Undesirable substances in ruminant nutrition – The bright and the dark side of the rumen

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LFGB § 3 Weitere Begriffsbestimmungen

16. **unerwünschte Stoffe**: Stoffe - außer Tierseuchenerreger -, die in oder auf Futtermitteln enthalten sind und

a) als **Rückstände** in von Nutztieren gewonnenen Lebensmitteln oder sonstigen Produkten eine Gefahr für die menschliche Gesundheit darstellen,
b) eine **Gefahr für die tierische Gesundheit** darstellen,
c) vom Tier ausgeschieden werden und als solche eine Gefahr für den Naturhaushalt darstellen oder
d) die **Leistung von Nutztieren** oder als Rückstände in von Nutztieren gewonnenen Lebensmitteln oder sonstigen Produkten die Qualität dieser Lebensmittel oder Produkte **nachteilig beeinflussen** können.

Consequences of ruminal metabolism of certain compounds for ruminant health: Dark: Potentially adverse Bright: Potential benefits

Mother substance	Main rumen metabolites	Dark	Neutral	Bright
Formononetin	Equol	x		
Biochanin A	p-ethylphenol			x
Zearalenone	α-zearalenol (ZOL), β-ZOL		x	x
Deoxynivalenol (DON)	De-epoxy-DON			x
Pyrrolizidine alkaloids	Methylated derivatives			(x)
Ergovaline	Lysergic acid	x		
Ergotamine	Ergotaminine, lysergic acid (?)	x	x	
Sulfur (in excess)	Sulfur hydrogen	x		
Tryptophan	3-methylindole	x		
PCDDs/PCDFs[1]	~		x	

[1]polychlorinated dibenzo-para-dioxins/ polychlorinated dibenzofurans
Note: Adaptation to the respective substrates and the surrounding milieu which can largely be modified by feeding might contribute to the overall effects.

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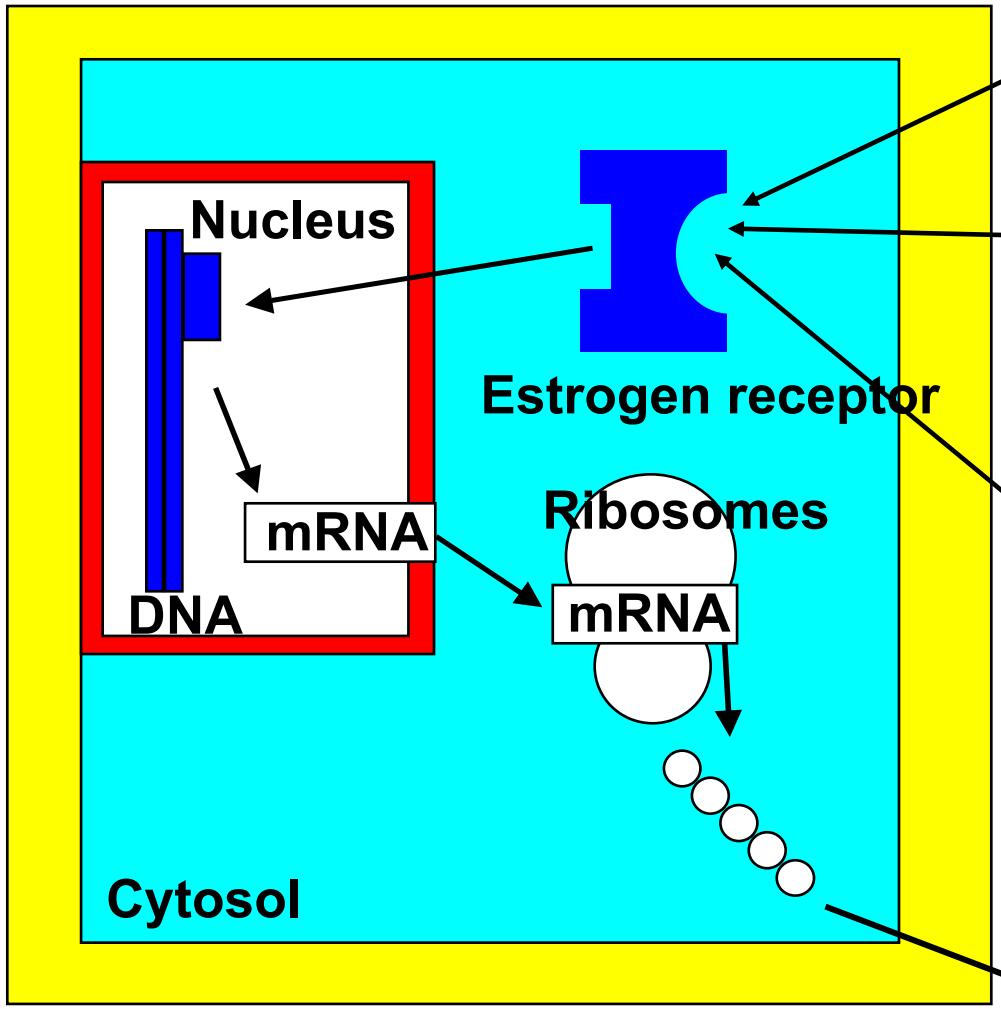
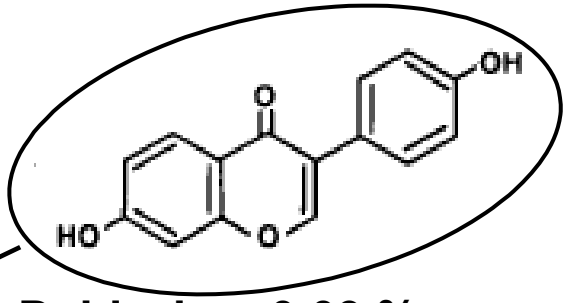
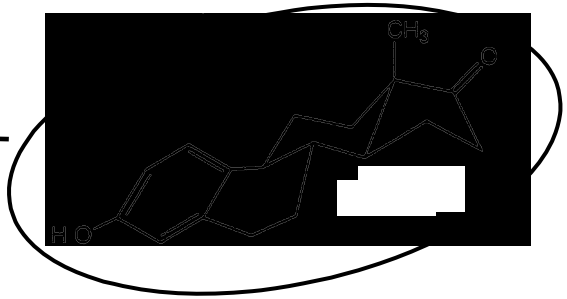
Mode of action of endogenous estradiol and some estrogen-like substances

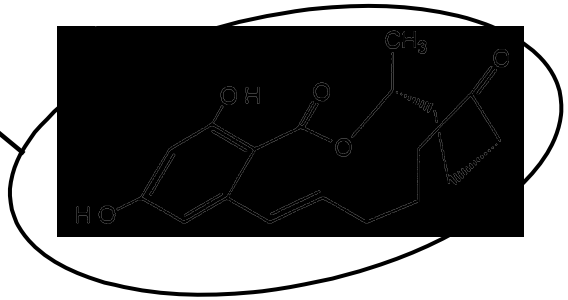




Daidzein = 0.09 %



Estradiol = 100 %



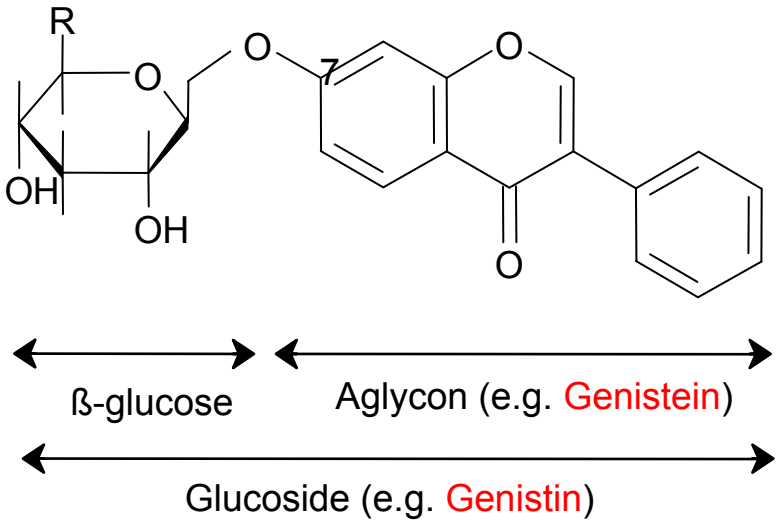
Zearalenone =1 %

(nach Fitzpatrick et al., 1989; Riley 1998; Miksicek, 1994)

Mean isoflavone content of soy bean meals of various origins (mg/kg DM, n=6, Hünerberg, 2008)

Origin	Daidzin	Genistin	Daidzein	Genistein	Total
Argentina	596[a]	1066[a]	172[a]	82[a]	**3075[a]**
Brasilia	298[b]	607[b]	122[b]	81[a]	**1570[b]**
USA	326[b]	535[b]	53[c]	24[b]	**1944[b]**
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
PSEM	35.0	38.1	10.5	8.3	116.0

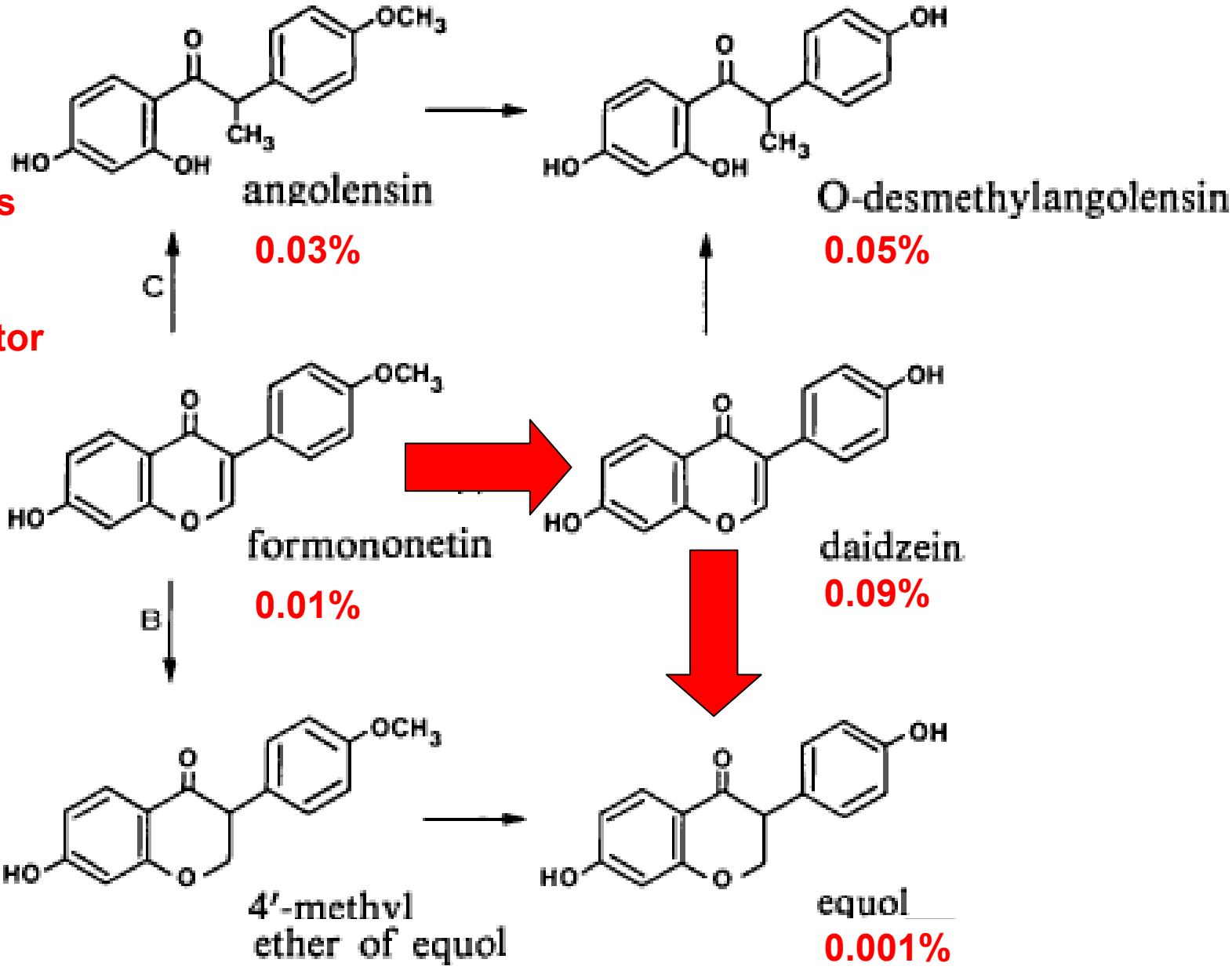
ab - values with different superscripts are significantly different (p<0.05)



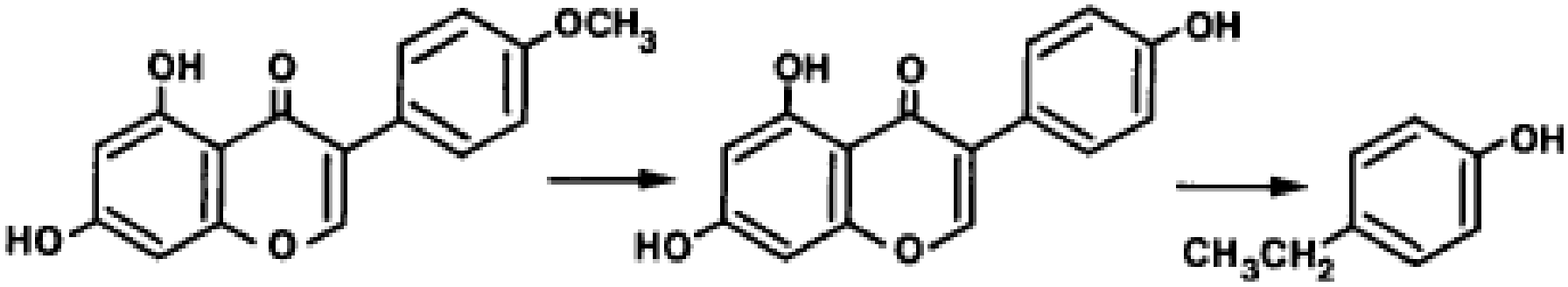
Cleavage occurs in rumen!

Metabolism of formononetin in the sheep (Price and Fenwick, 1985)

All substances bind to the sheep uterine cytosol receptor (relative affinities)!



Metabolism of biochanin A in the sheep (Price and Fenwick, 1985)

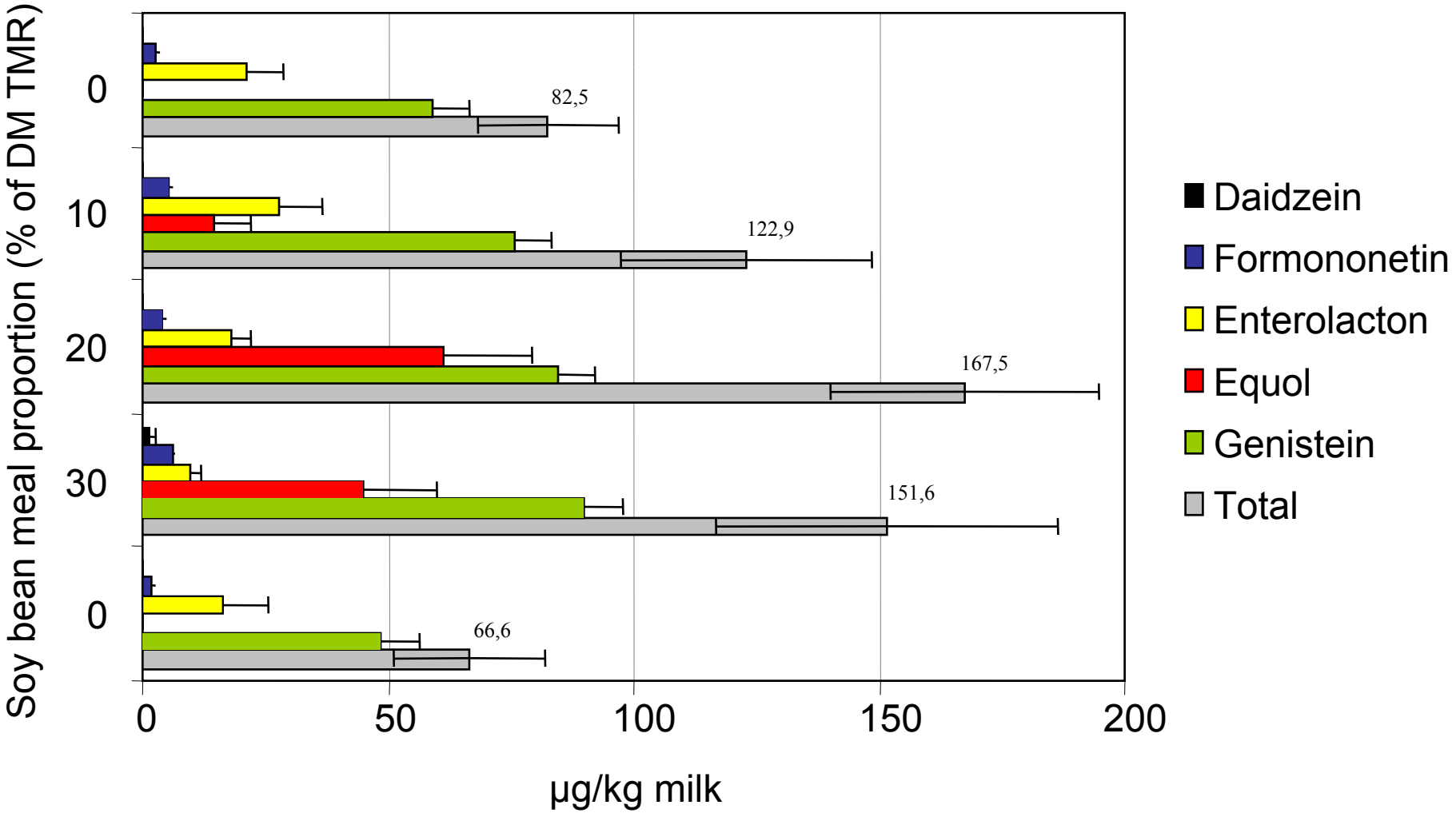


biochanin A genistein *p*-ethylphenol

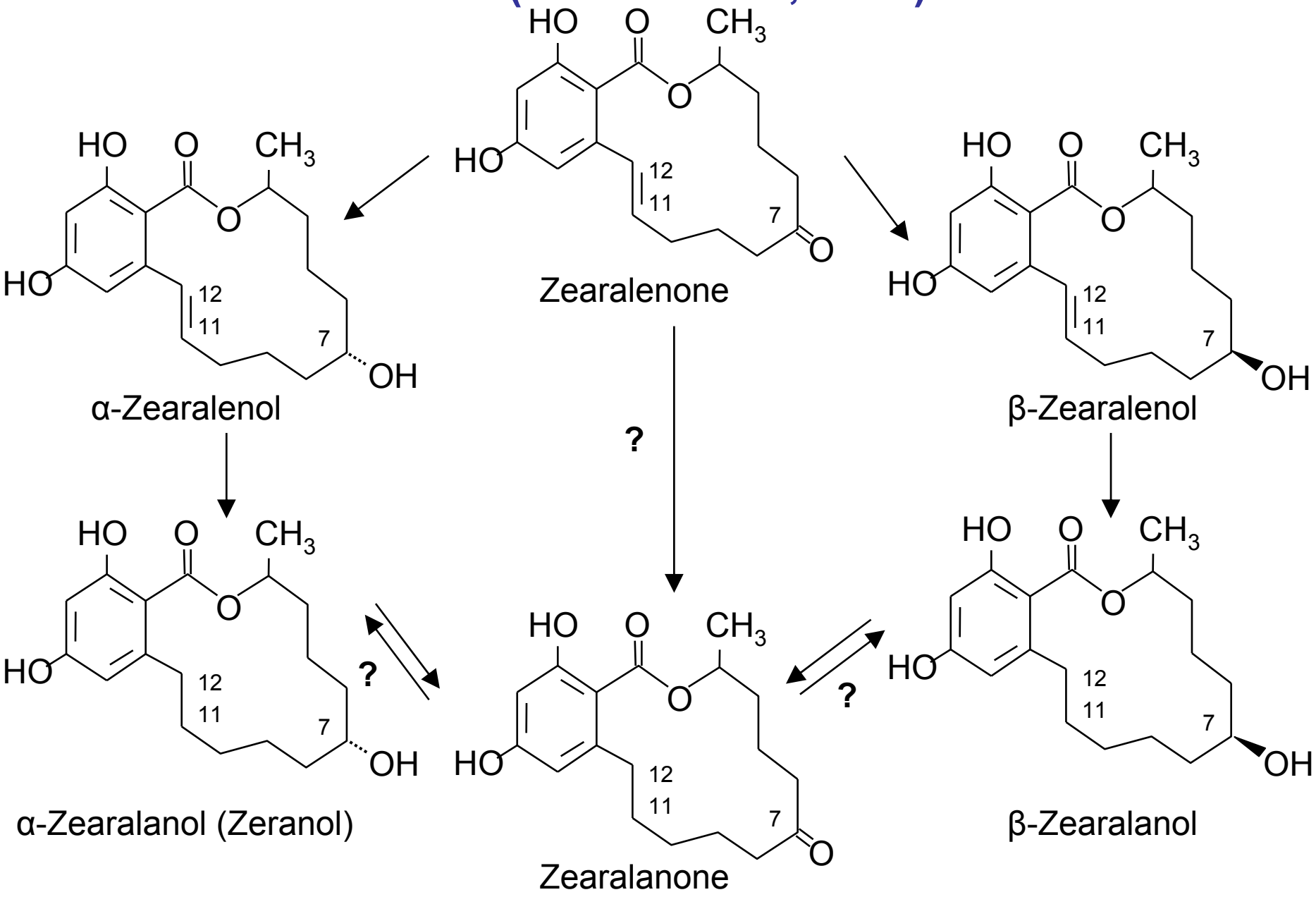
uterotropic **uterotropic** **not uterotropic**

Biochanin A and genistein were about 20 times less active when introduced intraruminally as compared to intramuscular injection!

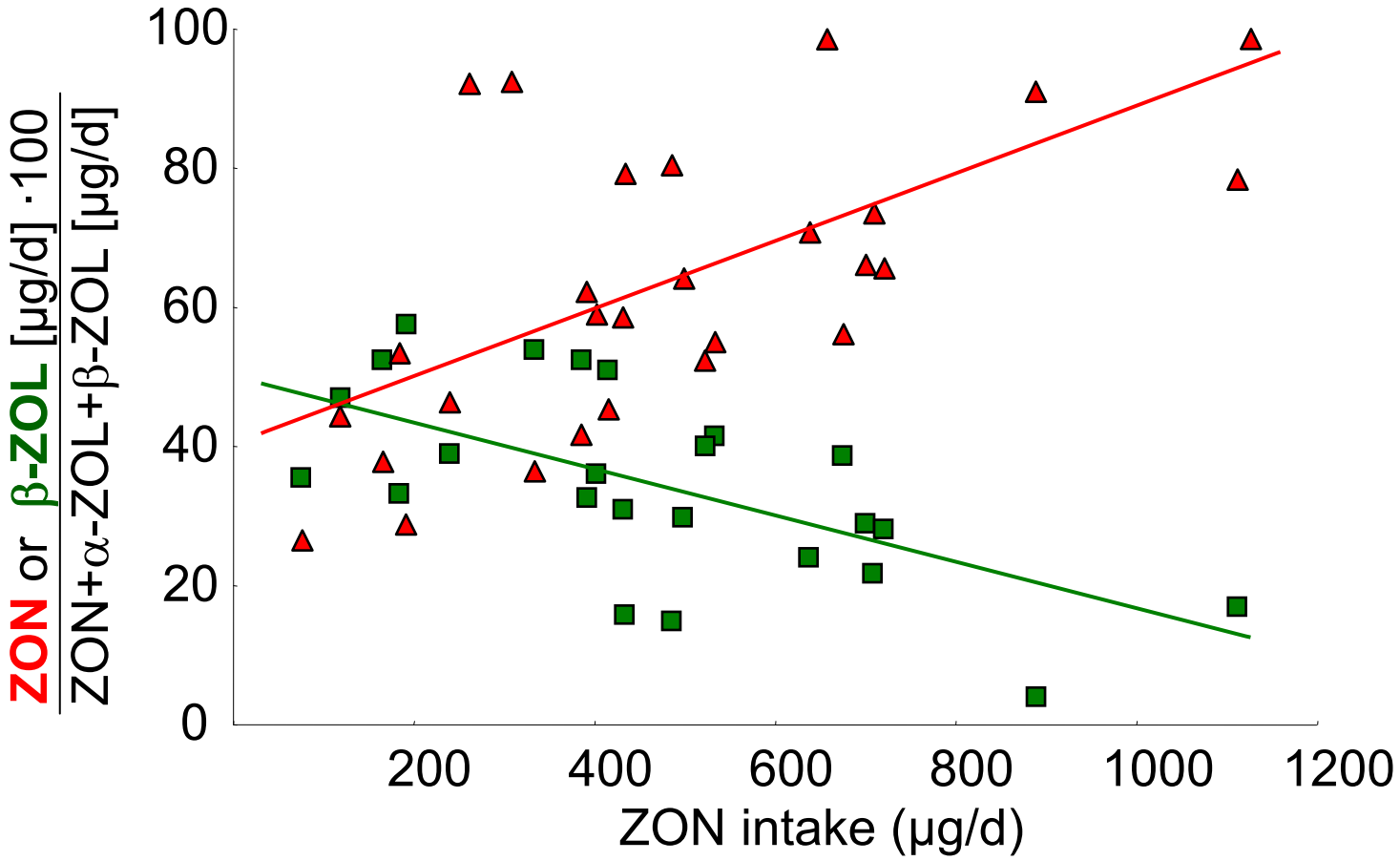
Mean isoflavone content of milk from cows fed graded levels of soy bean meal (Hünerberg, 2008)



Zearalenone and its major in vivo metabolites in pigs and cattle (Zöllner et al., 2002)



Increased feed intake (= increased ruminal passage rate) resulted in a decreased ruminal reduction of zearalenone to β-ZOL at a similar dietary ZON concentration (0.06 mg/kg DM) (Seeling et al., 2005)



ZON = 40 + 0.048*** • x, ***P < 0.001, r^2 = 0.39

β-ZOL = 49 – 0.034*** • x, ***P < 0.001, r^2 = 0.25

Simplified evaluation of the significance of selected estrogen-like substances in dairy cattle rations

Concentrate proportion (%)	30				
	Components		Zearalenone	Daidz(e)in	Genist(e)in
	(% of conc.)	(g/kg DM)	(mg/kg DM)	(mg/kg DM)	(mg/kg DM)
Wheat	22	66	0,05		
Soybean meal	25	75	0,01	800	100
Maize	50	150	1		
Mineral feed	3	9			
Grass silage		350			
Maize silage		350	0,5		
Sum (mg/kg DM)			0,33	60	8
Estrogenicity (% of estradiol)			1	0,001	0,004
Estradiol equivalents (mg/kg DM)			0,003	0,001	0,000
Estradiol equivalents (%)			79	14	7

Note: Ruminal metabolism of the substances and its efficiency are not considered!

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Ergovaline	Lysergic acid	x		
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Sulfur (in excess)	Sulfur hydrogen	x		
Tryptophan	3-methylindole	x		
PCDDs/PCDFs[1]	~		x	

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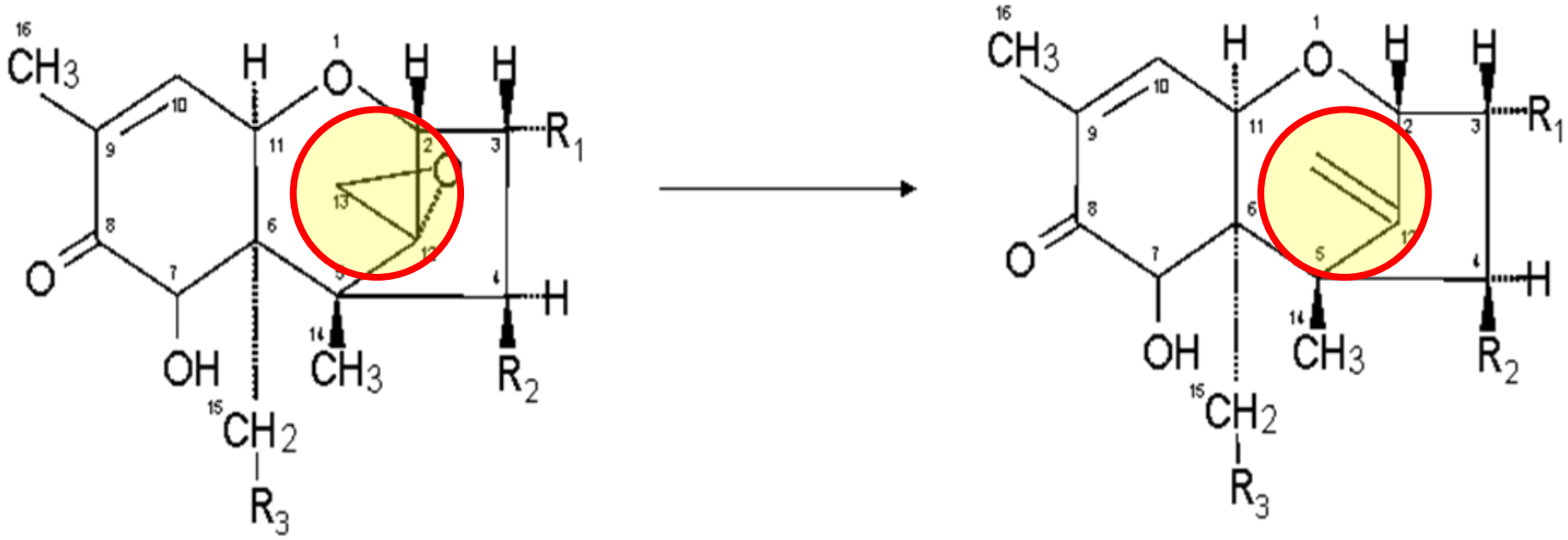
Biotransformation of deoxynivalenol (King et al., 1984)



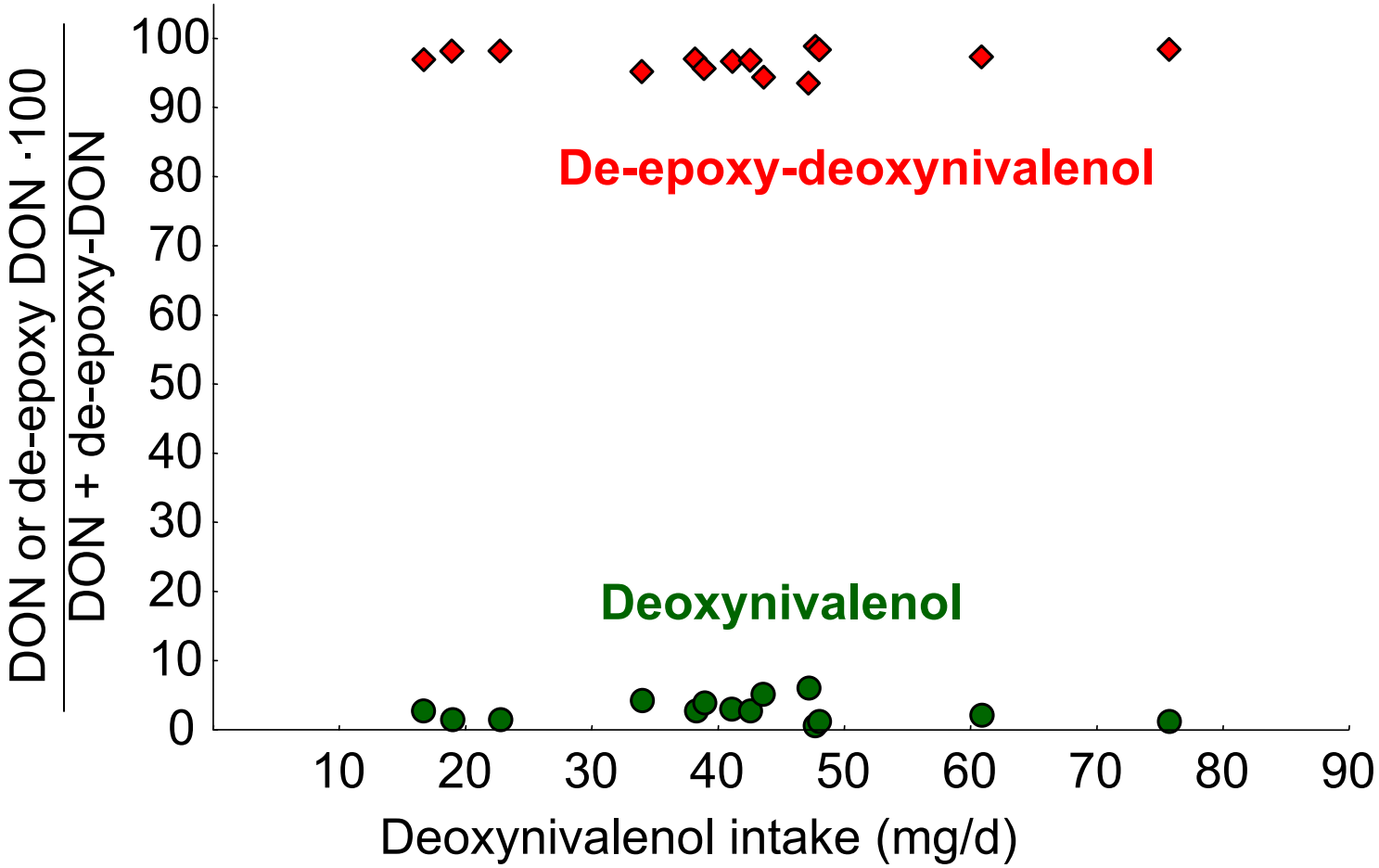
Deoxynivalenol

de-epoxy-Deoxynivalenol

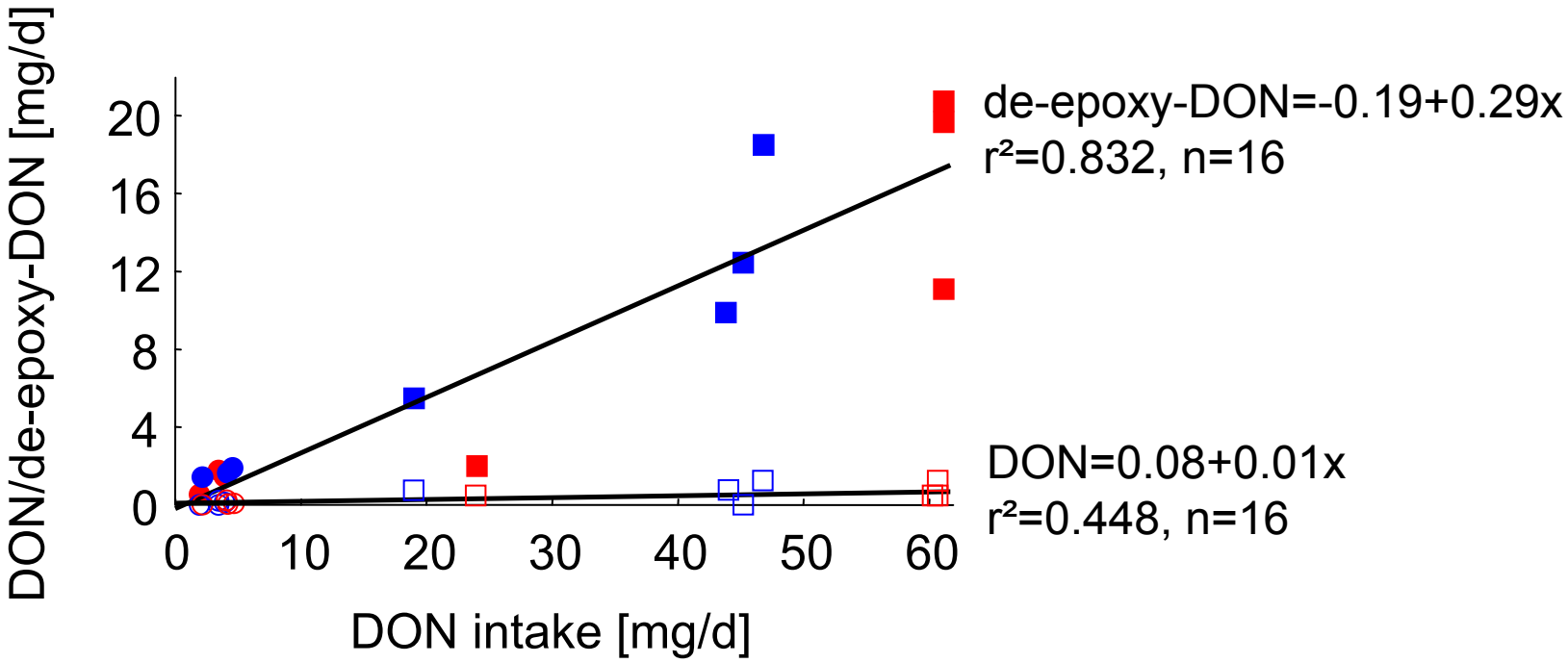
De-epoxydation

- **occurs via intestinal micro-organisms**
- **is supposed to be a detoxification**

Increased feed intake (= increased ruminal passage rate) resulted not in a decreased ruminal deoxynivalenol (DON) reduction to de-epoxy-DON at a similar dietary DON concentration (3.4 mg/kg DM) (Seeling et al., 2006)



The concentrate proportion did not influence the deoxynivalenol (DON) and de-epoxy-DON-flow at the duodenum (Dänicke et al., 2009)



● de-epoxy-DON, ○ DON – control – 30% concentrate
● de-epoxy-DON, ○ DON – control – 60% concentrate

■ de-epoxy-DON, □ DON – 3.3 mg DON/kg T – 30% concentrate
■ de-epoxy-DON, □ DON – 4.5 mg DON/kg T – 60% concentrate

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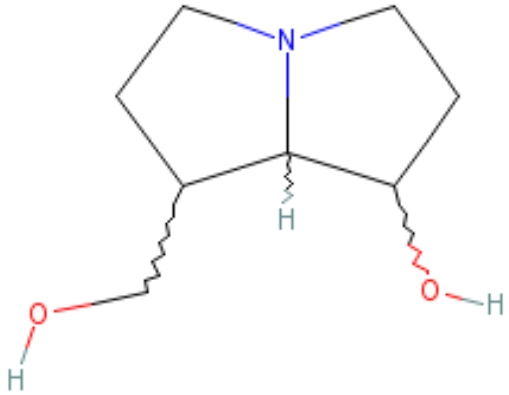
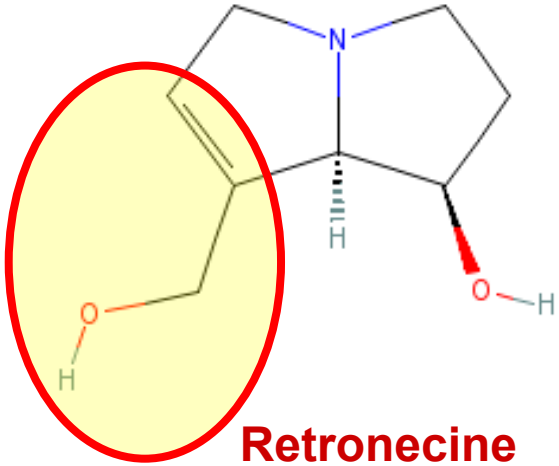
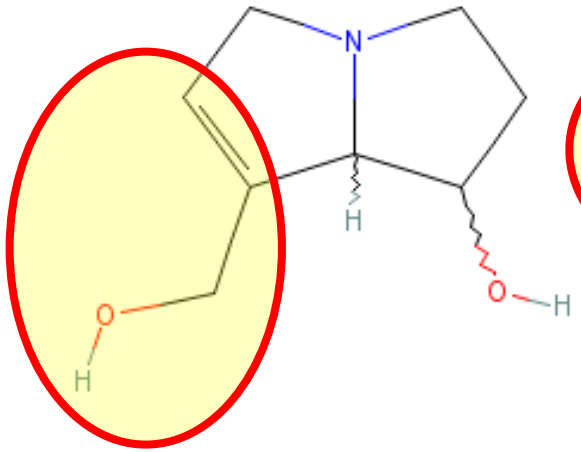
Basic structure of the four necine bases forming toxic pyrrolizidine alkaloids (PAs) (EFSA, 2007)



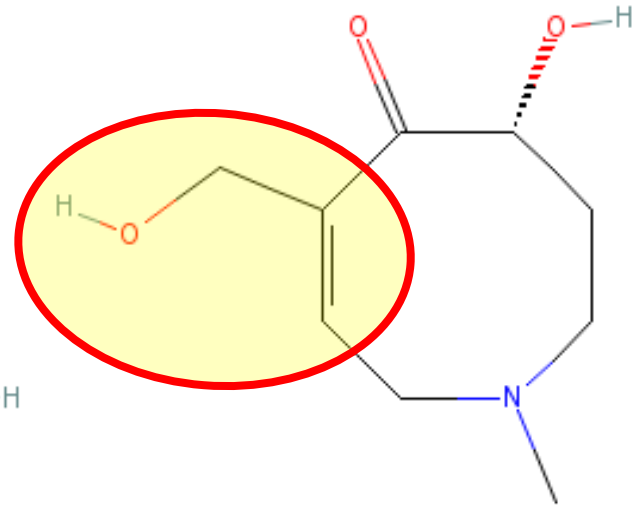
Platynecine



Retronecine



Heliotridine

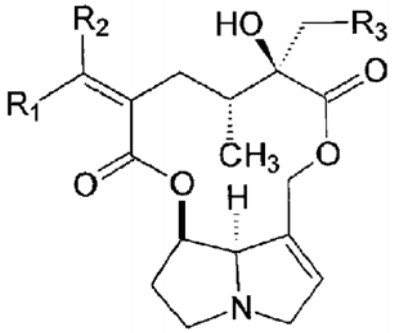


Otonecine

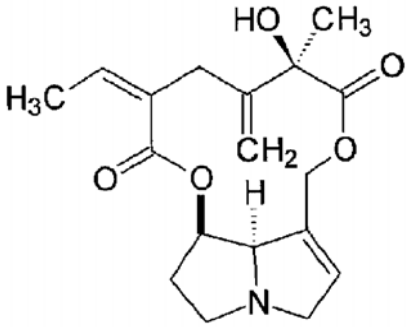
- 350 individual compounds produced by more than 6000 plant species (*Boraginaceae, Compositae* [*Asteraceae*] and *Leguminosae* [*Fabaceae*])
- Contents between 0.001 % to 5 %, comprising of a mixture of PAs

- For hepatotoxicity, there must be a 1,2-double bond and a branch in an esterified side chain

Senecio jacobaea (tansy ragwort) pyrrolizidine alkaloids (macrocyclic diesters of the necine base retronecine) (Hovermale and Craig, 2002)

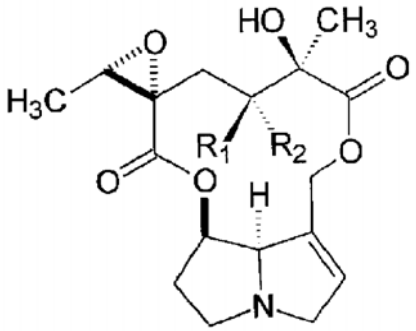


	R_1	R_2	R_3	
(1)	CH_3	H	H	Senecionine
(3)	H	CH_3	H	Integerrimine
(7)	CH_3	H	OH	Retrorsine

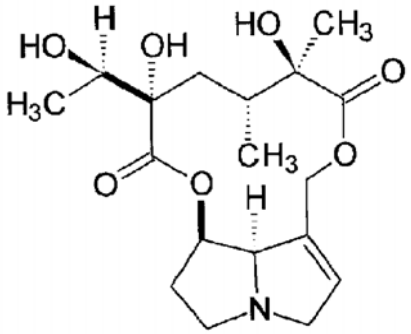


(2) Seneciphylline

Total PA content: 200-3200 mg/kg DM (Macel et al., 2004)



	R_1	R_2	
(4)	H	CH_3	Jacobine
(5)	-CH_2-		Jacozine

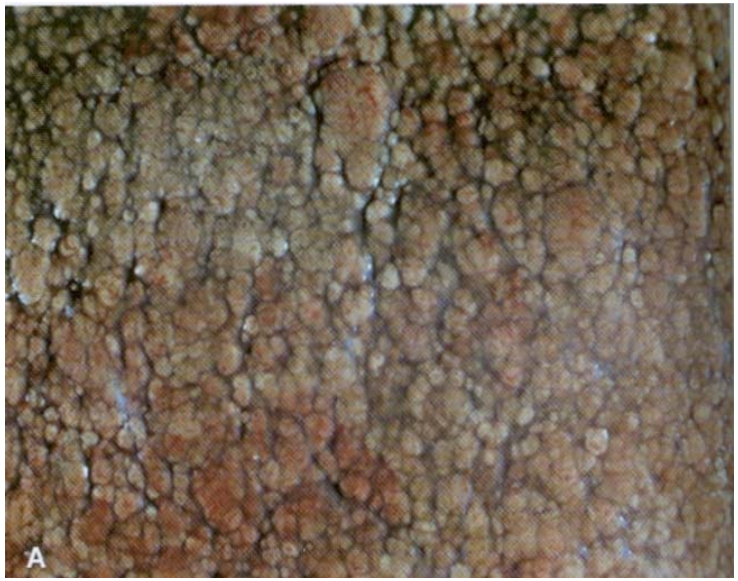


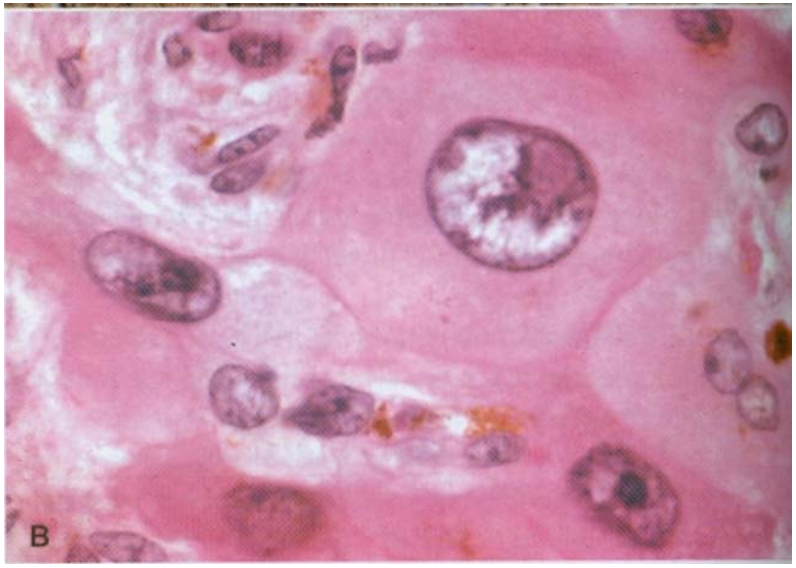
(6) Jacoline

Early flowering stage of *Senecio jacobaea* as seen on pasture June 28, 2006, where a herd outbreak of pyrollizidine alkaloidosis was diagnosed (Walsh and Dingwell, 2007)

Photograph of the pasture, and concentration of *Senecio jacobaea*, where the beef herd was grazing in June 2006, while investigating an outbreak of pyrollizidine alkaloidosis (Walsh and Dingwell, 2007)

Chronic hepatotoxicity in cattle caused by pyrollizidine alkaloids (McGavin, 2007)





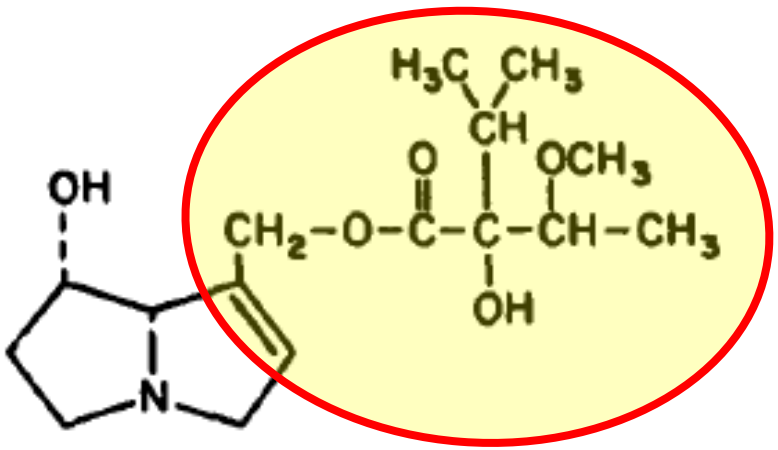
Fibrotic liver covered by an irregular capsule, and enlarged hepatocytes (megalocytes)

EU legislation on pyrrolizidine alkaloids (PA) containing plant materials used as feed

Undesirable substances (or plants)	Product intended for animal feed	Maximum content in mg/kg relative to a feedingstuff with a moisture content of 12 %
Weed seeds and unground and uncrushed fruits containing alkaloids, glucosides or other toxic substances separately or in combination including	All feedingstuffs	3000
(a) *Lolium temulentum* L.,		1000
(b) *Lolium remotum* Schrank,		1000
Crotalaria spp.		100

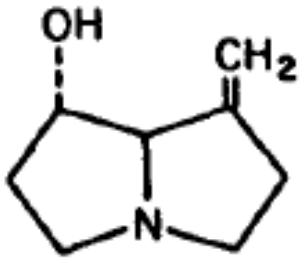
<u>Note:</u> These upper limits refer to weed seeds or uncrushed feeds and not to the total or individual PAs content!

Metabolism of the pyrrolizidine alkaloid heliotrine in sheep rumen (Cheeke, 1988)

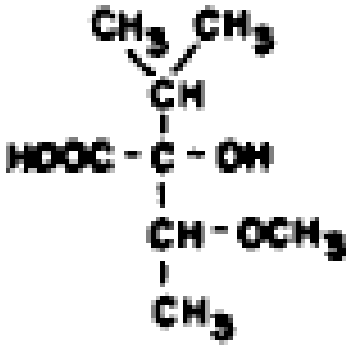


Heliotrine

rumen microorganisms

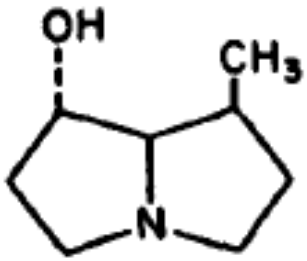


1-methylene derivative



HELIOTRIC ACID

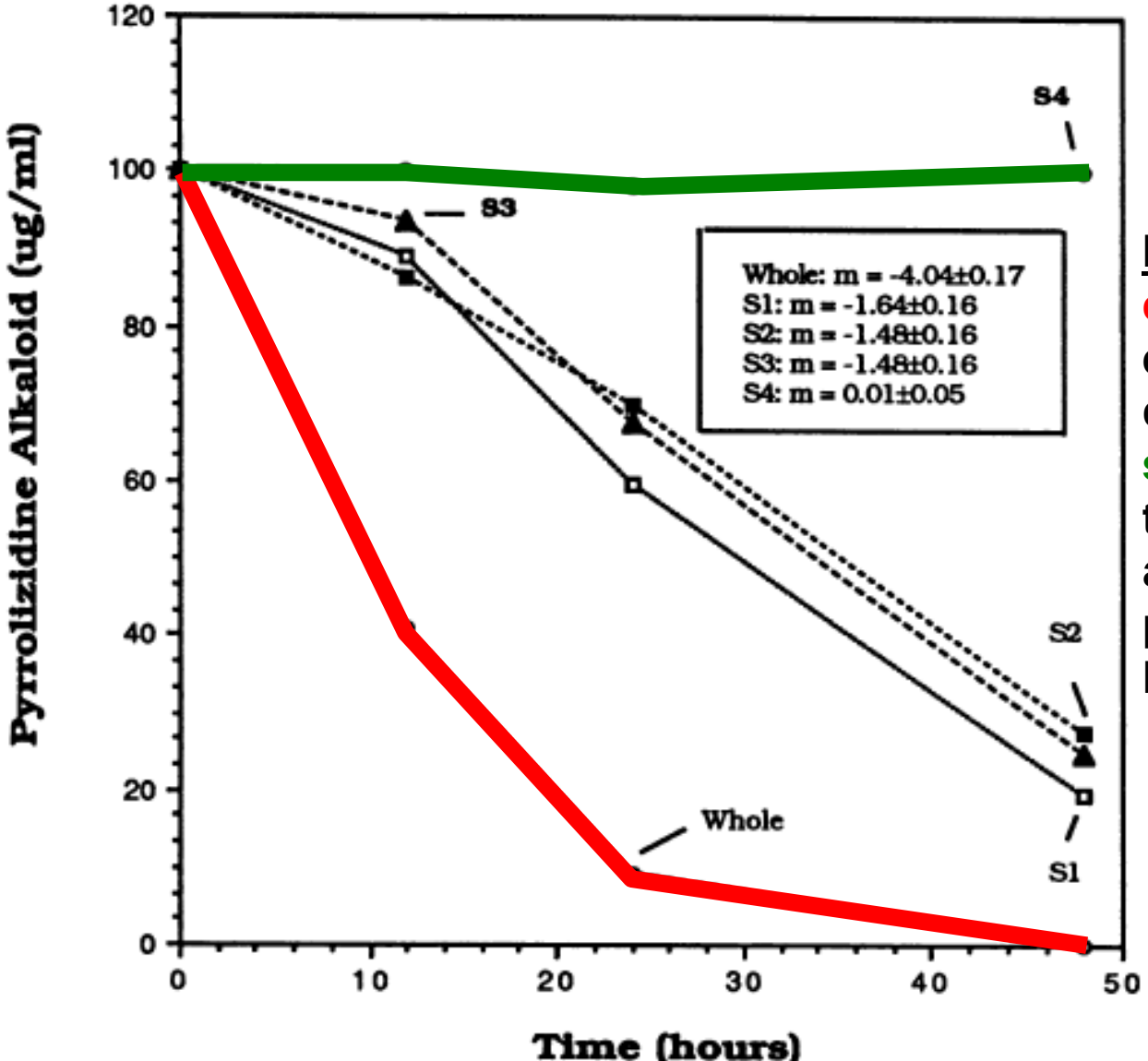
Europäische Sonnenwende (*Heliotropium europaeum*)



1-methyl derivative

<u>Note:</u> Methylation also occurs with macrocyclic PAs by certain ruminal bacteria but to a very small extent

Concentrations of *Senecio jacobaea* pyrrolizidine alkaloids (PAs) remaining after *in vitro* incubation with ovine ruminal fluid (Craig et al., 1992)



Note: Whole (not centrifuged) rumen fluid enabled a more rapid PAs disappearance than supernatants suggesting that plant debris associated bacteria and protozoa are involved in PAs disappearance

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Tryptophan	3-methylindole	x		
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Clavicipitaceae

Claviceps purpurea (mainly on rye, triticale and wheat)

Neotyphodium coenophialum (mainly in perennial rye grass (*Lolium perenne*) and tall fescue (Festuca grass, *Festuca arundinacea*)

Conidia and sclerotia of *Claviceps purpurea*

Festuca arundinacea - Tall Fescue: can be infected by *Neotyphodium coenophialum*

Toxic alkaloids of the *Clavicipitaceae*

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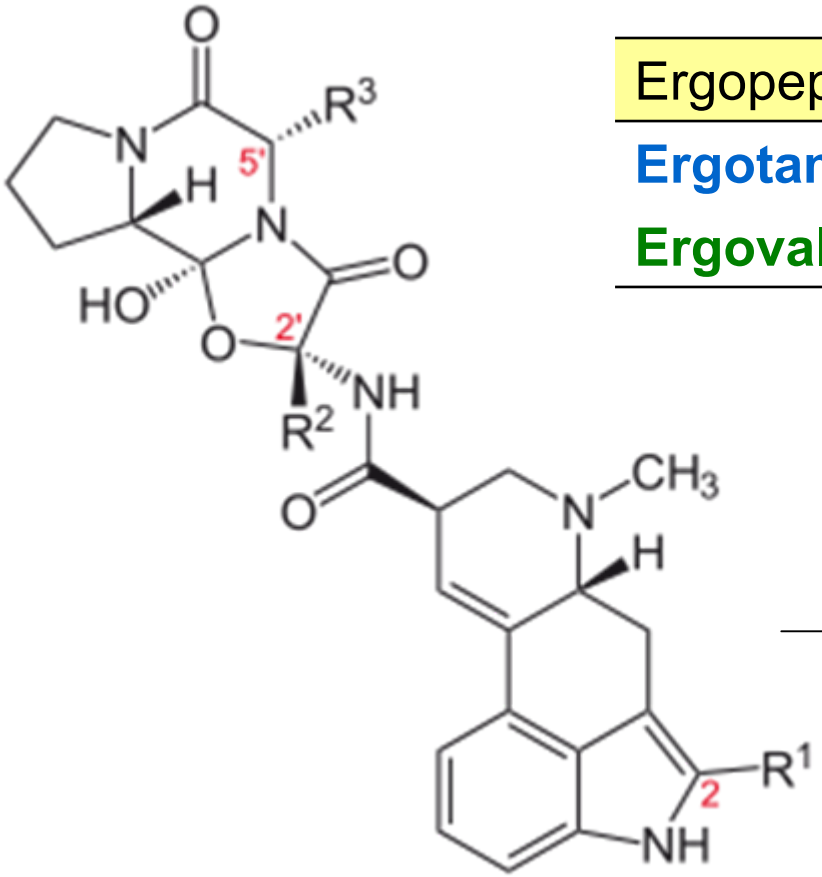
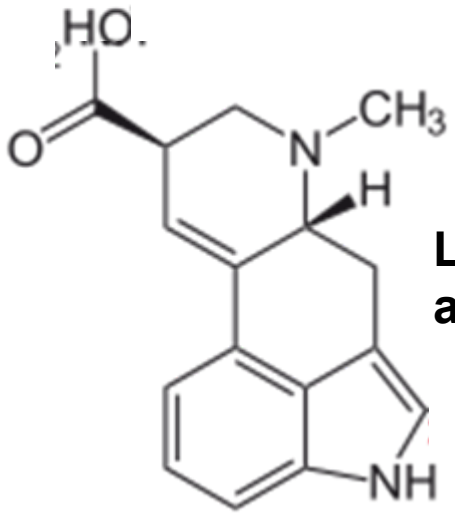


Ergopeptin	R2 (Pos. 2′)	R3 (Pos. 5′)
Ergotamine	**CH_3**	**$CH_2C_6H_5$**
Ergovaline	**CH_3**	**$CH(CH_3)_2$**

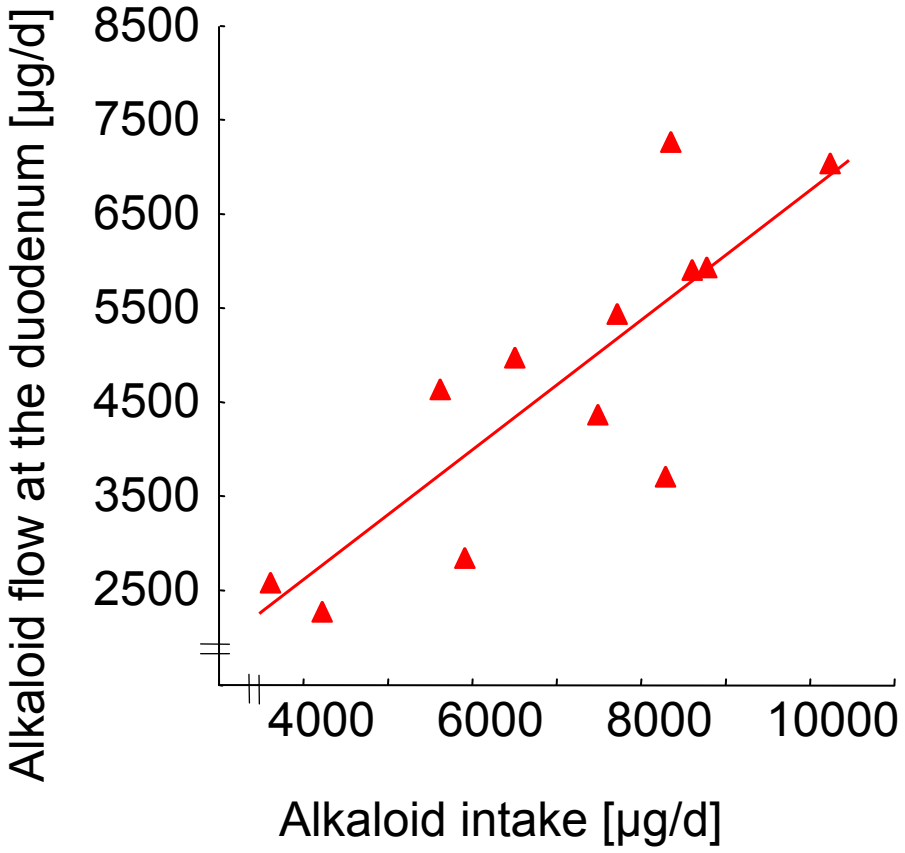
DeLorme et al. (2007)



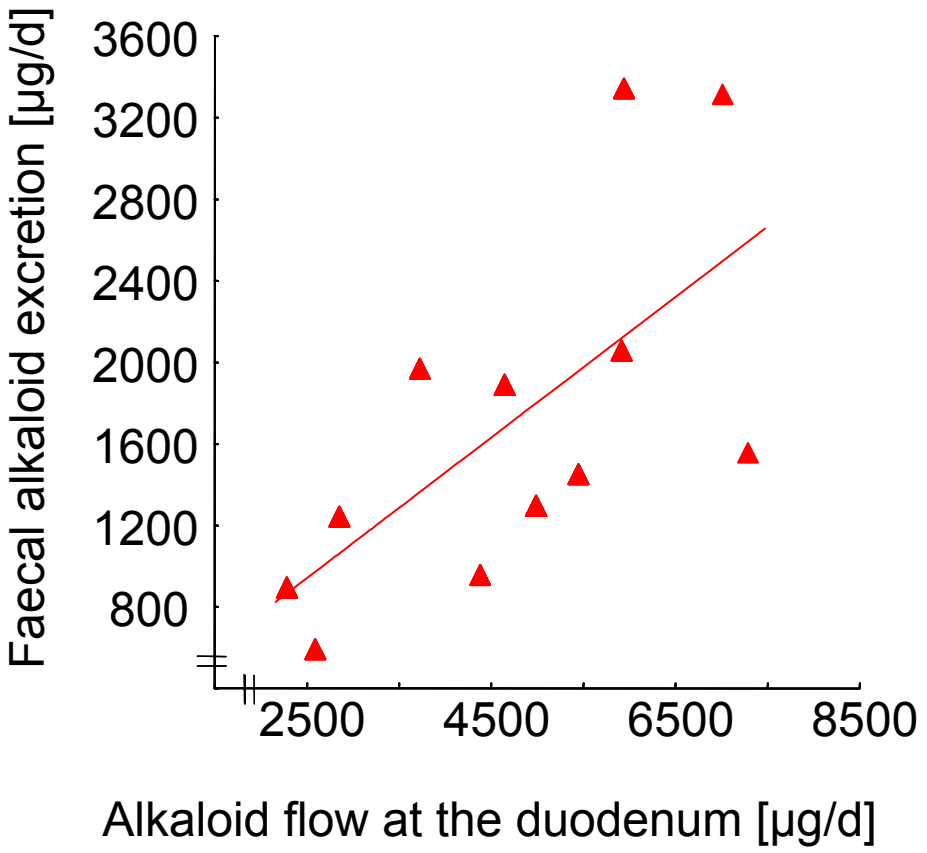
Lysergic acid

Ergot-alkaloid flow at the duodenum of dairy cows in dependence on alkaloid intake (**left**) and faecal alkaloid excretion in dependence on alkaloid flow at the duodenum (**right**) (Schumann et al., 2009)

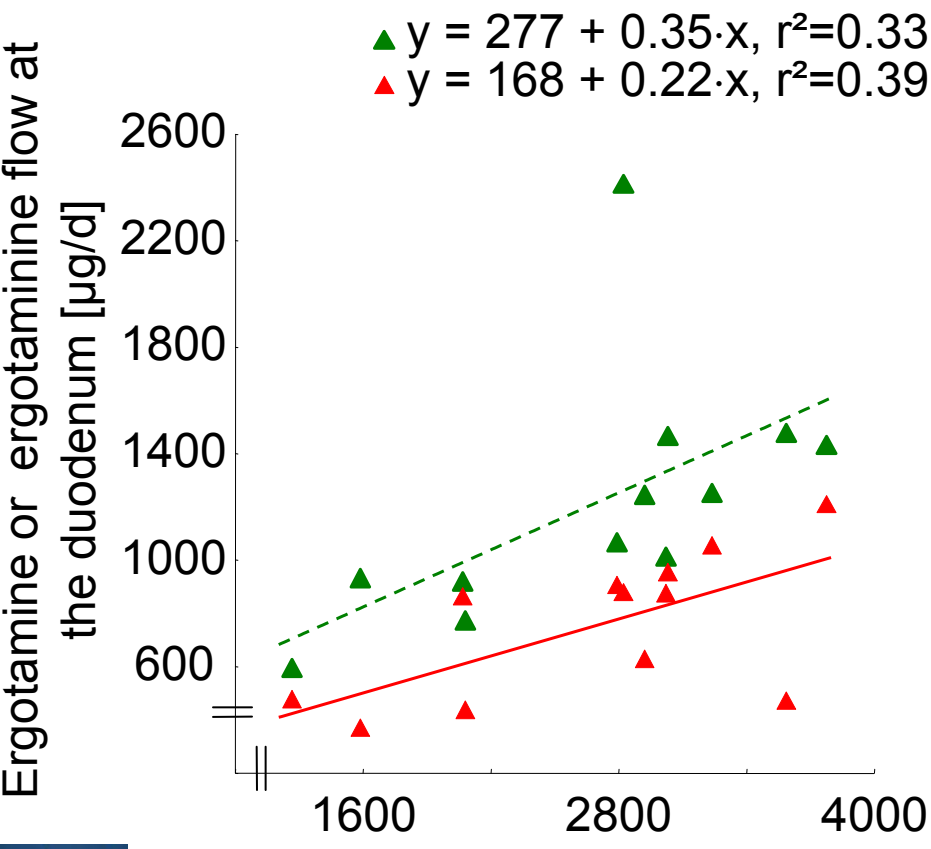
y = -213 + 0.70·x, r²=0.69



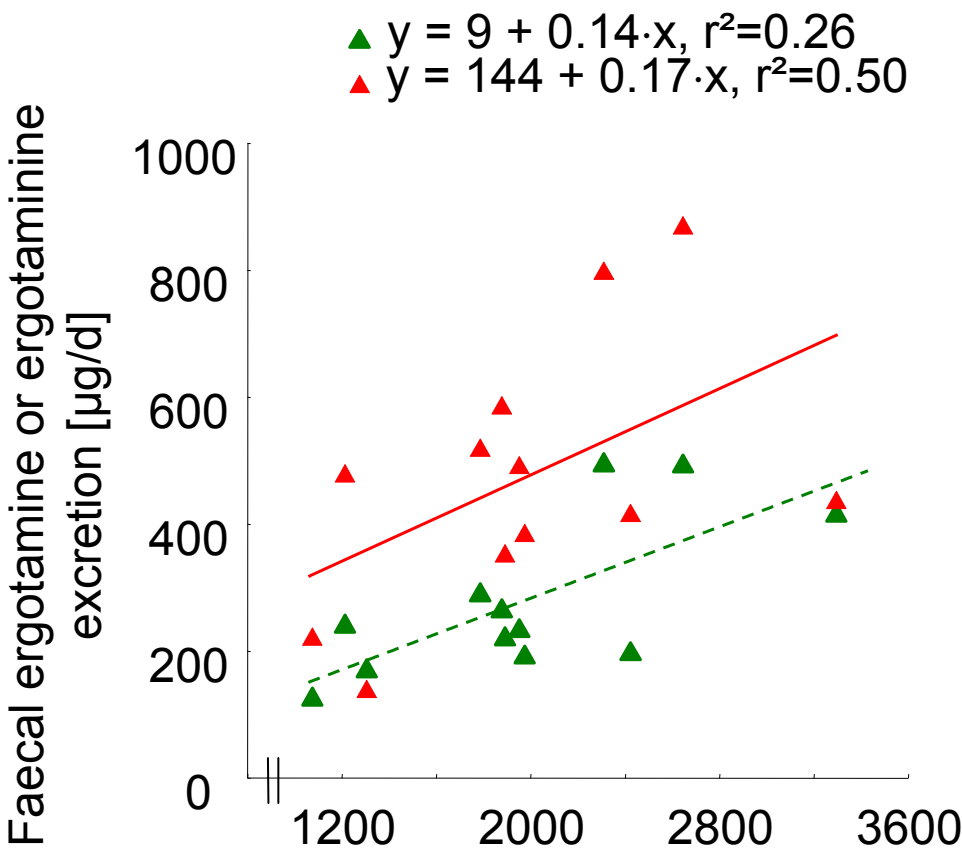
y = 74 + 0.35·x, r²=0.44



Ergotamine and ergotaminine flow at the duodenum of dairy cows in dependence on intake (left) and their faecal excretion in dependence on the corresponding flow at the duodenum (right) (Schumann et al., 2009)

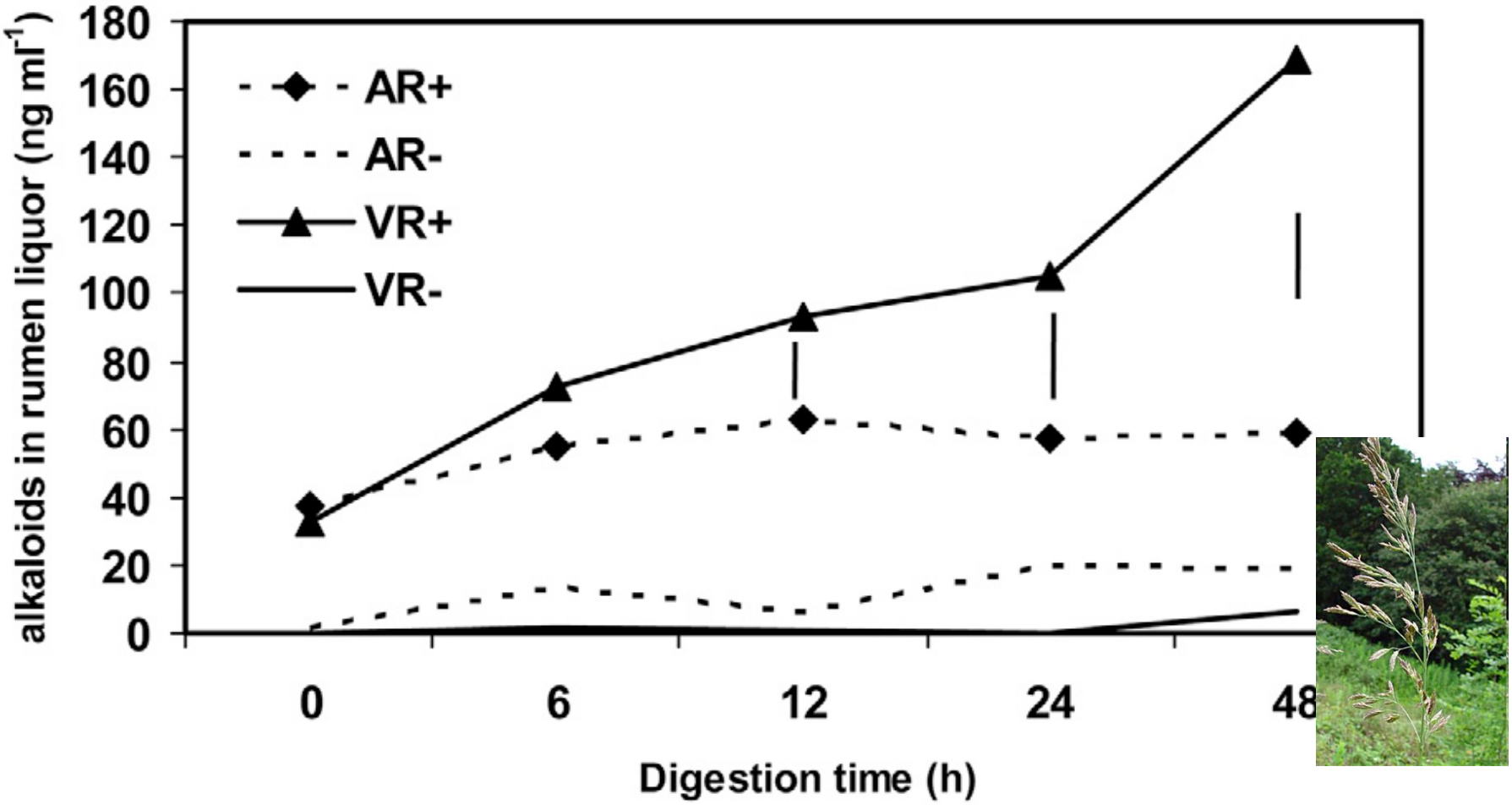


Ergotamine and ergotaminine intake [µg/d]

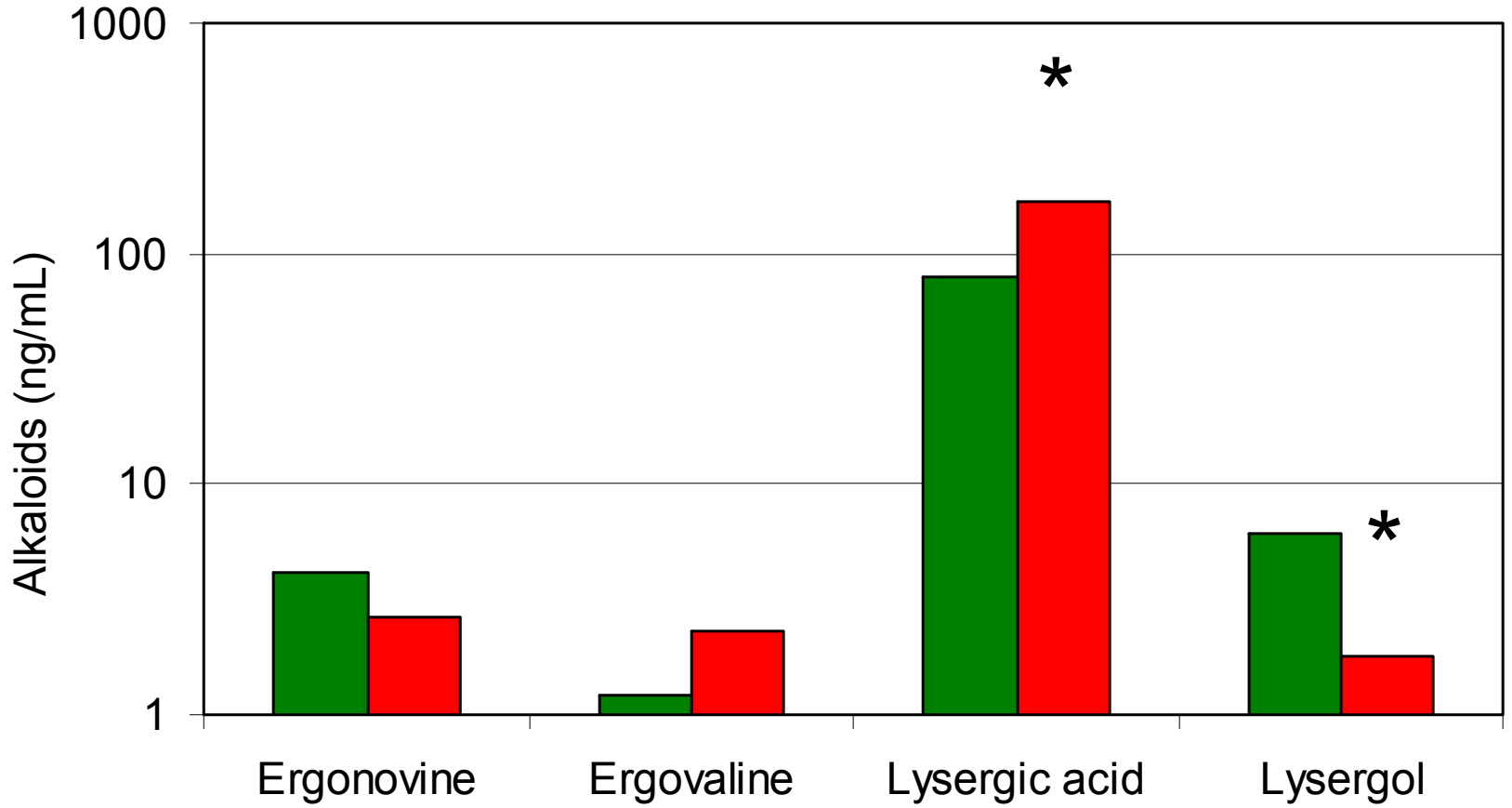


Ergotamine and ergotaminine flow at the duodenum [µg/d]

Total ergot alkaloids in rumen liquor inoculated with autoclaved (AR) or viable (VR) ruminal fluid for both endophyte-infected (+) and endophyte-free (−) tall fescue plant tissue sampled over a 48-h digestion period (Ayers et al, 2009)



Ergot alkaloids following extracted from ruminal fluids in which endophyte-infected tall fescue was fermented for 0 or 48 h (Ayers et al, 2009)



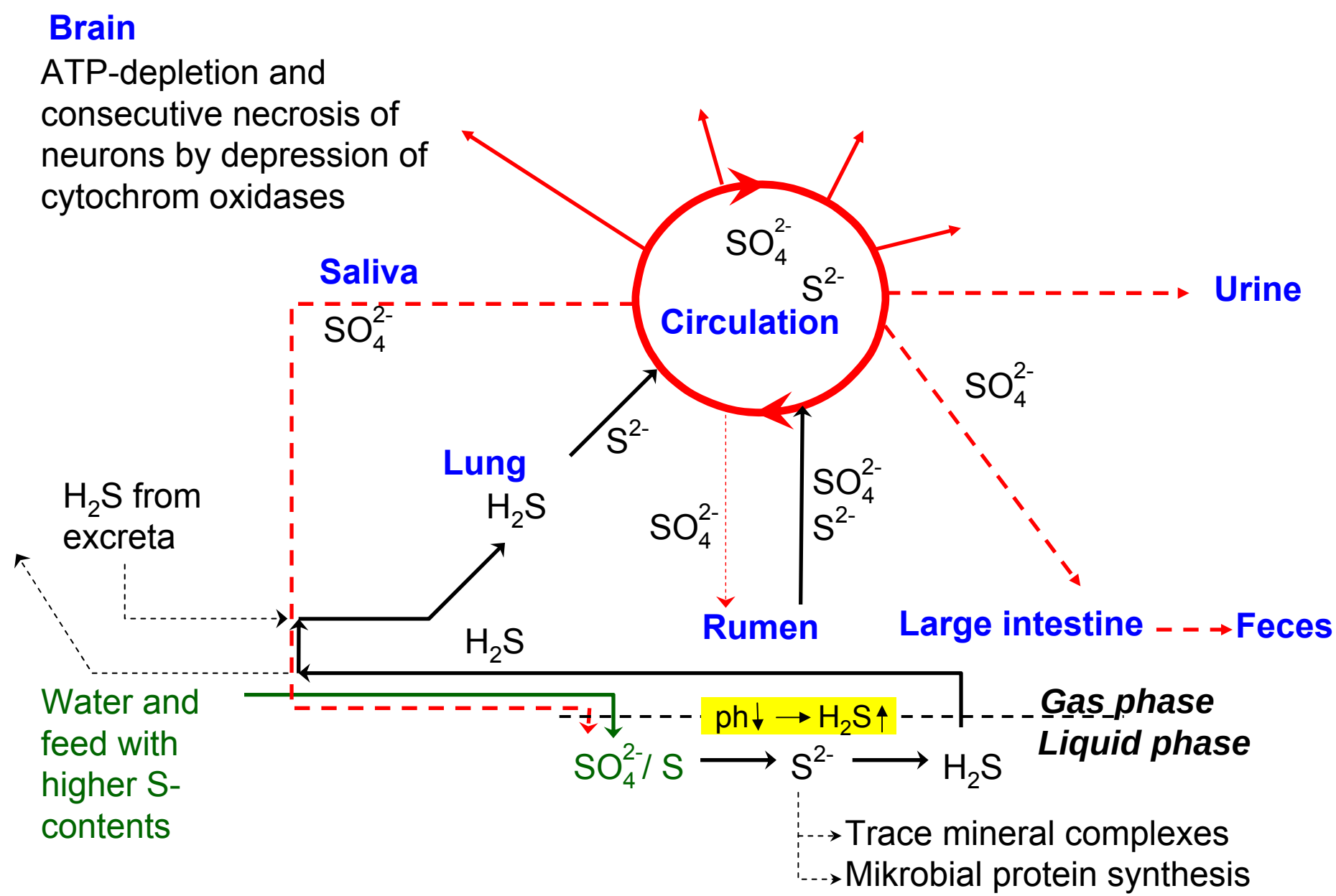
* Significantly different from **0 h** (without incubation)

Consequences of ruminal metabolism of certain compounds for ruminant health: Dark: Potentially adverse Bright: Potential benefits

Mother substance	Main rumen metabolites	Dark	Neutral	Bright
Formononetin	Equol	x		
Biochanin A	p-ethylphenol			x
Zearalenone	α-zearalenol (ZOL), β-ZOL		x	x
Deoxynivalenol (DON)	De-epoxy-DON			x
Pyrrolizidine alkaloids	Methylated derivatives			(x)
Ergovaline	Lysergic acid	x		
Ergotamine	Ergotaminine, lysergic acid (?)	x	x	
Sulfur (in excess)	Sulfur hydrogen	x		
Tryptophan	3-methylindole	x		
PCDDs/PCDFs[1]	~		x	

[1]polychlorinated dibenzo-para-dioxins/ polychlorinated dibenzofurans
Note: Adaptation to the respective substrates and the surrounding milieu which can largely be modified by feeding might contribute to the overall effects.

Sulfur toxicity for ruminants (literature compilation)



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Sulfur (in excess)	Sulfur hydrogen	x		
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PCDDs/PCDFs[1]	~		x	

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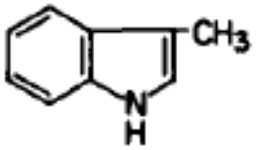
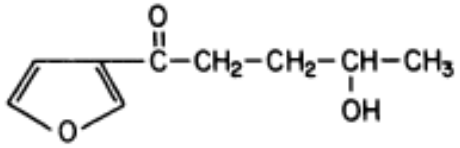
Tryptophan and 4-ipomeanol induced acute bovine pulmonary edema and emphysema (ABPE)



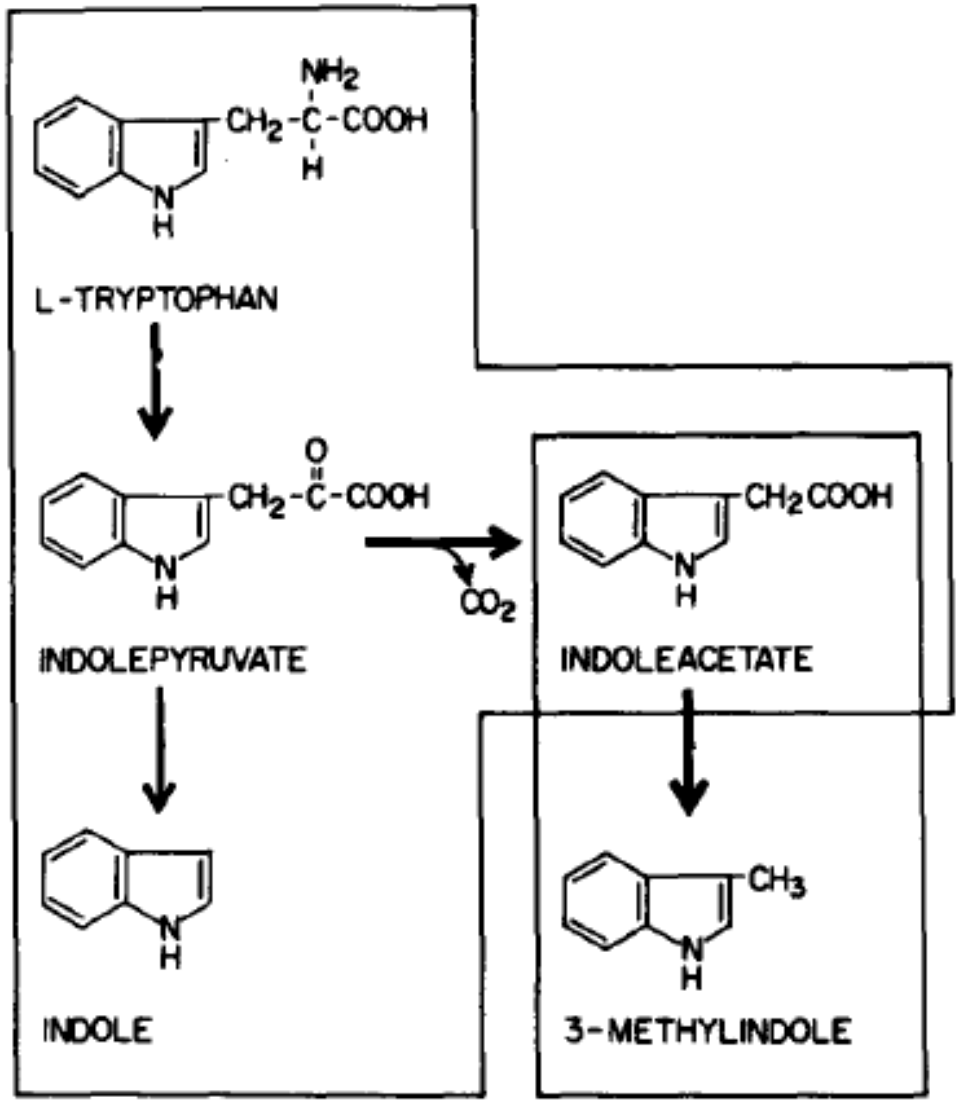
3-METHYLINDOLE

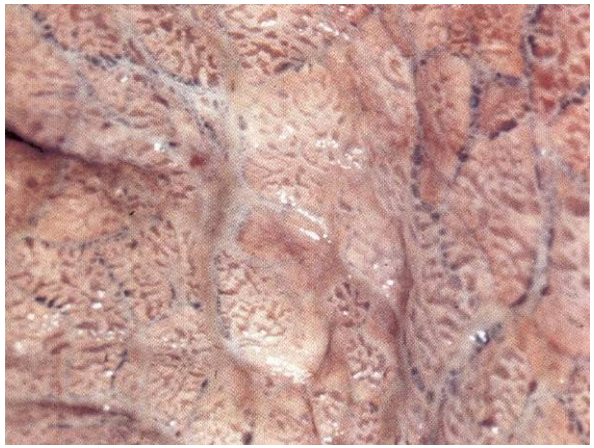


4-IPOMEANOL

Clinical symptoms include increased respiration rate and labored breathing. In severe cases, there is an expiratory "grunt", frothing at the mouth and the head is extended and lowered.

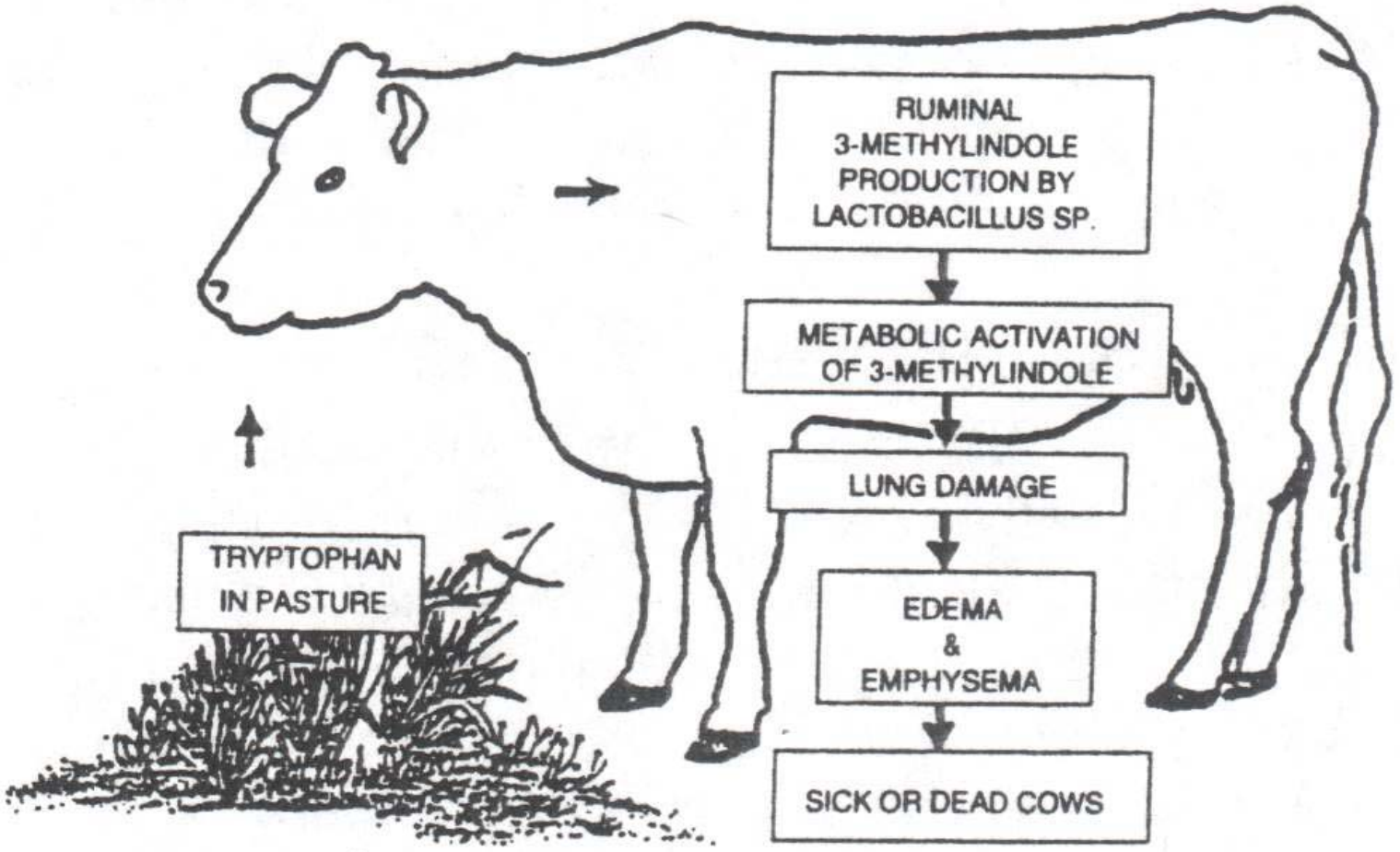
Summary of tryptophan fermentation by ruminal bacteria leading to the formation of the lung toxic 3-methylindole (Carlson and Breeze, 1984)





Acute bovine pulmonary edema and emphysema (ABPE) (Trachea and lungs)

Acute Bovine Pulmonary Edema and Emphysema – Summary of pathogenesis



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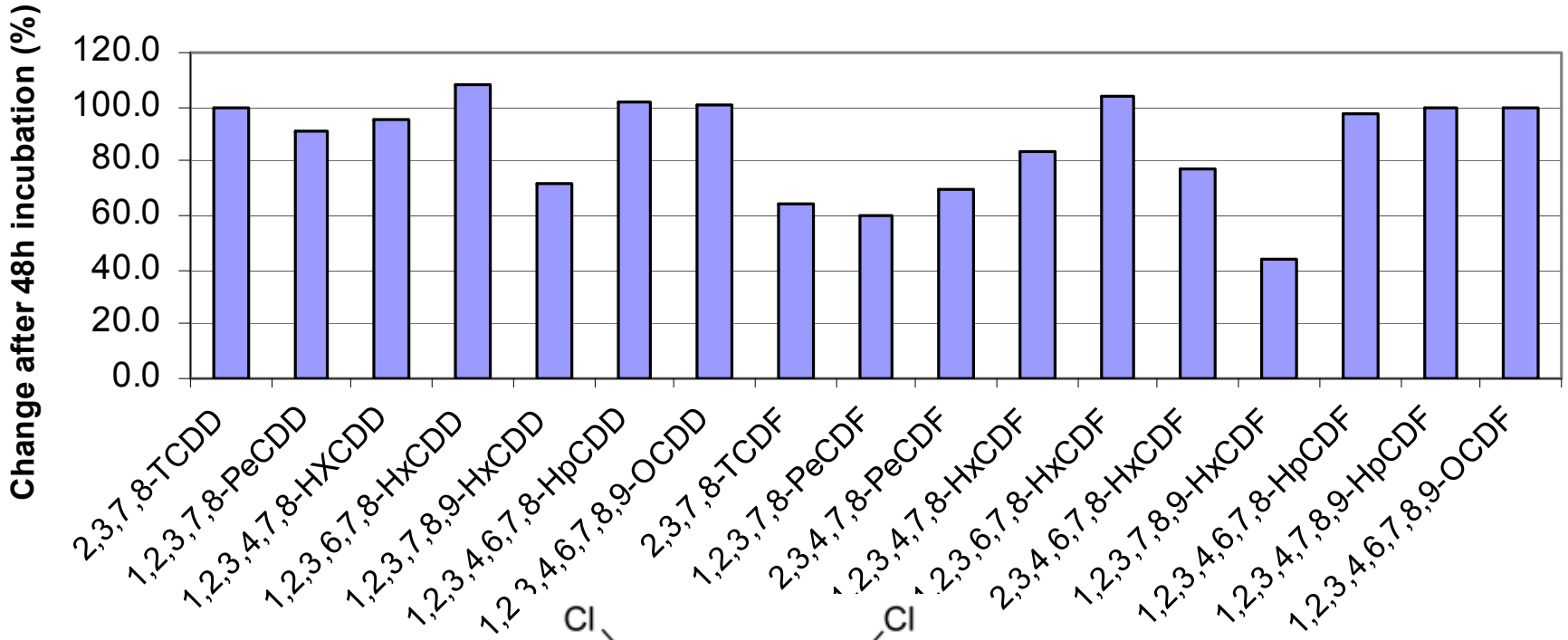
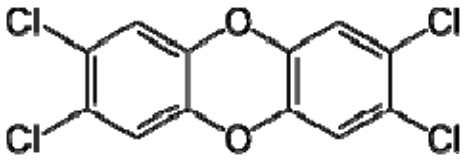
Pyrrolizidine alkaloids	Methylated derivatives			(x)
Ergovaline	Lysergic acid	x		
Ergotamine	Ergotaminine, lysergic acid (?)	x	x	
Sulfur (in excess)	Sulfur hydrogen	x		
Tryptophan	3-methylindole	x		
PCDDs/PCDFs[1]	~		x	

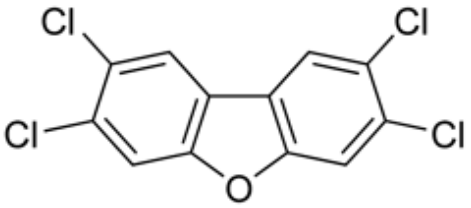
[1]polychlorinated dibenzo-para-dioxins/ polychlorinated dibenzofurans
Note: Adaptation to the respective substrates and the surrounding milieu which can largely be modified by feeding might contribute to the overall effects.

Concentrations of various dioxins due to the fermentation of pentachlorophenol-treated wood by rumen microorganisms *in vitro* (Fries et al., 2002)





2,3,7,8-TCDD



2,3,7,8-TCDF

Each fermentation sample contained 0.5 g of substrate, which was 1% PCP-treated wood in ground hay. Fermentations were stopped by acidification to pH 2.

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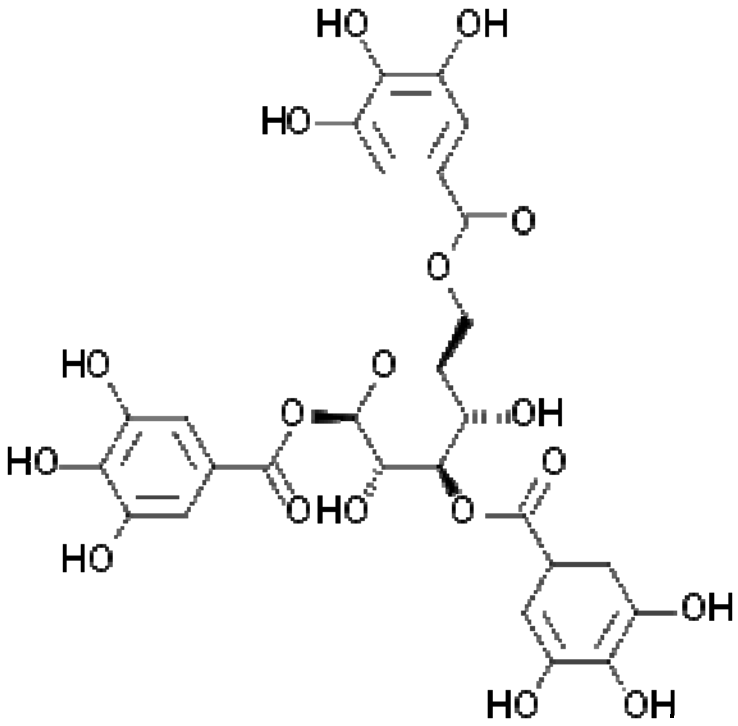
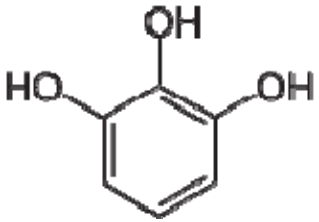
PCDDs/PCDFs[1]	~		x	

[1]polychlorinated dibenzo-para-dioxins/ polychlorinated dibenzofurans
Note: Adaptation to the respective substrates and the surrounding milieu which can largely be modified by feeding might contribute to the overall effects.

Conclusions

- The rumen bears the potential for inactivation of a number of substances while others might become undesirable by ruminal action.
- Adaptation to the respective substrates and the surrounding milieu which can largely be modified by feeding might contribute to the overall effects.
- "Bright side" substances, which are readily detoxified by ruminal action can be fed to ruminants while "dark side" substances have to be avoided.





Corilagin (=Gallotannin)

pyrogallol

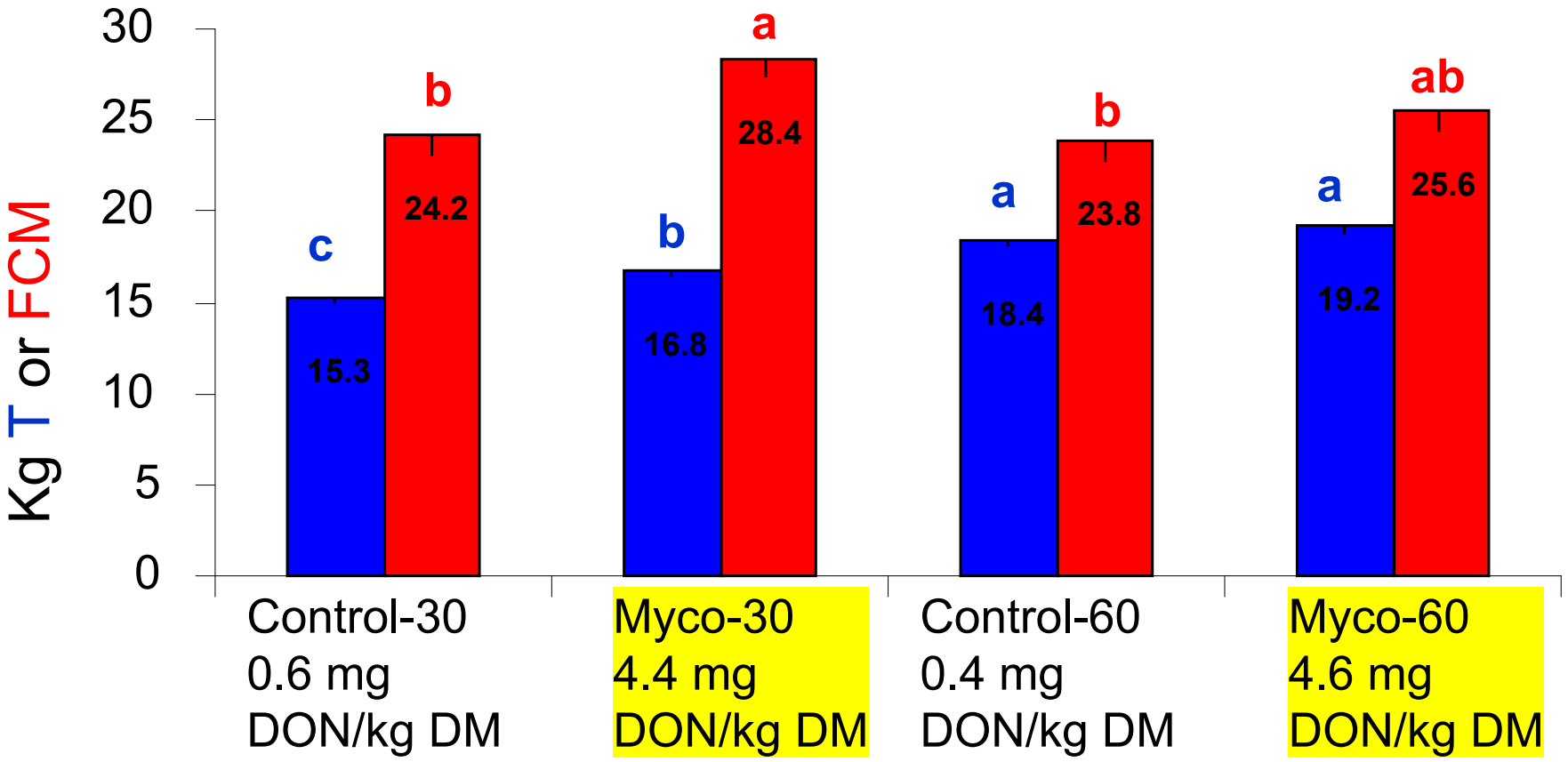
Effects of pure isoflavones (after Stob 1983)

Animal	Compound	Dose	Effect
Mouse	biochanin A	10–40 mg/g diet	uterine hypertrophy
	daidzein	5–15 mg/g diet	uterine hypertrophy
	formononetin	15–40 mg/g diet	uterine hypertrophy
	genistein	5–20 mg/g diet	uterine hypertrophy
	genistein	15 mg/day, diet	infertility, both sexes
	genistein	10 mg injected	displacement of oestradiol from uterine receptors
	genistin	5 mg/day, diet	uterine hypertrophy
	genistin	0·2% diet	infertility, females
	genistin	9–72 mg/day, diet	testes atrophy, depressed growth
Rat	genistein	0·5% diet	testes atrophy, depressed growth
	genistein	0·4 mg, injected	increased protein, phospholipid synthesis in uterus
	genistin	0·5% of diet	testes atrophy, depressed growth
Sheep	biochanin A	1 g, injected	uterine hypertrophy
	formononetin	24 g, injected	uterine hypertrophy
	genestein	1 g, injected	uterine hypertrophy

Oestrogenic isoflavone content of soya and its products (Price and Fenwick, 1985)

Sample	Daidzin (mg/100 g)	Daidzein (mg/100 g)	Genistin (mg/100 g)	Genistein (mg/100 g)
Soyabean meal	62	48	127	40
Soyabean meal	11·7, 0	0, 2·2	74·7, 102·4	4·0, 2·4
Soyabean meal	56·7, 56·1	4·9, 14·5	65·5, 81·3	9·7, 18·7
Soyabean meal	42	17·8	151	108
Soyabean flakes	59·6 ± 8	5·6 ± 0·7	215 ± 9	6·7 ± 8
Soyabean flour	48–77	8–48	58–154	4–46
Soyabean cake		30 ± 5		18·6 ± 2·7
Soyabean flakes	114	2·5	188·5	4·4
Soya-based animal ration	7		42–45	7

Neither the DM intake nor the FCM were negatively influenced by feeding a deoxynivalenol (DON) contaminated triticale (n=8; 12.-30. week in lactation) (Keese et al., 2008)



ab – Different superscripts denote significant group differences ($p<0.05$)

Schlussfolgerungen

Schwefel

Die **kritischen** Schwefelgehalte der Gesamtration liegen zwischen **0.3 und 0.5% in der T**. Bei der Überprüfung der Ration muss das Tränkwasser[1] mit einbezogen werden (Orientierungswert Tränkwasser: 500 mg Sulfat/L).

Deoxynivalenol (DON) und Zearalenon (ZON)

Bei Einhaltung der **Richtwerte** für kritische Konzentrationen von **5 mg DON und 0.5 mg ZON je kg Gesamtration (88% T)** ist nach experimentellen Befunden nicht von einer Beeinträchtigung der Leistung und Tiergesundheit auszugehen – Generell sollte eine Minimierung der DON- und ZON-Bildung auf dem Feld angestrebt werden.

Schlempen

Beim Einsatz von Schlempen (DDG bzw. DDGS) aus der Ethanolherstellung sind **erhöhte S-Gehalte** und die **Aufkonzentrierung von Mykotoxinen** aus Sicht der Futtermittsicherheit zu berücksichtigen!

[1] **Wasseraufnahme Milchkühe (kg/Tag)** = - 26,12 + **1,516 * mittlere Außentemperatur (°C)** + 1,299 * Milchmenge (kg/Tag) + 0,058 * Lebendmasse (kg) + 0,406 * Na-Aufnahme (g/Tag); (n = 12821, r^2=0,60, Meyer et al., 2008)

LD50-values of several PAs after intraperitoneal injection (WHO-IPCS, 1988)

PA	LD_{50} (mg/kg)
Retrorsine	34
Senecionine	50
Seneciphylline	77
Lasiocarpine	77
Symphytine	130
Monocrotaline	175
Senkirkine	220
Retrorsine *N*-oxide	250
Lasiocarpine *N*-oxide	547

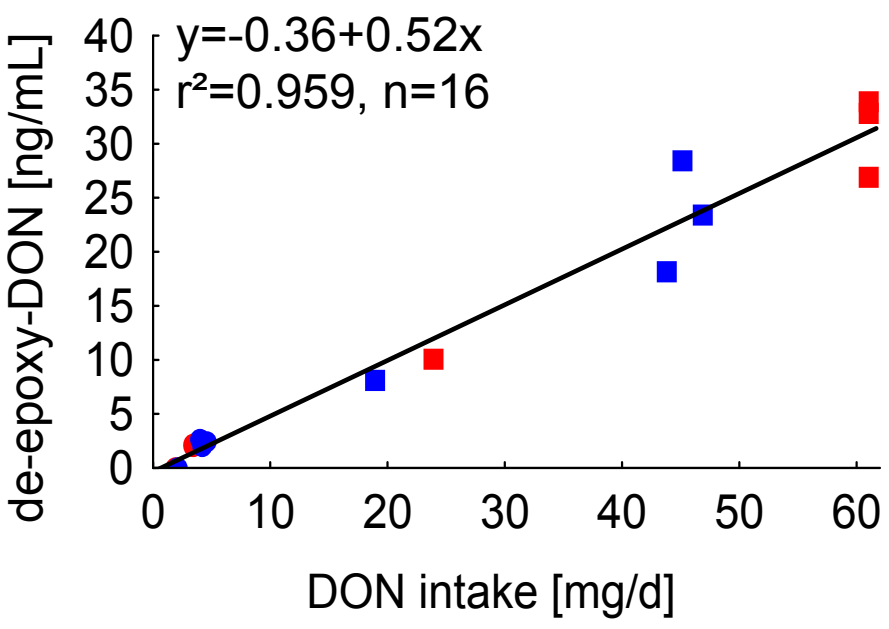
Ruminal degradation products of various mycotoxins and consequences for the toxicity

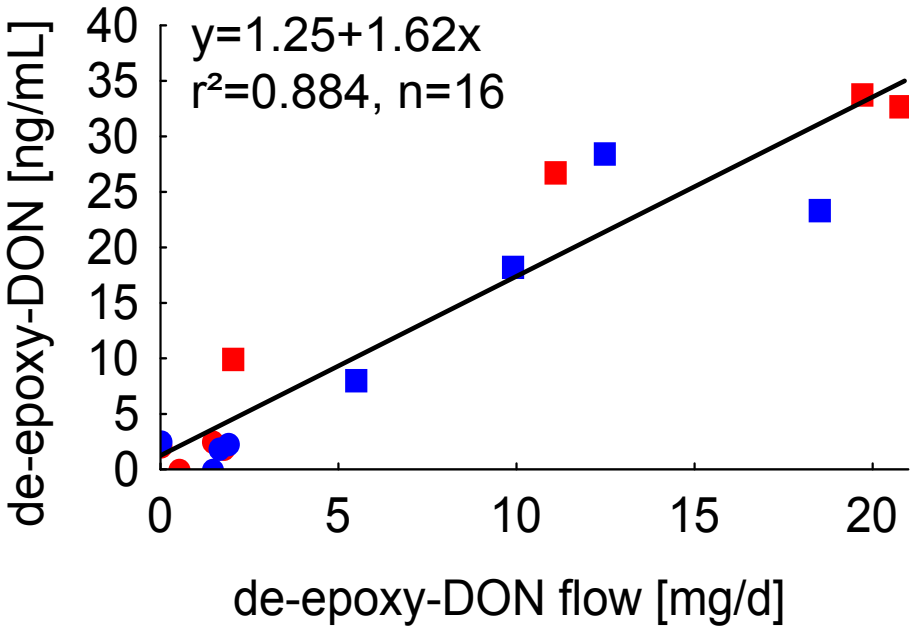
Ingested toxin	Ruminal toxin metabolites	Consequence for toxicity
Deoxynivalenol (DON)	De-epoxy-DON	↓
15-acetyl-DON, 3-acetyl-DON	DON, De-epoxy-DON	↓
Nivalenol (NIV)	De-epoxy-NIV	↓
T-2 Toxin	HT-2 Toxin, De-epoxy-HT-2 Toxin, T-2 Triol, De-epoxy-T-2 Triol	↓
Zearalenone (ZON)	α-zearalenol (ZOL), β-ZOL, zearalanone, α-zearalanol (ZAL), β-ZAL	=↑
Ochratoxin A (OTA)	OT-α	↓
Fumonisin B1	No metabolism	=
Aflatoxin B1	Aflatoxicol	=

↓ - Decrease, ↑ - Increase, = - no change

The degree of the ruminal metabolism is modified by general nutrition (e.g. ruminal pH-value, chymus-passage rate) and results in varying proportions of the initial toxin of the sum of the toxin and ist degradation products (Literature compilation)

De-epoxy-deoxynivalenol (DON) concentration in plasma in dependence on DON-intake (left) and on the de-epoxy-DON-flow at the duodenum (right)





● de-epoxy-DON, ○ DON – control – 30% concentrate
● de-epoxy-DON, ○ DON – control – 60% concentrate

■ de-epoxy-DON, □ DON – 3.3 mg DON/kg T – 30% concentrate
■ de-epoxy-DON, □ DON – 4.5 mg DON/kg T – 60% concentrate

Anaerobic metabolism or biotransformation of different concentrations of PA under denitrifying and methanogenic conditions (Craig et al., 1992)

Medium	Time required for complete PA disappearance at PA concn of[a]:				
	50 µg/ml	100 µg/ml	500 µg/ml	1,000 µg/ml	2,000 µg/ml
Denitrifying	NBD[b]	NBD	NBD	NBD	NBD
Methanogenic	24 h	24 h	48 h	7 days	NBD
McDougalls	24 h	24 h	48 h	7 days	NBD

[a] In all cases, autoclaved sterile controls failed to metabolize the amended PA.
[b] NBD, not biodegraded.

Note: Although there was a disappearance of PAs under methanogenic conditions no increase in methane formation was noticed which suggests that PAS were not completely mineralized but rather transformed to unidentified metabolites!

Relative Bindungsaffinität für den humanen Oestrogenrezeptor (Miksicek, 1994)

17β-Estradiol	1.0
Coumestrol	7.5
Zearalenon	80
β-Zearalenol	150
Genistein	250
Phloretin	250
Daidzein	1000
Biochanin A	20000

The RBAs were calculated as the concentration excess, relative to 17β-estradiol, required to give 50% inhibition of specific binding of 17β-[3H]estradiol to the estrogen receptor over expressed in COS-7 cells

Estimation of sulfur intake by a dairy cow

Feedstuff	Intake (kg T/d)	S (g/d)
Roughage	8 – 11	13 – 45
Concentrates for balance	2	3 – 18
Concentrates for milk yield	7 – 8	9 – 45
Minerals	0,2 – 0,3	2 – 4 (7-9 with acid salts)
Water	100 – 110 L	3 – 20
		30 – 132
Tolerance at 0.4 % S in the ration (20kg T/d)		**80**