UNIVERSITEIT GENT

FACULTY OF PHARMACEUTICAL SCIENCES

HUMAN SKIN KINETICS OF CYCLIC DEPSIPEPTIDE MYCOTOXINS

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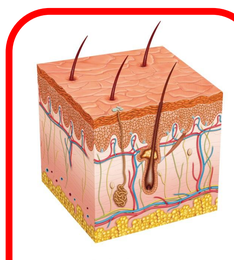
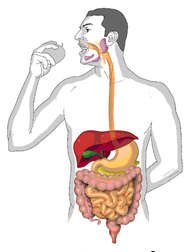
INTRODUCTION

Alternaria, *Paecilomyces, Halosarpheia, Verticillium, Fusarium* and *Beauveria* sp.

Inhalation



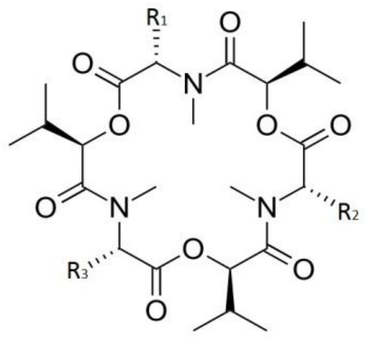
Skin



Food

Fungal origin

Exposure



Cyclic depsipeptides BEA + ENNs

Emerging mycotoxins

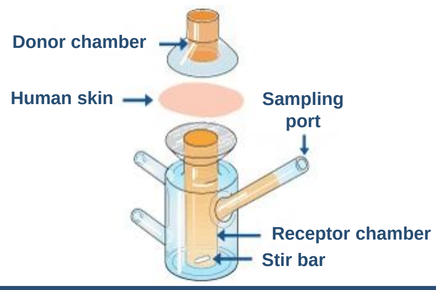
Bioactive peptides

- Mytochondrial dysfunction
- DNA damage → genotoxic (?)
- Cytotoxic
- Cation complexing ionophores
- ACAT inhibitors
- Antibacterial, insecticidal
- Influence immune system

EXPERIMENTAL

1. HUMAN SKIN KINETICS

Static *in-vitro* Franz diffusion cells
Intact vs. superficially damaged (tape-stripped 20x) skin
Receptor fluid: 1% HPBCD in PBS
Donor solution: 1 mg/mL in 60:40 EtOH/H_2O (V/V)
Quantification with UHPLC-MS/MS (MRM)



2. DERMAL DAILY EXPOSURE (DDE)

K_p → DDE

RESULTS and DISCUSSION

1. HUMAN SKIN KINETICS

a) Intact vs. damaged skin

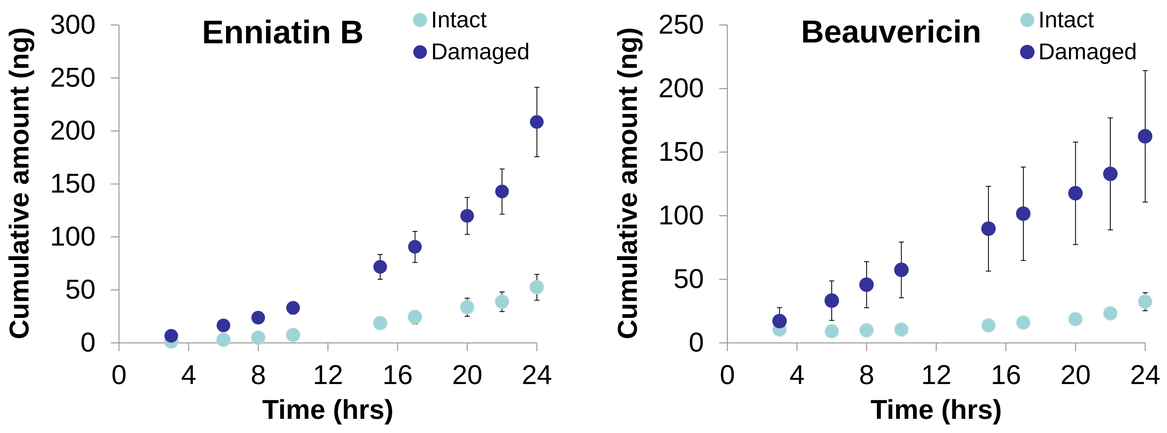


Figure 1: Cumulative amount (ng) vs. time (h) curves for ENN B (left) and BEA (right).

MT	K_p (x 10^{-6} cm/h)	
	Intact	Damaged
BEA	2.35 ± 0.52	9.76 ± 3.56
ENN B	9.44 ± 1.94	30.15 ± 3.99
ENN B1	5.62 ± 1.19	23.29 ± 2.83
ENN A	2.80 ± 0.42	5.78 ± 1.27
ENN A1	3.03 ± 0.63	12.83 ± 2.73
ENN D	4.67 ± 1.02	19.07 ± 0.28
ENN E	4.26 ± 0.86	13.46 ± 2.12

Table 1: Permeability coefficients (mean ± SEM, n = 3 – 11).

b) In-silico K_p comparison

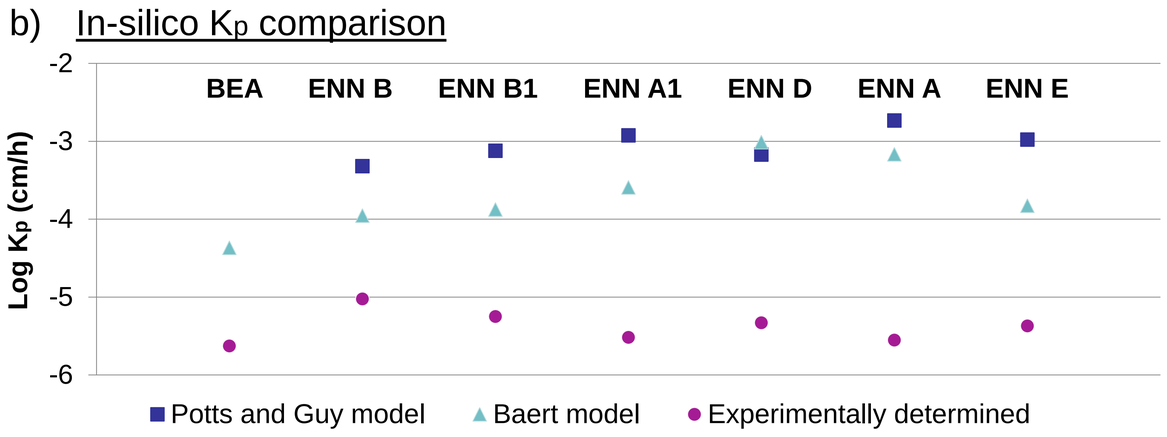
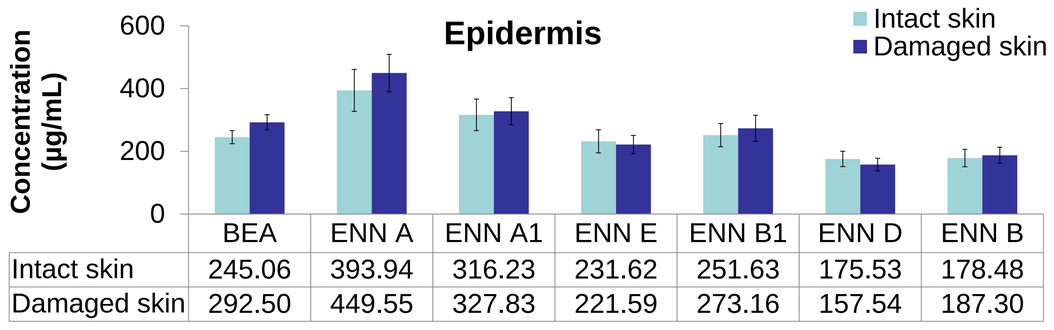
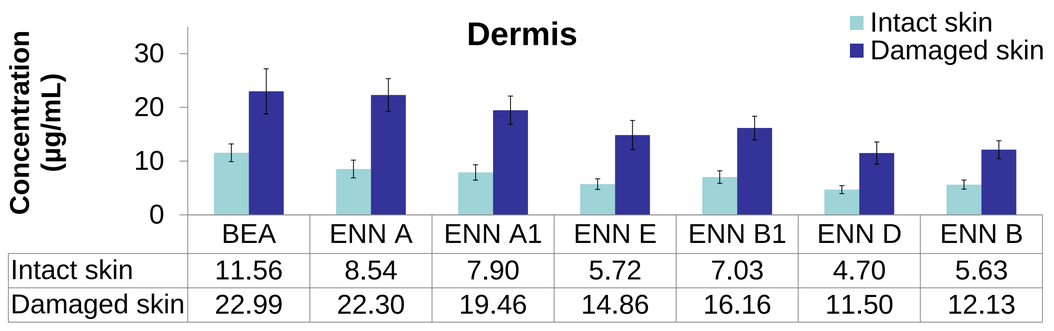


Figure 2: Comparison experimentally determined and in-silico calculated K_p's.

c) Local skin concentrations



	BEA	ENN A	ENN A1	ENN E	ENN B1	ENN D	ENN B
Intact skin	245.06	393.94	316.23	231.62	251.63	175.53	178.48
Damaged skin	292.50	449.55	327.83	221.59	273.16	157.54	187.30



	BEA	ENN A	ENN A1	ENN E	ENN B1	ENN D	ENN B
Intact skin	11.56	8.54	7.90	5.72	7.03	4.70	5.63
Damaged skin	22.99	22.30	19.46	14.86	16.16	11.50	12.13

Figure 3: Normalised (1 mg/mL application) skin concentrations (epidermis + dermis).

2. RISK ASSESSMENT AFTER DERMAL EXPOSURE

a) Local skin effects

Locally found skin concentrations compared to literature data → possible epidermal apoptosis, immunological disorders.

b) Systemic effects

Scenario (1st approximation): industrial exposure to contaminated fruit/nuts:

1) Mycotoxin exposure concentration [MT]: based on reported literature.
2) Estimation of TDI = 5 µg/(kg BW · day): using NOAEL from limited literature data.
3) Calculation of DDE's: using our experimentally determined K_p's.

Mycotoxin:	ENN A	ENN A1	ENN B	ENN B1	BEA
Intact	0.0311 – 0.0870	0.0017 – 0.0047	0.0301 – 0.0842	0.0277 – 0.0774	0.0004 – 0.0010
Damaged	0.0641 – 0.1795	0.0072 – 0.0201	0.0961 – 0.2690	0.1146 – 0.3209	0.0015 – 0.0043

Table 2: Non-genotoxic – genotoxic estimated DDE's (ng/(kg BW · day).

TDI > DDE's → no acute systemic toxicity risk for industrial food related workers.

CONCLUSIONS

- **Intact vs. damaged skin:** 2 – 5 times increase of K_p, J_{ss} and Q_{1d} for damaged skin.
- **In-silico K_p comparison:** significant difference independent of models used → more appropriate models required for (cyclic)(depsi)peptides.
- **Local skin effects:** skin reservoir properties → local skin effects possible: epidermal apoptosis, immunological disorders.
- **Risk assessment after dermal exposure:** first estimation: no acute systemic toxicity risk based on limited data available.

REFERENCES

Taevernier L, Veryser L, Roche N, Peremans K, Burvenich C, Delesalle C, De Spiegeleer B, Human skin penetration of emerging mycotoxins (beauvericin and enniatins). Journal Of Exposure Science And Environmental Epidemiology, 2014, *submitted for publication*.

Taevernier L, Veryser L, Vandercruyssen K, D'Hondt M, Vansteelandt S, De Saeger S, De Spiegeleer B, UHPLC-MS/MS method for the determination of the cyclic depsipeptide mycotoxins beauvericin and enniatins in *in-vitro* transdermal experiments. Journal of Pharmaceutical and Biomedical Analysis, 2014, doi: 10.1016/j.jpba.2014.07.021.