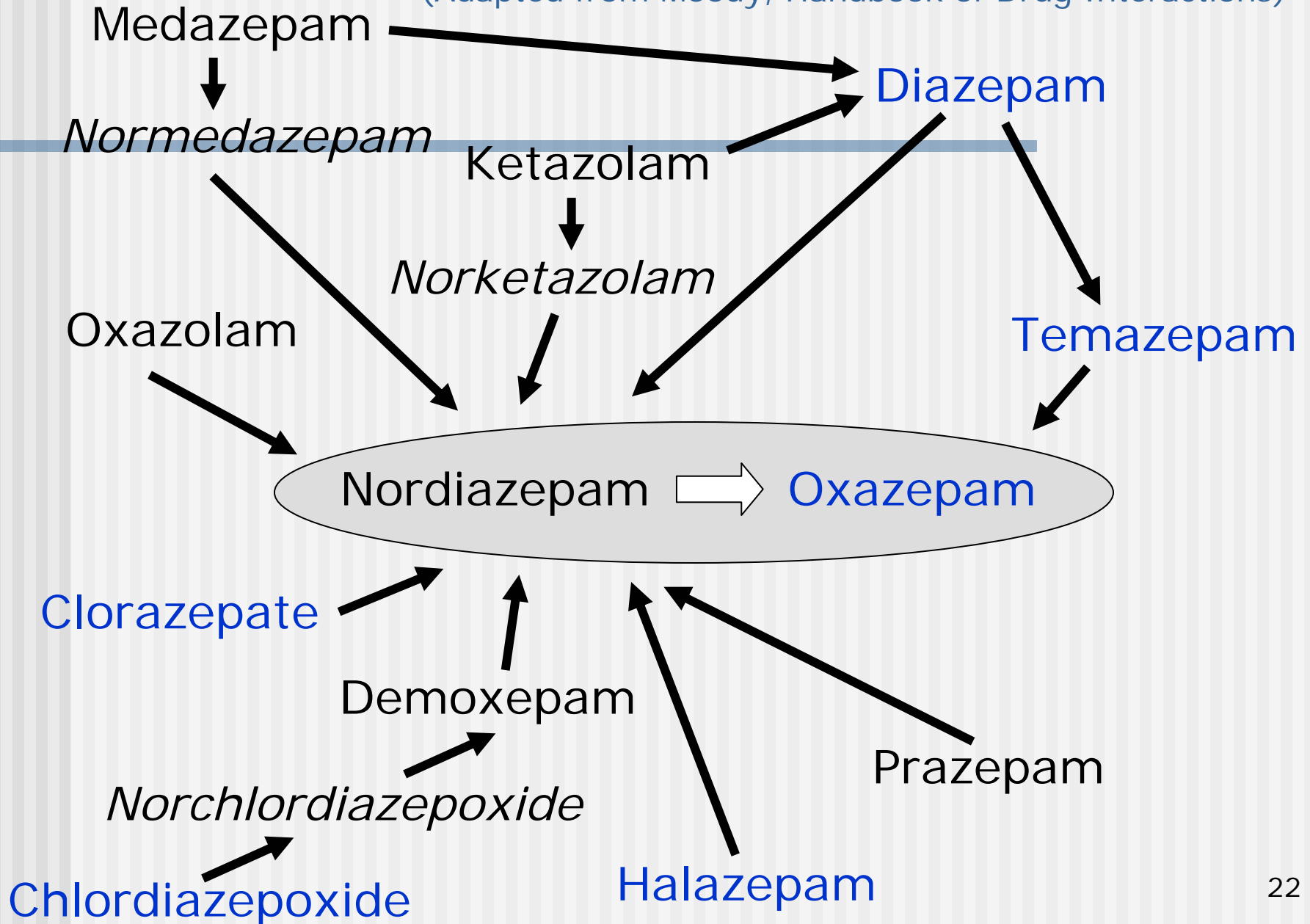
“azolam”



- Alprazolam
- Estazolam
- Midazolam
- Triazolam

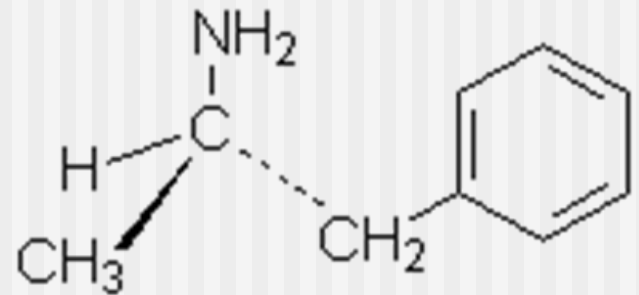
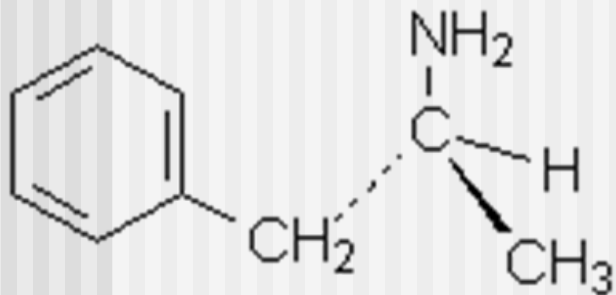
Diazepam-type Metabolism

(Adapted from Moody, Handbook of Drug Interactions)



Methamphetamine/Amphetamine: Metabolism and Stereo-isomerism

- Methamphetamine → Amphetamine
- Both can exist as stereo-isomers (d/l)
 - Cannot “superimpose structures”
 - Requires special tests to distinguish



The chiral isomers (L & D) are mirror images of each other. 23

Interpretation can be challenging!



What Laboratory Drug Tests Don't Reveal

- Time of drug use
 - Amount of drug use
 - Frequency of drug use
-

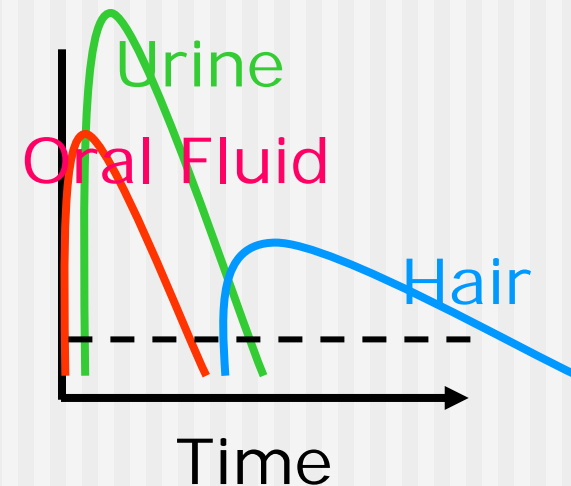
- But concentration, metabolite ratios together with toxicological info.....
 - Helps to establish boundaries
 - Days, weeks months
 - 1 mg, 10 mg, 100 mg, 1000 mg
 - Some specimen types provide more information than others; depends upon the question!

What Laboratory Drug Tests Reveal

- Drug or drug class
 - But not always what was administered (Drug source)
 - Sometimes easy
 - Sometimes difficult/impossible
- Metabolite(s)
- Parent/metabolite ratio
- Concentration/quantity
- Isomeric ratio
 - Requires a special test
 - Important for amphetamines
- Specimen information, e.g., creatinine content, specific gravity

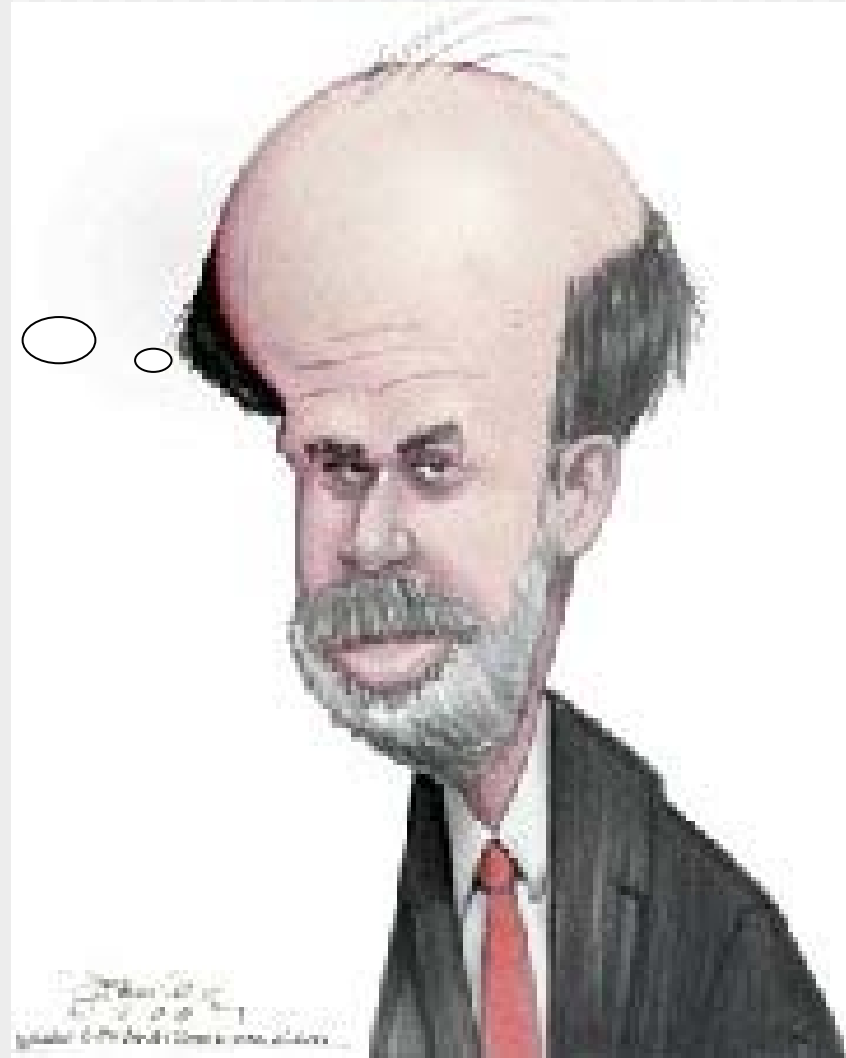
Summary

- Each type of specimen provides a “unique” historical picture
- Results between specimens do not have to agree
- Understanding characteristics and differences between specimens is essential to interpretation of drug tests



The End!

I wonder if I
left time for
questions?



Appendix Slides

PK & Chemical Parameters of Opioids

Drug	Dose, mg	T1/2, hrs	Fabs (oral)	pKa	Log P
Hydrocodone	5-10	4-6	-	8.9	0.14
Hydromorphone	6-10	2.4-4.1	0.51	8.08	0.16
Oxycodone	2.5-10	2-4	0.42	8.5	0.24
Oxymorphone	5-10	7-9	0.10	8.5	-.11
Morphine		1.3-6.7	0.25	8.1	0.08
Codeine	30-60	1.4-3.5	0.50	8.2	0.54
Fentanyl	0.1-0.2	3-12	-	8.4	High
Buprenorphine	2-8	3-40	-	8.2	High

Testing Terminology

- Threshold (“Cutoff”): Determines presence (positive) or absence (negative) of a drug/metabolite above or below a chosen concentration
- Detection time: average duration of time a drug or metabolite is detectable; frequently based on single dose data
- Lag time: time after drug use before appearance of drug in sufficient concentration to produce a positive test
- Gap: intervening time between positive specimens when some are negative
- LOQ/LOD: limit of quantitation/limit of detection
- TLCP: time to last consecutive positive
- TLP: time to last positive

Metabolism of Morphine-Related Opioids

Drug Administered

Metabolite

Drug & Metabolite	Heroin	Morphine	Codeine	Hydrocodone	Dihydrocodeine*	Hydromorphone	Oxycodone	Oxymorphone	Pholcodine
Diacetylmorphine	Yes	No	No	No	No	No	No	No	No
6-Acetylmorphine	Yes	No	No	No	No	No	No	No	No
Morphine	Yes	Yes	Yes	No	No	No	No	No	Yes
Codeine	No	No	Yes	No	No	No	No	No	No
Hydrocodone	No	No	Yes	Yes	Yes	No	No	No	No
Hydrocodol**	No	No	Yes?	Yes	Yes	No	No	No	No
Hydromorphone	Yes?	Yes	Yes?	Yes	Yes?	Yes	No	No	Yes?
Hydromorphol**	Yes?	Yes?	Yes?	Yes	Yes	Yes	No	No	Yes?
Oxycodone	No	No	No	No	No	No	Yes	No	No
Oxycodol**	No	No	No	No	No	No	Yes	No	No
Oxymorphone	No	No	No	No	No	No	Yes	Yes	No
Oxymorphol**	No	No	No	No	No	No	Yes	Yes	No
Pholcodine	No	No	No	No	No	No	No	No	Yes

*Dihydrocodeine is same as 6-alpha-Hydrocodol

**Two isomers may be produced; 6-alpha- and 6-beta-isomers

Yes = Reported metabolite

Yes? = Not reported, but possible based on known metabolic pathways, very minor amounts

No = No reported metabolic pathway

? = Not studied, but not likely

Drug Disposition in Blood, Urine, Saliva and Hair

Drug	Blood/ Plasma	Urine	Saliva (Oral Fluid)	Hair
Cannabis	THCCOOH > THC	<u>THCCOOH</u>	THC >> THCCOOH	THC >> THCCOOH
Cocaine	BZE > COC > EME; CE (ethanol)	<u>BZE</u> > COC	BZE > COC; CE (ethanol)	COC > BZE; CE (ethanol)
Heroin/morphine	MOR-G > MOR > 6-AM > HER	<u>MOR-G</u> > <u>MOR</u> > 6-AM > HER	6-AM ≈ MOR > HER	6-AM > MOR
Codeine	COD-G > COD > MOR > NCOD	<u>COD-G</u> > <u>COD</u> > MOR > NCOD	COD > MOR	COD > MOR > NCOD
PCP	PCP	<u>PCP</u> > HO-PCP	PCP	PCP
Amphetamine	AMP	AMP	AMP	AMP
Methamphetamine	METH > AMP	METH > AMP	METH > AMP	METH > AMP
MDA/MDMA/MDEA	MDA/MDMA/ MDEA	MDA/MDMA/ MDEA	MDA/MDMA/ MDEA	MDA/MDMA/ MDEA

Interpretation---SPECIAL ISSUES

Opiate Source Differentiation?

- You have a positive test for morphine
- Where did it come from?
- Possible sources
 - Heroin
 - Codeine
 - Morphine
 - Poppy seeds
- Aids in interpretation
 - 6-AM (heroin)—heroin biomarker
 - Other heroin biomarkers, e.g., 6-AC, papaverine
 - Codeine (ratio of codeine to morphine)
 - Sometimes easy, sometimes difficult

Interpretation---SPECIAL ISSUES

Benzodiazepine Source Differentiation?

- You have a positive test for oxazepam
- Where did it come from?
- Possible sources (US only)
 - Chlordiazepoxide
 - Diazepam
 - Chlorazepate
 - Halazepam
 - Temazepam
- Aids in interpretation
 - Look for parent drug and other metabolites
 - Temazepam only goes to Oxazepam
 - Rx history; foreign travel
 - Sometimes easy, sometimes difficult

Interpretation---SPECIAL ISSUES

Methamphetamine Source Differentiation?



- You have a positive test for methamphetamine
- Where did it come from? What is isomeric composition?
- Possible sources (US)
 - Illicit methamphetamine (mostly d-isomer, but can be d/l)
 - Desoxyn®
 - Selegiline (metabolized to methamphetamine and amphetamine)
 - Vicks and other generic nasal sprays (l-methamphetamine)
 - Drugs metabolized to methamphetamine (and amphetamine)
 - Benzphetamine (US); Famprofazone; Fencamine; Furfenorex
- Aids in interpretation
 - Use of nasal sprays
 - Obtain d/l-analysis
 - Rx history; foreign travel
 - Sometimes easy, sometimes difficult