BUILDING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR A CARCINOGENIC FOOD CONTAMINANT

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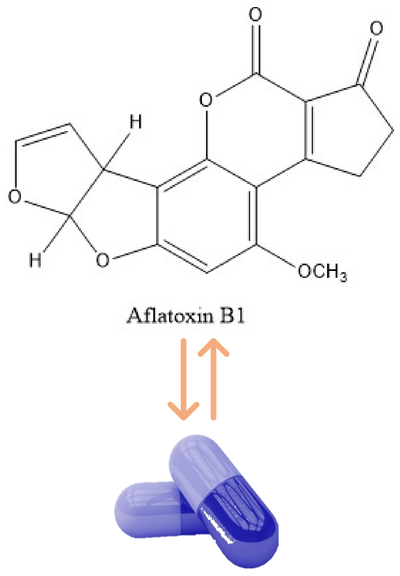
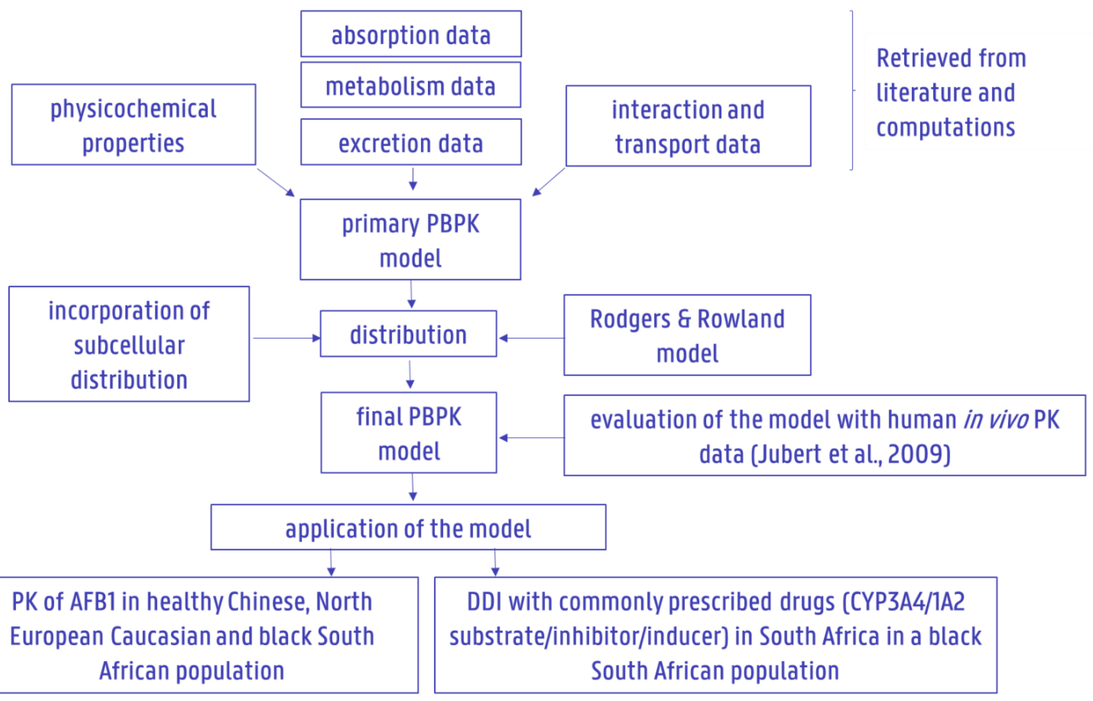
Introduction

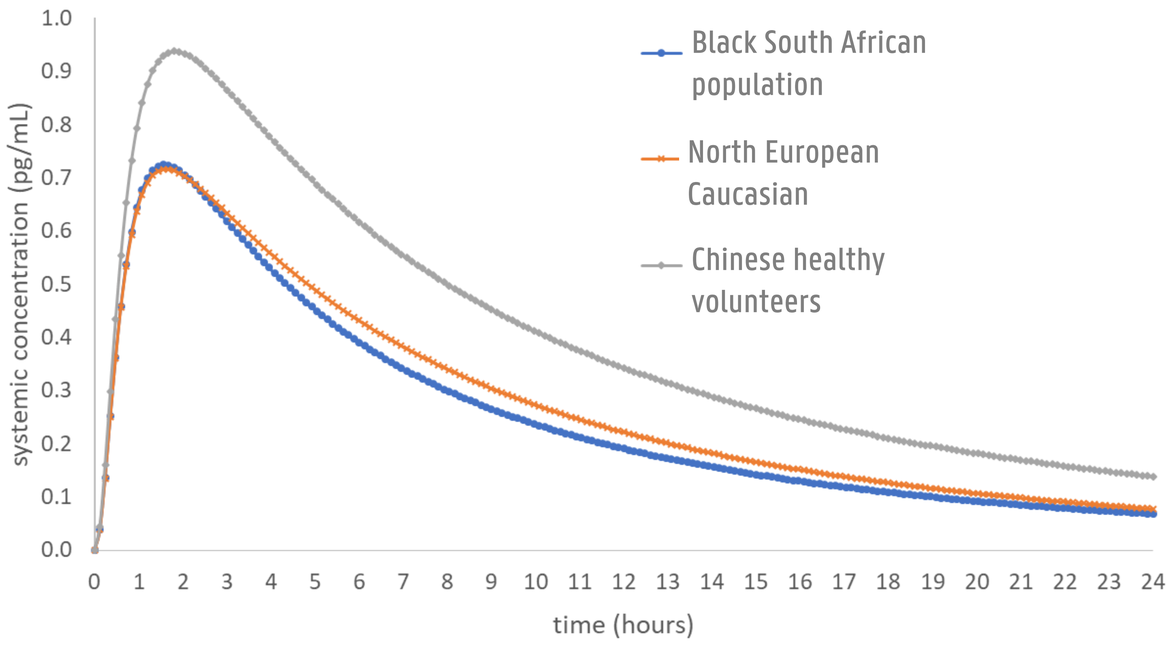


Mycotoxins are secondary metabolites produced by fungi, which contaminate food and feed commodities. Aflatoxin B1 (AFB1) is a carcinogenic mycotoxin, commonly found in Sub Saharan Africa. Repeated exposure to mycotoxins not only has an impact on public health, but could also lead to interactions with other substances in the body - such as medicinal drugs - by altering pharmacokinetics (PK) and/or pharmacodynamics (PD). A physiologically-based pharmacokinetic (PBPK) model was built using SimCYP®(v21). The model was based on *in-house* performed *in vitro* experiments and literature data. The verification of the model was executed via comparison with *in vivo* human PK data. The model was applied in three different populations to compare PK across populations and in a black South African population to explore the potential interaction with commonly prescribed drugs.

Model development



AFB1 across populations



	Chinese healthy volunteers	North European Caucasian	black South African
mean C_{max} (pg/mL)	0.967	0.740	0.755
mean T_{max} (h)	1.92	1.67	1.64
mean $AUC_{0\text{-}inf}$ (pg/mL.h)	9.85	6.78	6.24
mean CL (L/h)	4.62	6.52	8.78
F_{sub}	0.36	0.29	0.29

→ *PK-parameters of AFB1 clearly vary between populations, especially the mean clearance*

Model verification

	Observed data	Predicted data	Predicted/ Observed ratio
C_{max} (pg/mL)	0.941 ± 0.154	1.02 ± 0.035	1.08
$AUC_{0\text{-}24h}$ (pg/mL.h)	12.4 ± 1.8	9.87 ± 0.825	0.80
T_{max} (h)	1.02 ± 0.31 h	1.64 ± 0.075 h	1.61

→ *Predictions were within twofold of the human in vivo data = verification of the developed substrate file*

AFB1 and drugs

	Control (AFB1 alone)	Ratio of PK parameters (with drug/without drug)		
		+ atazanavir (200 mg) QD	+ phenytoin (100 mg) QD	+ efavirenz (600 mg) QD
C_{max} (pg/mL)	1.19	1.39	0.79	0.66
T_{max} (h)	0.96	1.14	0.93	0.75
$AUC_{0\text{-}inf}$ (pg/mL.h)	11.7	2.09	0.66	0.36
CL (L/h)	5.82	0.54	1.52	2.63
		+ carbamazepine (200 mg) QD	+ fluconazole (50 mg) QD	+ ritonavir (600 mg) BID
C_{max} (pg/mL)		0.83	1.13	1.56
T_{max} (h)		0.96	1.05	1.16
$AUC_{0\text{-}inf}$ (pg/mL.h)		0.74	1.25	2.50
CL (L/h)		1.28	0.81	0.47
		+ ciprofloxacin (250 mg) QD	+ rifampicin (600 mg) QD	+ phenobarbital (100 mg) QD
C_{max} (pg/mL)		1.27	0.54	0.64
T_{max} (h)		1.35	0.74	0.84
$AUC_{0\text{-}inf}$ (pg/mL.h)		1.47	0.26	0.45
CL (L/h)		0.55	4.13	2.30

→ *AFB1 had no influence on drug metabolism at clinically relevant doses (results not shown since ratios were equal to 1)*

→ ***CYP1A2 and CYP3A4 perpetrator drugs have an impact on the PK of AFB1***

Conclusion

AFB1 did not have an impact on the PK of drugs but the co-administered drugs did have an impact on the PK of AFB1, potentially leading to higher or lower toxicity of the mycotoxin when concomitantly ingested. Some metabolites of AFB1 are more toxic than AFB1 itself, therefore impact of drugs on AFB1 PK needs to be taken into account.

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