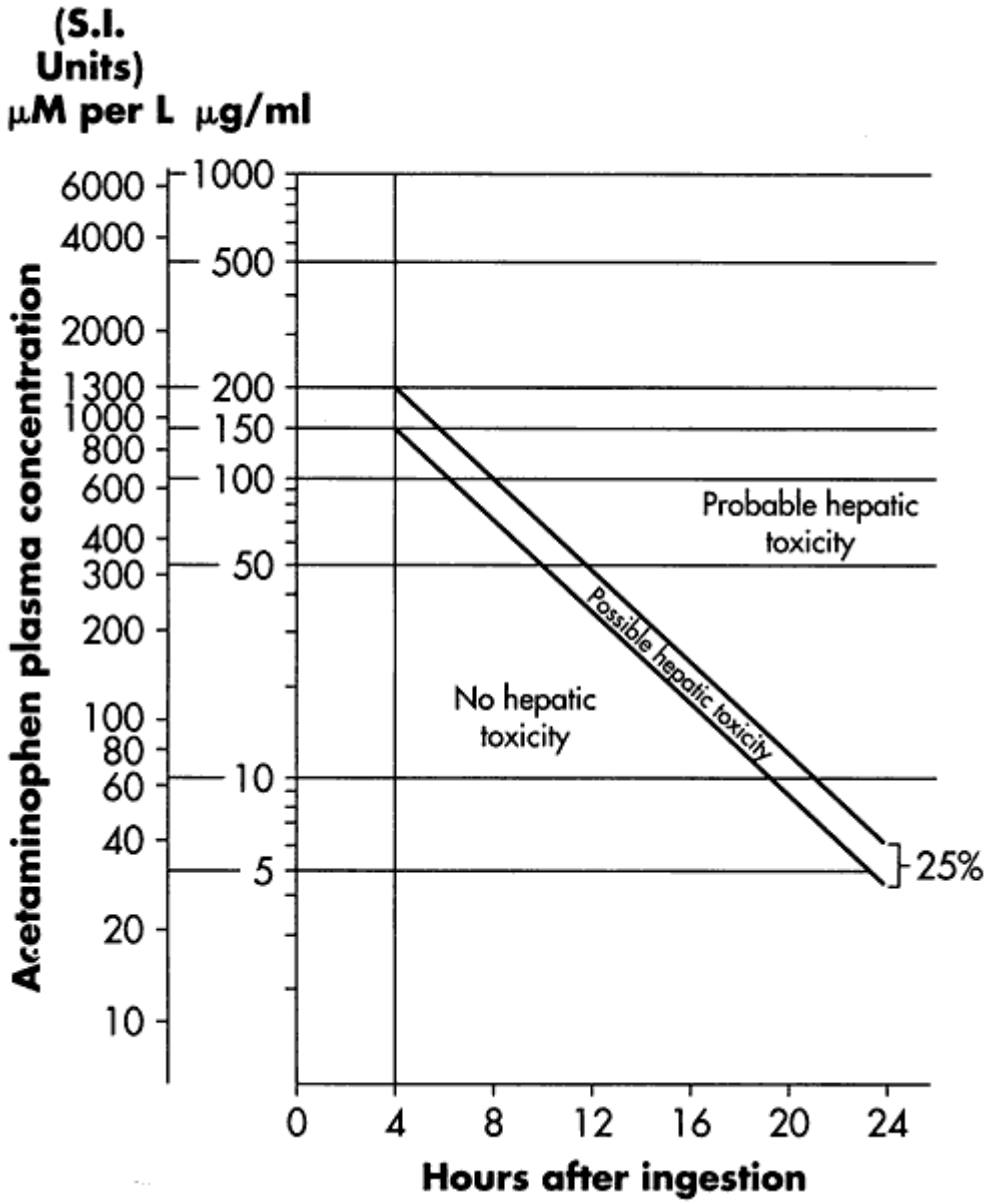
Paracetamol (DCI)

General	
• Class of the drug:	Analgesics
• Synonym(s):	Acetaminophen, N-acetyl-*p*-aminophenol
• Common trade name(s) in Switzerland:	Panadol®, Dafalgan®, Dolprone®, Kafa®, Tylenol®, Zolben®…
• Conversion factors:	*mg/l x 6.62 = µmol/l* *µmol/l x 0.151 = mg/l*
Clinical pharmacology	
• Indications for TDM:	Suspicion of toxicity
• Protein binding:	5 – 15 % at therapeutic concentration until 50% in overdose
• Elimination half-life:	1 – 4 hours (may be higher in case of intoxication = toxicity indication)
• Volume of distribution:	0,75 – 1 l/kg
• Metabolism:	
- Main metabolic pathways:	Extensive by hepatic route; forms inactive sulfates (main children pathway) and glucuronides (main adult pathway)
- Active metabolite(s)?	Toxic metabolite in case of intoxication (oxydase pathway, essentially CYP2E1): N-acetyl-p-benzoquinonimine, normally rapidly detoxified by glutathione in the liver. In overdose, production of the toxic metabolite exceeds glutathione capacity and the metabolite reacts directly with hepatic macromolecules, causing liver injury.
- Inhibitor or inductor of the cytochrome P450 system?	No
- Other significant pharmacokinetic interactions:	Enzymatic inductors may promote oxidative pathway (CYP2E1) to toxic metabolite. Chronic alcoholism: enzymatic induction, lowered glutathione capacity, higher risk of liver injury
• Elimination of parent drug:	Hepatic > 90% Renal < 5%
• Typical therapeutic range:	5 – 20 mg/l
• Potentially toxic concentration:	Nomogram for prediction of acetaminophen hepatotoxicity: - > 150 – 200 mg/l 4 hours after ingestion (Alcoholic, cirrhotic, associated hepatotoxic substances: > 100 mg/l at 4 hours) - > 100 mg/l at 8 hours - > 50 mg/l at 12 hours - > 30 mg/l at 15 hours

Pre-analytics	
• Time to steady-state since beginning of treatment or change of posology:	Acute intoxication: modified kinetic if massive ingestion Therapeutic dosage: time to steady state 5 – 20 hours (orally, continuous treatment)
• Time for blood sampling:	Acute intoxication: min. 4 hours after ingestion, max. 24h. Therapeutic: 1 hour after ingestion (Cmax)
• Type(s) of sample:	Serum or plasma
• Stability:	8h at room temperature, 48h at 4- 8°C, for longer conservation freeze at - 20°C
Analytics	
• Position(s) in the analysis list/Method:	8627.01 Immunoassay, Colorimetric
Remarks	Variable, method related, cross-reactivity with toxic metabolite. Possible interference (false positive) of hyperbilirubinemic samples (Clin Chem 49 (2003) 695) Antidotes: N-acetylcysteine
References	• *J. Fenton, The laboratory and the poisoned patient, AACC Press, Washington, 1998, 31-36* • *K. Olson, Poisoning and drug overdose, Appleton&Lange, 1990, 57-58* • *N.W. Tietz, Clinical guide to laboratory tests, 3rd Edition, Saunders, 1995, 788-789* • *Compendium Suisse des médicaments, 2005* • *White S, Wong SHY, Clin Chem 44 (1998) 1110* • *Manyike PT et al, Clin Pharmacol Ther 67 (2000) 275*


(S.I. Units)
μM per L
μg/ml
Acetaminophen plasma concentration
6000
4000
2000
1300
1000
800
600
400
300
200
100
80
60
40
20
10
1000
500
200
150
100
50
10
5
Probable hepatic toxicity
Possible hepatic toxicity
No hepatic toxicity
25%
0
4
8
12
16
20
24
Hours after ingestion