Drug metabolism in Göttingen Minipigs: key information for species selection in safety testing of pharmaceuticals

Steven Van Cruchten

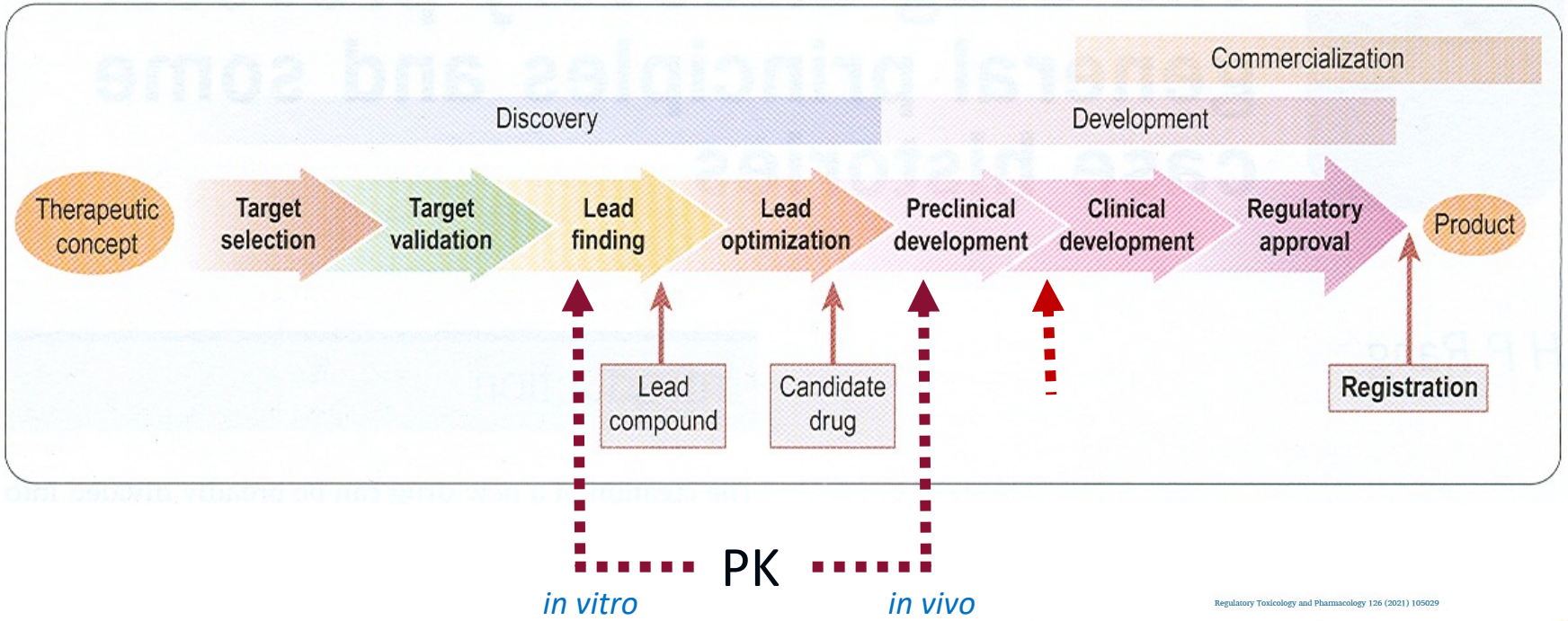
Steven.VanCruchten@uantwerpen.be

Outline

- In vitro drug metabolism assays in species selection
- Drug metabolism in adult nonrodent species

- *Drug metabolism in paediatric population*
  - *Drug metabolism in paediatric disease models*
- *Metabolism of ASOs in paediatric population*

In vitro drug metabolism assays: nonrodent species



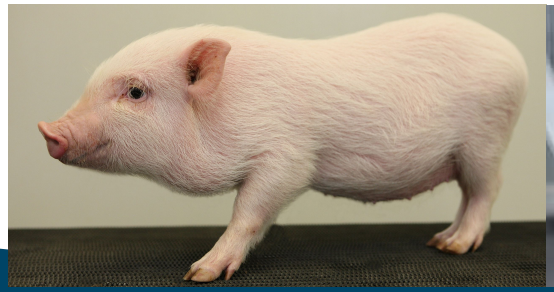
Cellular /tissue
- Hepatocytes
- Liver slices

✓ ✓

Subcellular
- microsomes
- S9 fraction

Recombinant

✓ ✓ ✓



✓ ✓ ✓

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Species selection for nonclinical safety assessment of drug candidates: Examples of current industry practice

Rostam Namdari [a,1], Keith Jones [b,*,1], Samuel S. Chuang [c], Steven Van Cruchten [d], Zuhal Dincer [e], Noel Downes [f], Lars Friis Mikkelsen [g], Joanna Harding [h], Sven Jäckel [i], Björn Jacobsen [j], Jacqueline Kinyamu-Akunda [k], Andréanne Lortie [l], Sofiene Mhedhbi [m], Susanne Mohr [j], Michael W. Schmitt [l], Helen Prior [n]

In practice:

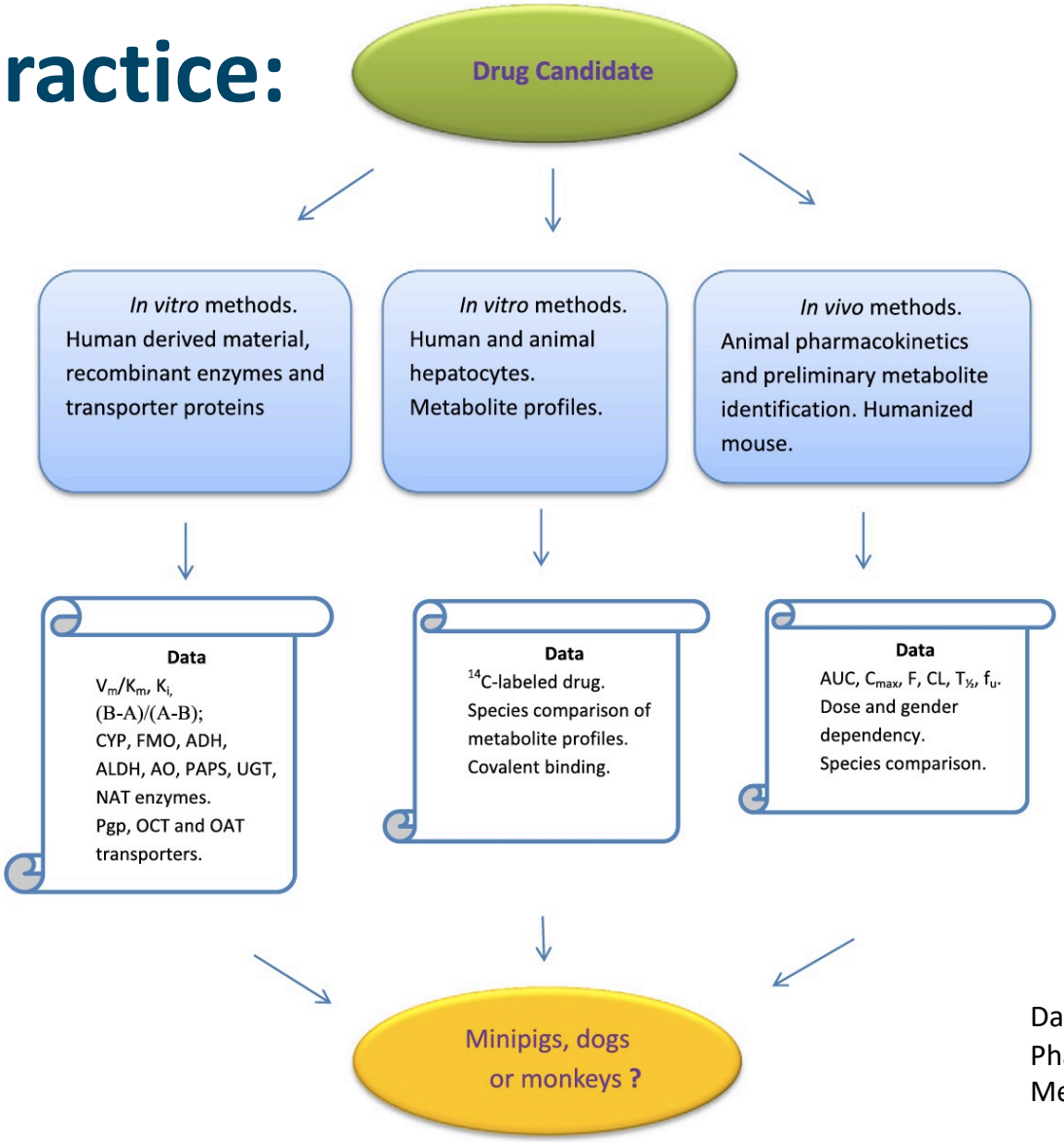


Fig. 1. ADME methods and data produced early in the development phase of a new drug.

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

CYP activity in man and nonrodents

Table 2
CYP activity ratios in monkeys, minipigs and dogs relative to humans.

		Turpeinen et al. 2007			Sharer et al. 1995		
Substrate	Human CYP	Cynomolgus monkey	Göttingen minipig	Beagle dog	Cynomolgus monkey	Rhesus monkey	Beagle dog
Ethoxyresorufin-O-deethylase[a, b]	1A2	10	1	6	11	14	2
Coumarin 7-hydroxylase[a, b]	2A6	5	1	0.2	2	1	0.2
Chlorzoxazone 6-hydroxylase[a]	2E1	1	0.5	0.5	NA	NA	NA
NDMA N-demethylase[b]	2E1	NA	NA	NA	1	1	1
Tolbutamide 4-hydroxylase[a, b]	2C9	0.5	0.4	0.0	0.6	0.5	0.0
Omeprazole 5-hydroxylase[a]	2C19	2	0.2	0.0	NA	NA	NA
S-mephenytoin 4'-hydroxylase[b]	2C19	NA	NA	NA	2	1	0.3
Dextromethorphan O-demethylase[a]	2D6	2	5	0.4	NA	NA	NA
Bufuralol 1'-hydroxylase[b]	2D6	NA	NA	NA	16	16	1
Midazolam 1'-hydroxylase[a]	3A4	1	1	1	4	3	3
Erythromycin N-demethylase[b]	3A4	NA	NA	NA	19	13	6
Omeprazole sulphoxidation[a]	3A4	1	0.2	0.1	NA	NA	NA

[a]Turpeinen et al. (2007); [b]Sharer et al. (1995).
CYP activity ratios (CYP_{animal}/CYP_{human}) with probe substrates. The colours - green, - yellow and - red indicate that there are minor (<5 and >0.2), medium (<10 and >5 or <0.2 and >0.1) or major differences (>10 or <0.1) in enzyme activity, respectively, in animals compared with humans. A fivefold or higher activity in the animal species compared with the activity in humans might result in an insufficient exposure of the drug candidate in the animal species. Also an activity which is only 0.2 (1/5) or less than that in humans could result in an insufficient exposure of metabolites in the animal species.

Clearance of compounds - species

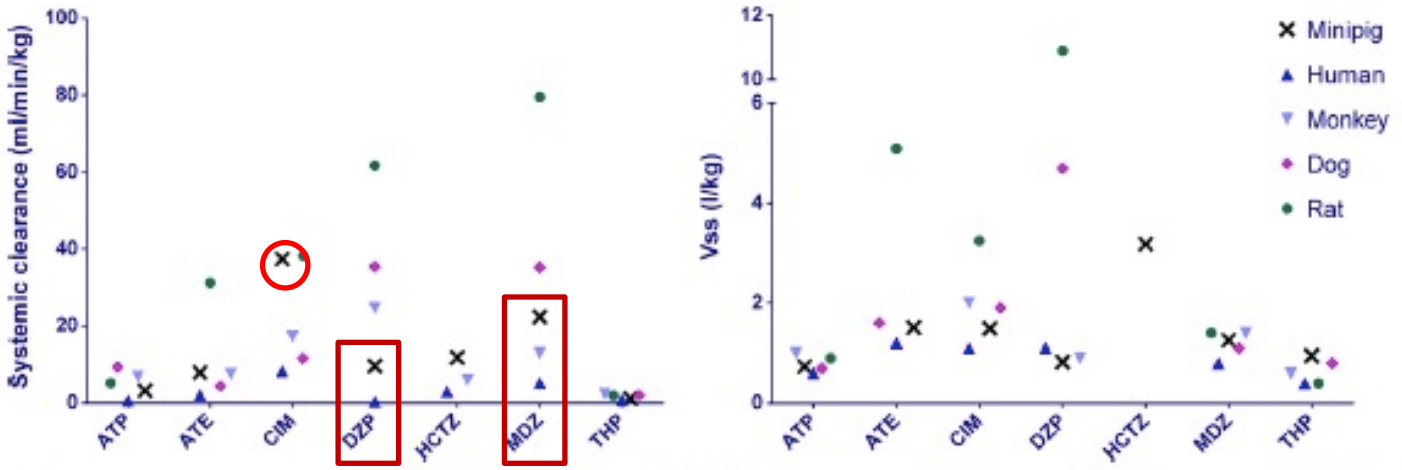
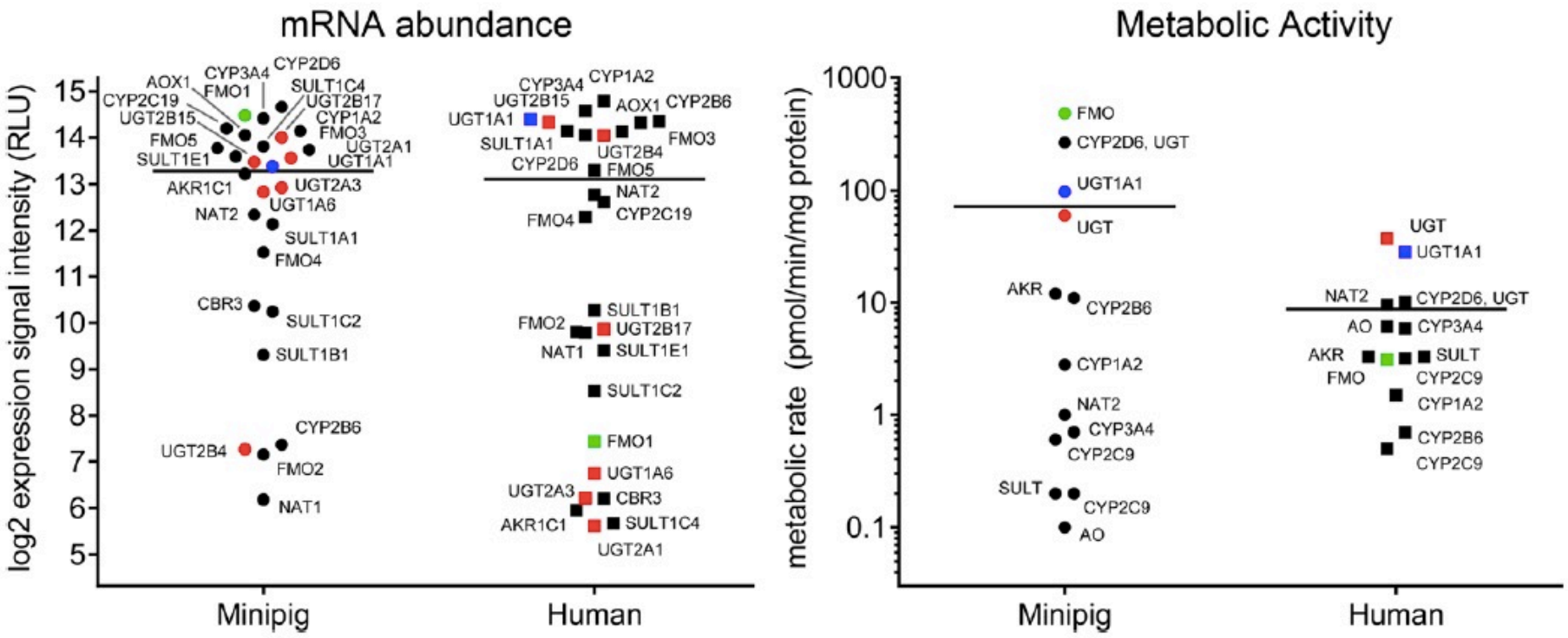


Fig. 3 Comparison of parameters values estimated by NCA analysis on the PK of antipyrine (ATP), atenolol (ATE), cimetidine (CIM), diazepam (DZP), hydrochlorothiazide (HCTZ), midazolam (MDZ) and theophylline (THP) in minipigs to values extracted from the literature for human, monkey, dog and rat. All data are available in Supplementary Material I.

Lignet et al. Pharm Res. 2016, 33:2565-79.

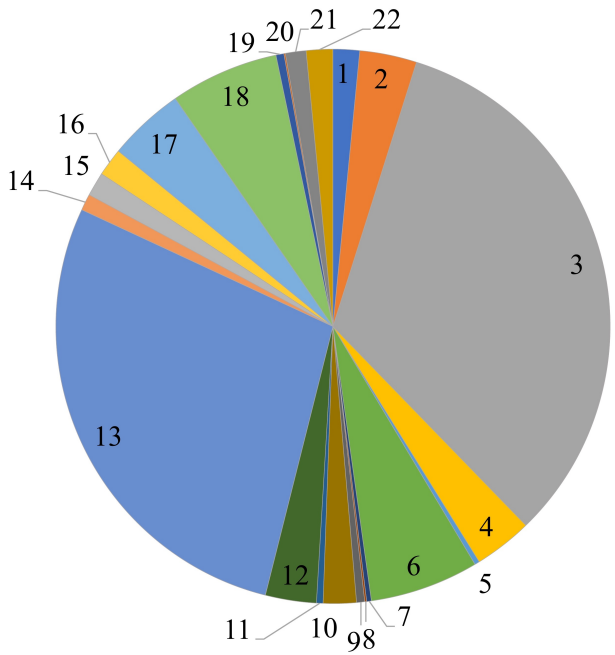
mRNA abundance and activity data



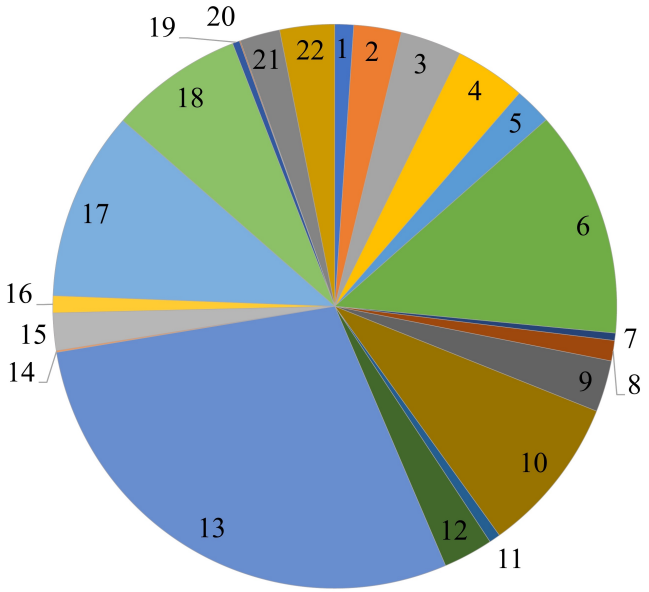
Heckel et al. BMC Genomics. 2015, 16:932.

Protein abundance: gender differences

FEMALE



MALE



1. CYP1A1 | 2. CYP1A2 | 3. CYP2A19 | 4. CYP2B22 | 5. CYP2C32 | 6. CYP2C33
7. CYP2C33v3 | 8. CYP2C34 | 9. CYP2C36 | 10. CYP2C42 | 11. CYP2C49 | 12. CYP2D6
13. CYP2D25 | 14. CYP2E1_1 | 15. CYP2E1_2 | 16. CYP3A22 | 17. CYP3A46 | 18. CYP4A21
19. CYP4V2_2a | 20. CYP4V2_2b | 21. CYP27A1 | 22. CYP51A1

F > M : CYP1A1, CYP1A2, **CYP2A19**, CYP2E1_2, CYP3A22

Buyssens et al. Front Pharmacol. 2021, 12:665644.

Göttingen Minipig: ideal animal model?

CYP	Rel. content in human liver (%)	Estim. fraction of drugs metabolized by indiv. CYP	Marker activity	Model system
1A2	12	4 %	caffeine	rat, rabbit, pig, minipig
2C9/10/19	20	11 %	diclofenac (2C9), (S)-mephenytoin (2C19)	monkey (*Maccacus mulatta*)
2D6	4	30 %	sparteine, debrisoquine, dextromethorphan	dog
2E1	6	2 %	chlorzoxazone	rat, rabbit, pig, minipig
3A4	30	52 %	nifedipine, erytromycin, alprazolam, dextrometorphan	pig, minipig

Zuber et al. J. Cell. Mol. Med. 2002, 6(2):189-198.

Species selection general tox studies

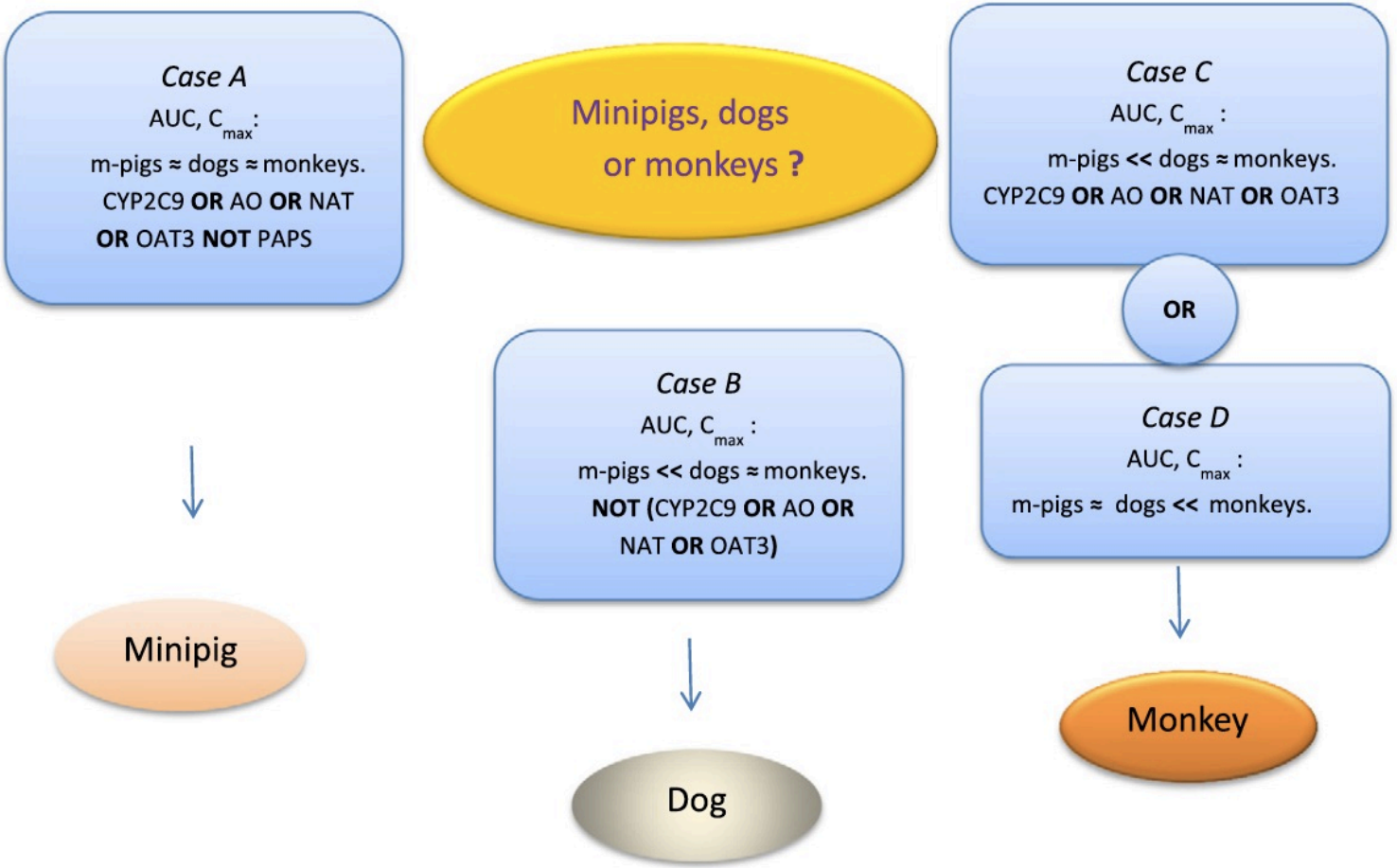


Fig. 2. Pharmacological relevant non-rodent species selection for toxicity studies.

Dalgaard et al. Journal of Pharmacological and Toxicological Methods. 2015, 74:80-92.

Conclusion in vitro drug metabolism: species comparison - selection

- Several in vitro drug metabolism assays for man, dog, minipig and nonhuman primates

- Recombinant enzymes for Göttingen Minipig still lacking, but under development

- Despite the presence of several in vitro drug metabolism assays for Göttingen Minipig, most companies do not include this nonrodent species in their testing battery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J Pharmacokinet Pharmacodyn (2016) 43:179–190
DOI 10.1007/s10928-015-9463-8

ORIGINAL PAPER

Organ data from the developing Göttingen minipig: first steps towards a juvenile PBPK model

Els Van Peer[1] · Noel Downes[2] · Christophe Casteleyn[1] · Chris Van Ginneken[1] · Arie Weeren[3] · Steven Van Cruchten[1]

Journal of Pharmacological and Toxicological Methods 62 (2010) 196–220

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Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

The utility of the minipig as an animal model in regulatory toxicology☆

Gerd Bode[a,*], Peter Clausing[b], Frederic Gervais[c], Jeanet Loegsted[d], Jörg Luft[e], Vicente Nogues[f], Jennifer Sims[g] and under the auspices of the Steering Group of the *RETHINK* Project

Basic & Clinical Pharmacology & Toxicology, 2014, 114, 387–394

Doi: 10.1111/bcpt.12173

Ontogeny of CYP3A and P-Glycoprotein in the Liver and the Small Intestine of the Göttingen Minipig: An Immunohistochemical Evaluation

Els Van Peer, Evy Verbucken, Moayad Saad, Christophe Casteleyn, Chris Van Ginneken and Steven Van Cruchten

Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Wilrijk, Belgium

(Received 12 September 2013; Accepted 29 October 2013)

Basic & Clinical Pharmacology & Toxicology, 2015, 117, 350–357

Doi: 10.1111/bcpt.12410

Age-related Differences in CYP3A Abundance and Activity in the Liver of the Göttingen Minipig

Els Van Peer[1], Lies De Bock[2], Koen Bousery[2], Jan Van Bocxlaer[2], Christophe Casteleyn[1], Chris Van Ginneken[1] and Steven Van Cruchten[1]

[1]Applied Veterinary Morphology, Department of Veterinary Sciences, University of Antwerp, Wilrijk, Belgium and [2]Laboratory of Medical Biochemistry and Clinical Analysis, Department of Bioanalysis, Ghent University, Ghent, Belgium

(Received 11 February 2015; Accepted 12 April 2015)

Pharm Res (2016) 33:2565–2579
DOI 10.1007/s11095-016-1982-5

RESEARCH PAPER

Characterization of Pharmacokinetics in the Göttingen Minipig with Reference Human Drugs: An *In Vitro* and *In Vi*

Floriane Lignet[1] · Eva Sherbetjian[1] · Nicole Kratochwil[1] · Russell Jones[1] · Claudia Suenderhauf[2] · Michael B. Otteneder[1] · Thomas Singer[1] · Neil Parrott[1]

Pharm Res (2017) 34:750–764
DOI 10.1007/s11095-017-2101-y

RESEARCH PAPER

In vitro Phase I- and Phase II-Drug Metabolism in The Liver of Juvenile and Adult Göttingen Minipigs

Els Van Peer[1] · Frank Jacobs[2] · Jan Snoeys[2] · Jos Van Houdt[2] · Ils Pijpers[2] · Christophe Casteleyn[1] · Chris Van Ginneken[1] · Steven Van Cruchten[1]

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Steven.VanCruchten@uantwerpen.be

University of Antwerp