Vitamin D and its Metabolites in Animal Health

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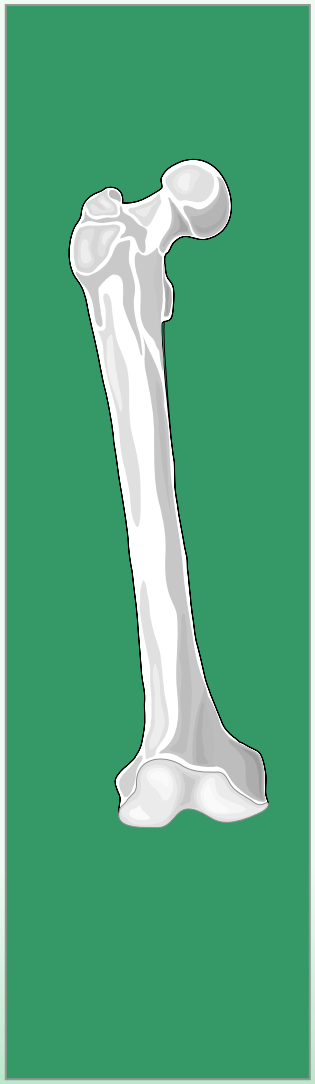
19. DERZSY NAPOK 2011

Growth, livability, and feed conversion of 1957 vs. 1991 broilers when fed typical 1957 and 1991 broiler diets.

Havenstein et al. Dept. of Poultry Science, North Carolina State University, USA

Breed	Diet	Weight [g] **Day 42**	Day 84	**Feed Conv.**	M[%]	**TD [%] (1991diet)**	TD [%] (1957diet)
1957	1957	**508**	1400	**3.00**	3.3	**1.2**	1.2
1991	1991	**2132**	4498	**2.04**	9.1	**48.6**	25.6

1957 Athens-Canadien Random breed (a typical 1957 breed)
1991 Arbor Acres (a typical 1991 breed)
M Mortalty
TD Tibial Dyschondroplasia



Calcium and its importance in bone quality

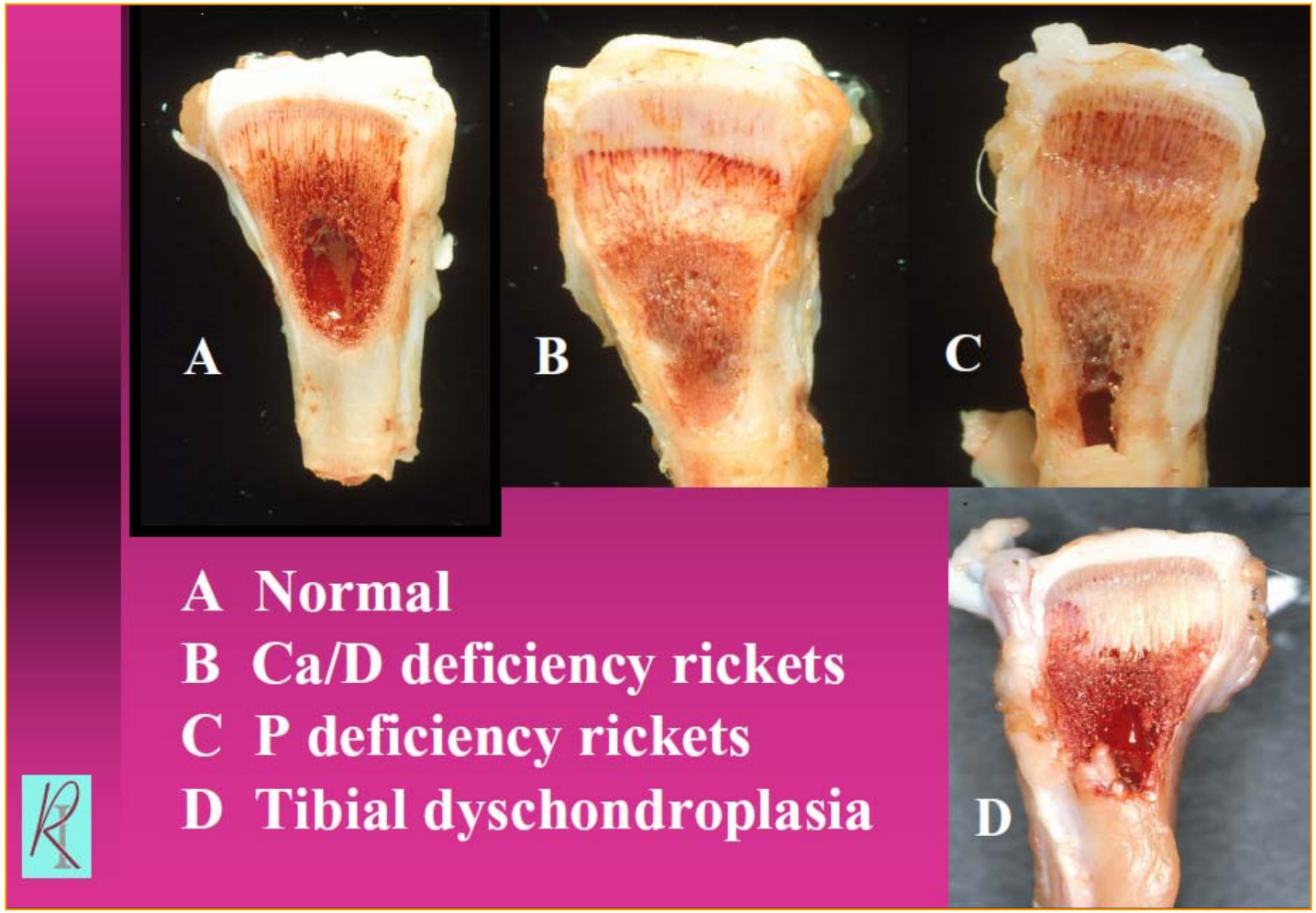
- Cortical and trabecular bone: Support function
- Medullar Bone: Mineral-pool with high turnover

Leg weaknesses

- different causes (genetics, feed, environment)

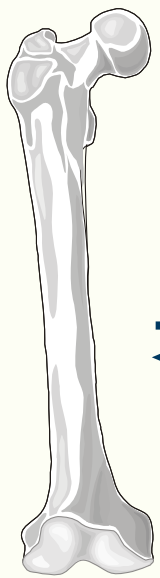
1. Bone growth disorders in young fast growing poultry, tibial dyschondroplasia as example
2. Osteoarthrosis (bone and joint disorderscaused by degenerative processes
3. Fractures because of osteoporosis in laying hens

leg problems in poultry rearing

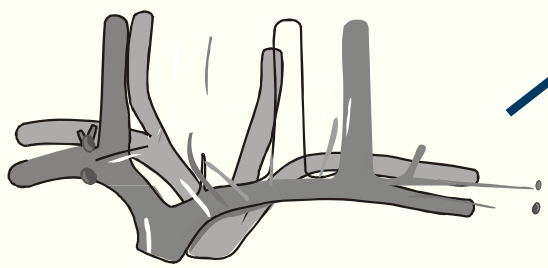


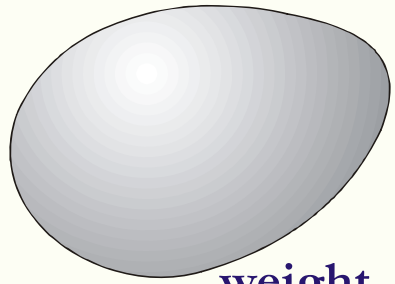
Courtesy by Prof. C. Whitehead

calcium turnover in the laying hen



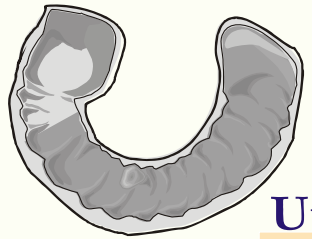
10-7 mol/L
>10-6 toxic





weight 55 - 70 g
shell 5 g
organic 4%
inorganic 95%
(calcite $CaCO_3$)

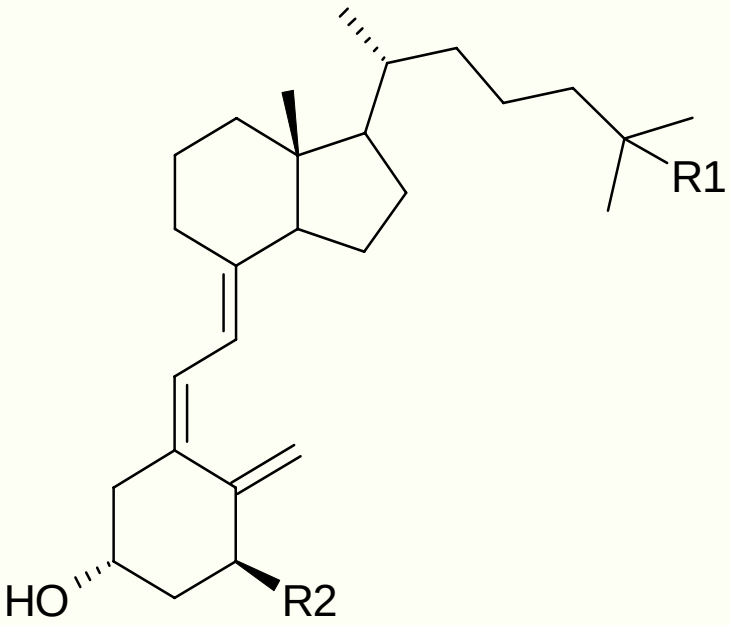
Ca^{++}
2.5 mmol/L



Hydroxylapatite:
$3*Ca_3(PO)_4*Ca(OH)_2$

Ca/P 2.5:1
95% of body Ca

Uptake:
Ca 4 - 5 g/d
P 0.4 g/d



R_1	R_2	
H	H	Vitamin D_3; Cholecalciferol
OH	H	$25(OH)D_3$, Calcidiol
OH	OH	$1\alpha,25(OH)_2D_3$, Calcitriol
OH	O-$[Gly]_n$	Calcitriol-glycosides (n = 1 - 10)

Activity:

Cholecalciferol (Vitamin D_3) **1 IU = 25 ng** official mass – activity relation

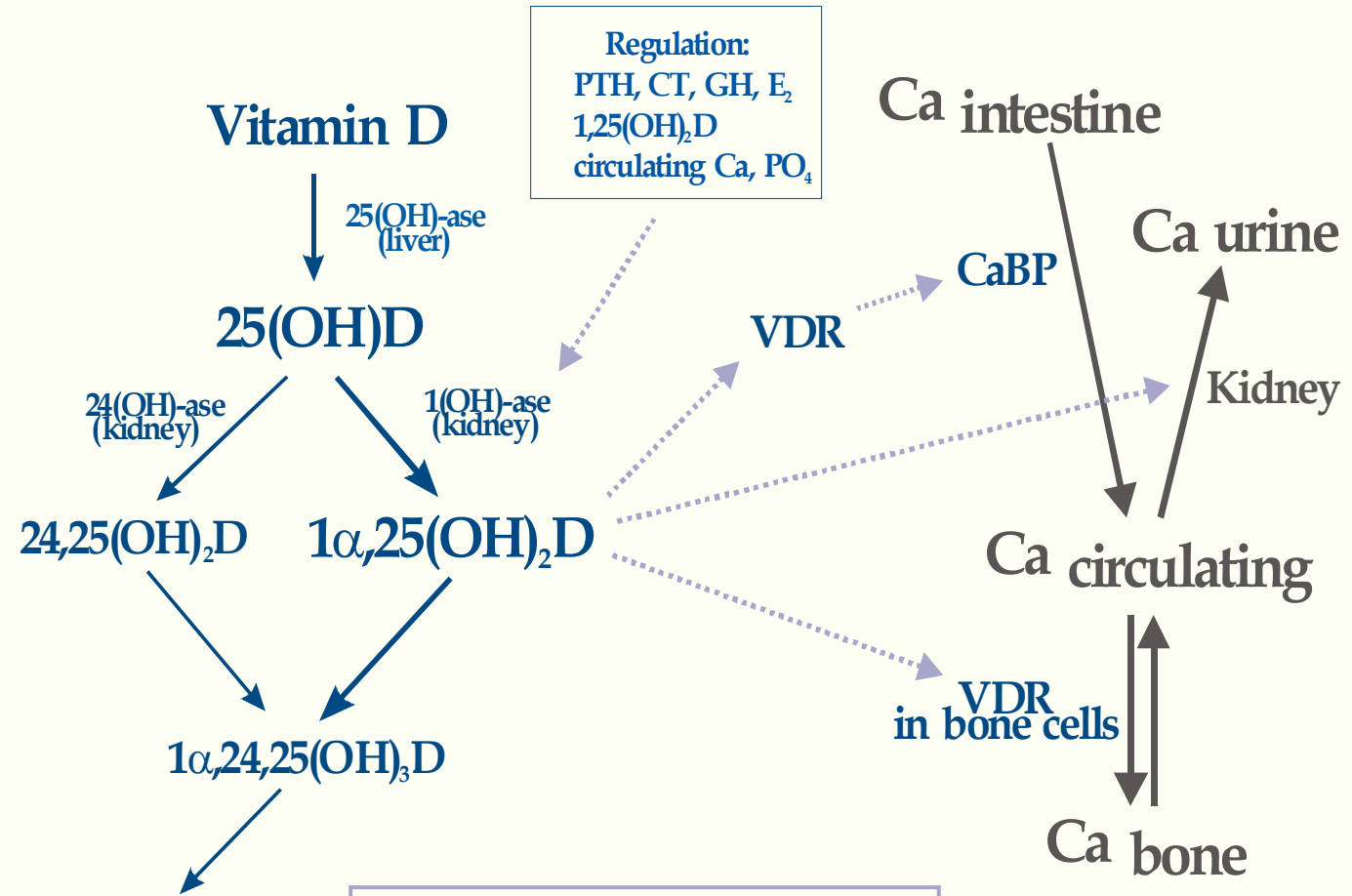
25-Hydroxyvitamin D_3 12 ng (2x more active, depending on biosassay)

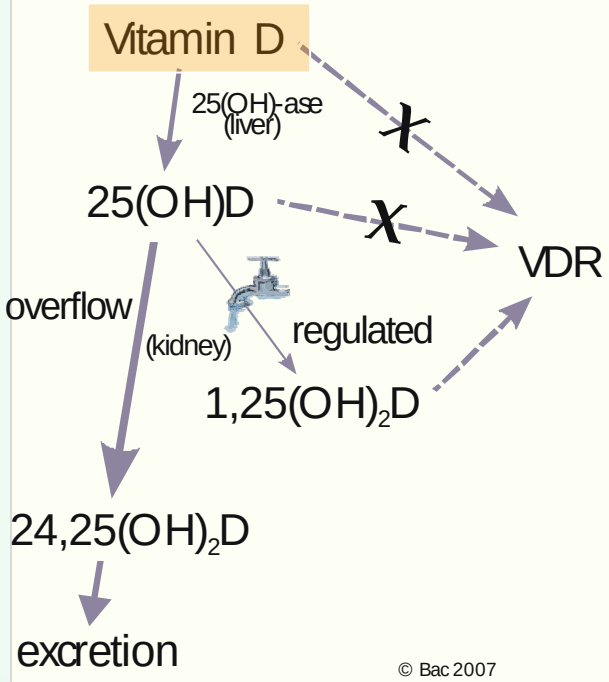
1,25-Dihydroxyvitamin D_3 5 ng (5x more active, depending on biosassay)

Ergocalciferol (Vitamin D_2) (10x less active in birds)

Herbonis

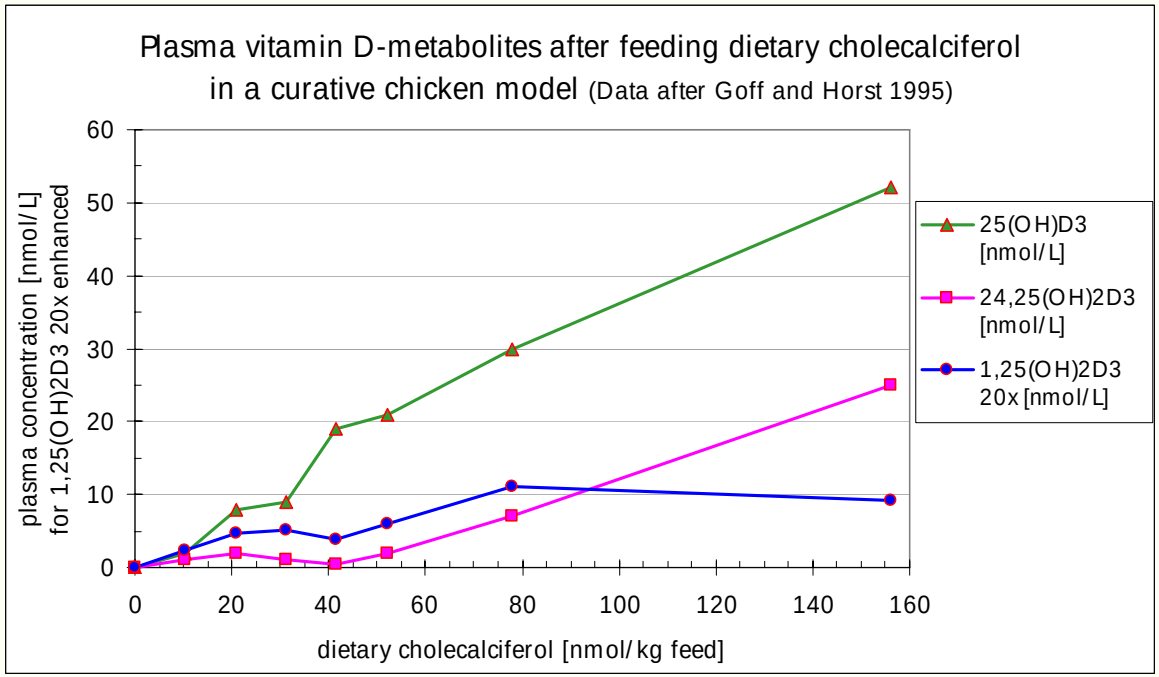
metabolism of vitamin D

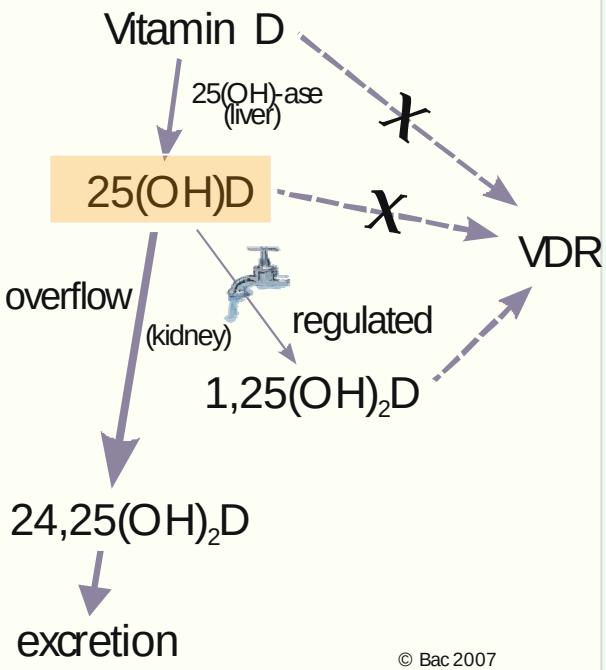




Vitamin D_3

- prevents and cures rickets
- but not tibial dyschondroplasia





25-Hydroxyvitamin D_3 (storage form)

- prevents and cures rickets
- improves performance
- tibial dyschondroplasia only partially
- Published experiments in peer reviewed journals
  - 75µg/kg is equipotent to 2µg/kg $1,25(OH)_2D_3$ (lowers incidence from 64% to 10%)
  - trials without effect

Fig. 3: Plasma levels of 25-hydroxy vitamin D (trial C0195)

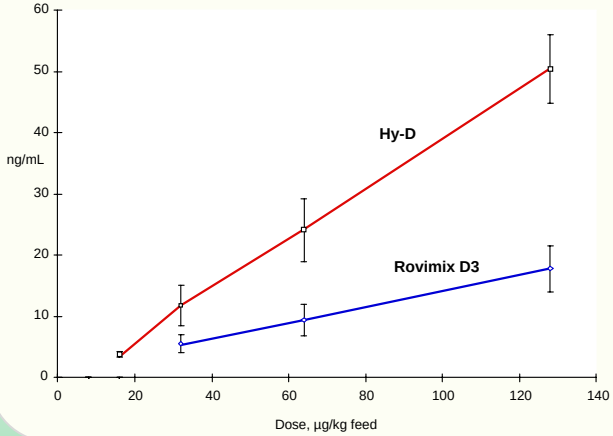
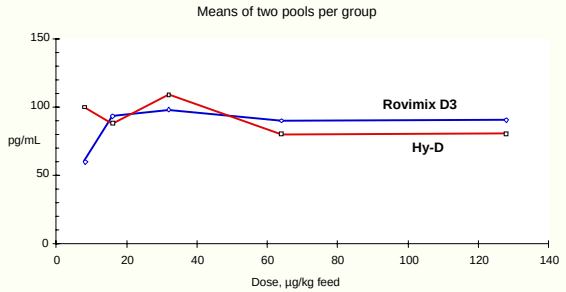


Fig. 4: Plasma levels of 1,25-dihydroxy vitamin D (trial C0195)



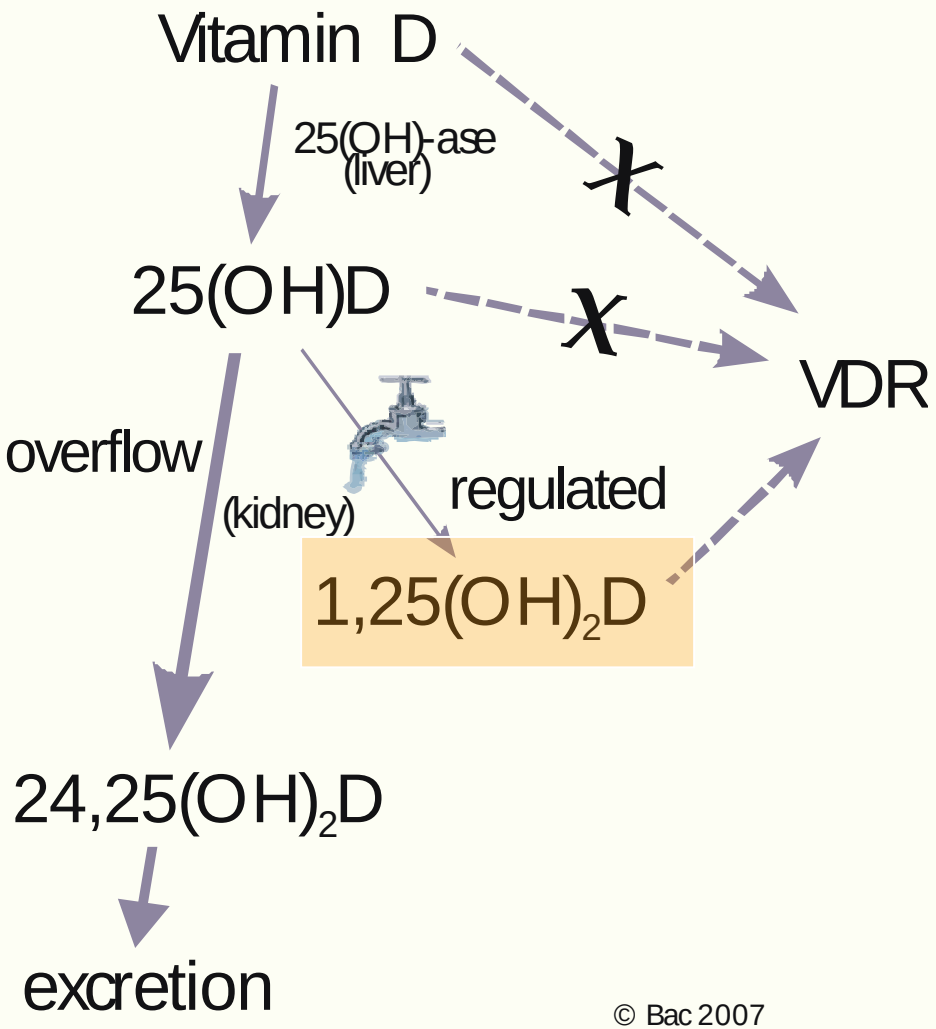
Herbonis

1,25-Dihydroxyvitamin D_3 (synthetic Calcitriol)

most active VDM, strictly controlled formation
genomic action through VD-Receptor in intestine
non-genomic ("fast") action in muscle and other tissue

- Cures rickets
- Most active compound in curing and preventing TD
  - Edwards et al. 10 µg/kg prevents TD
  - Whitehead et al. 2 µg/kg lowers TD from 25% -> 0%
- Active in improving egg shell strength
- Active in layer fatigue and osteoporosis (Whitehead et al.)

⇨ no product available for animal nutrition



Prevention of tibial dyschondroplasia or osteoporosis,
Egg shell quality

Slow processes may not be recognized by the calcium homeostatic regulation

$1\alpha,25(OH)_2D_3$, the active metabolite has a different quality of action

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Vitamin D from natural sources:

Sparse, fish liver oil is one of the richest source, because vitamin D is produced under the influence of sunlight by zoo- and phyto-plankton, the basis of the marine food chain.

Others (found in the 1980ties):

Solanum glaucophyllum		*Cestrum diurnum*
	Nicotiana sp.	
	Nierembergia veichtii	*Solanum lycopersicum*
	Trisetum flavescens	*alfaalfa*
most	10-50 times less	traces

Solanum glaucophyllum from the wild

cultivation

Herbonis

Solanum glaucophyllum

Wild forms and a cultivated variety, selected for high and uniform active content: Hervit® (non-GMO)

Active content:	wild:	VDM 0–20 ppm (as 1,25-Dihydroxyvitamin D_3)
	cultivation:	VDM 25-30 ppm
		>90% in glycosidic bound form
		<5% free 1,25-Dihydroxyvitamin D_3
		<5% 25(OH)D_3; vitamin D_3
Inactive content:		Primary plant metabolites, flavonoids

Toxic components: Jain et al.: alkaloid Solasodine

⇨ Hervit is controlled for a low alkaloid content and pesticides, heavy metals, microbial purity

Product characterization:

Active content:	1,25-dihydroxyvitamin D_3	specs; CoA
Inactive content:	Weende analysis	specs; CoA
Specific components:		pesticide residues by HPLC
	heavy metals	by AA
	microbial contamination	bacteriol.
	alkaloids	HPTLC, HPLC/MS
	others	HPTLC

Panbonis – Herbal Vitamin D_3

Standardized, formulated product for adding to feed

Content 10 ppm (as 1,25-Dihydroxyvitamin D_3)

Product properties:

Light green powder, particle size 100-500 µm (92%)

Good miscibility with feed

Storage stability (0 / 20 / 40 °C): 36mt >90%

Thermo stability at extruding, pelleting: >90%

Non-GMO product, controlled for heavy metals, pesticide residues and microbial contamination

Legal status:

CH	Registered as FA ‘Herbal Vitamin D’
EU	Notified as under Regulation EC767/2009 as SG standardized leaves
Asia	(Taiwan, Thailand, Malaysia, Japan) as ‘herbal FA’
SA	Brazil, Argentina, Chile, Mexico as ‘herbal FA’

Solbone-A-cws

A standardized, formulated extract with good cold water solubility

Content: 50 ppm (as 1,25-Dihydroxyvitamin D_3)

Application: via drinking water in poultry and swine rearing

Properties: Light brown powder with a malty taste
particle size 60-300 µm (90%)
Freely soluble in water to maximal 30% w/v

Storage stability:	0/20/40 °C:	24mt	>90%
Thermo stability:	100°C		>90%
Stability in water:	20°C (5 %),	3 days	>90%

Thermo stability solution 1g/L 120°C/3 min >80%

Registration:

CH	registration as FA in progress
EU	registration as FA in preparation
Asia	registered in Japan, Thailand others in progress
SA	registered in Brazil

Biological effects

herbal vitamin D_3 ($(1,25(OH)_2D_3$-glycosides)

- stable (storage, temperature)
- water soluble (Solbone-A-cws)

↓

in the Intestinal tract - 'slow release'

by digestive enzymes - broader tolerance

↓

free active Vitamin D

- natural active VDM
- fast onset of action

↓

resorption without overloading liver and kidneys

→

direct action on bones

- better Ca + P utilization

Poultry
- leg weaknesses in fast growing broiler chickens
- eggshell quality and osteoporosis of old laying hens

Swine
- calcium-related problems at farrowing
  - lactating sow
  - piglet survival

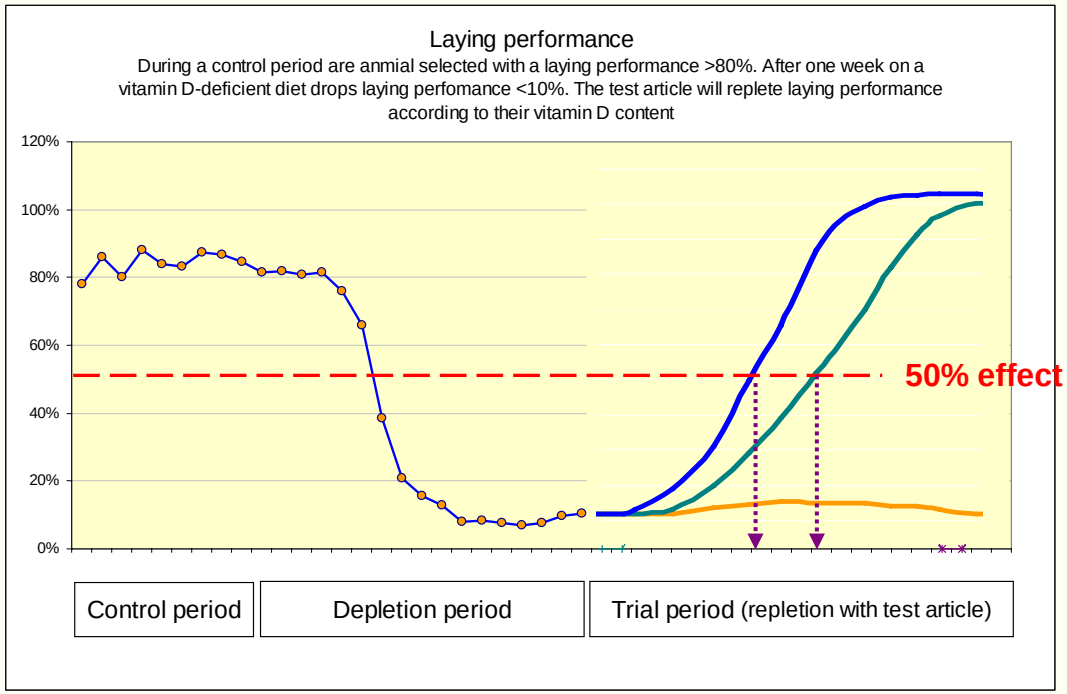
Ruminants
- calcium-related problems during calving
  - milk fever
  - meat quality

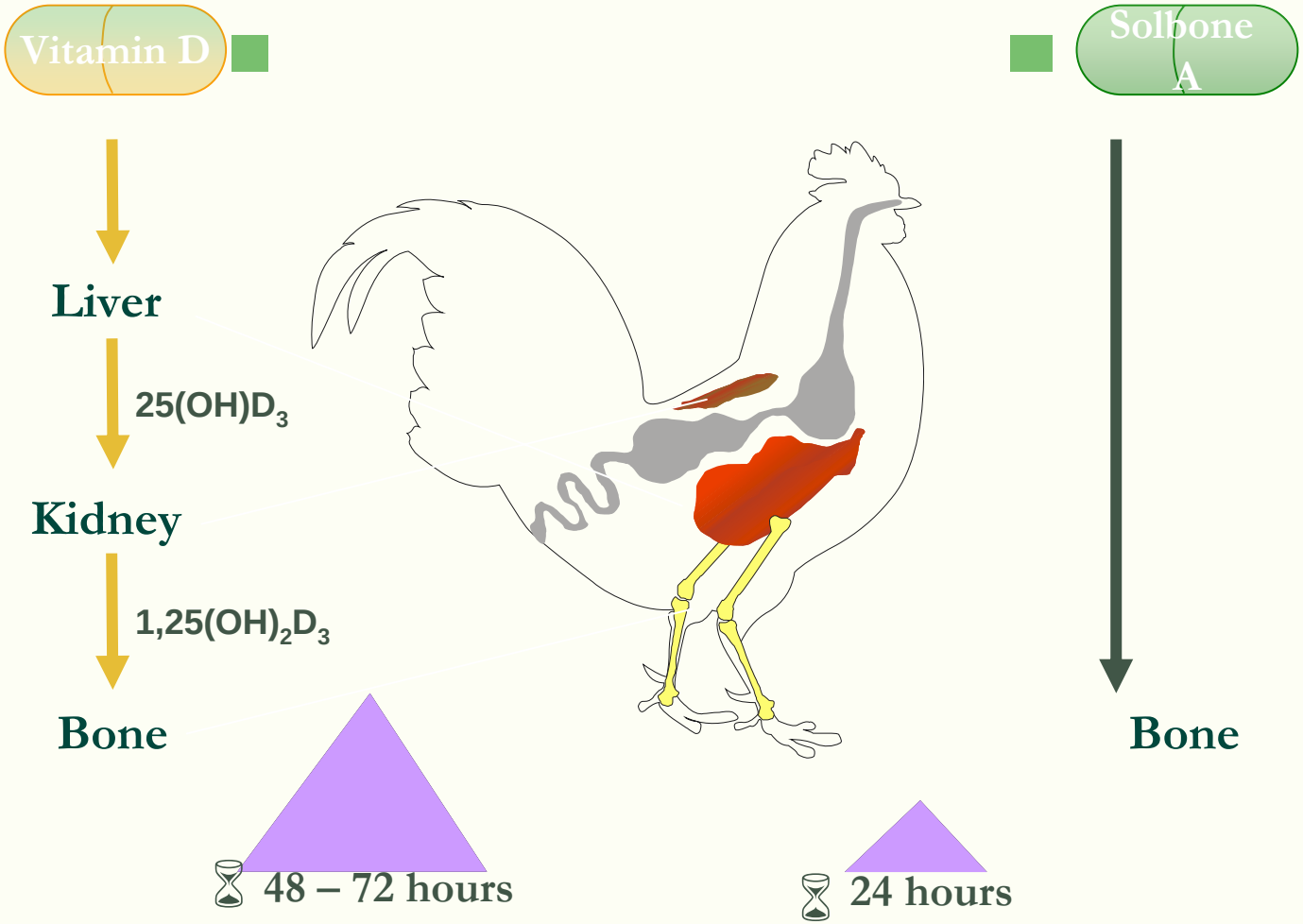
Others pets, horses (bone growth, osteoporosis, kidney insufficiency)

Bioassay for Vitamin D activity:

Japanese quail egg shell assay

Principle: Egg-laying quails are given vitamin D-depleted diet until laying performance drops to <10 %. Animals are then given the test diet for 3 weeks (LMU Munich, Germany)

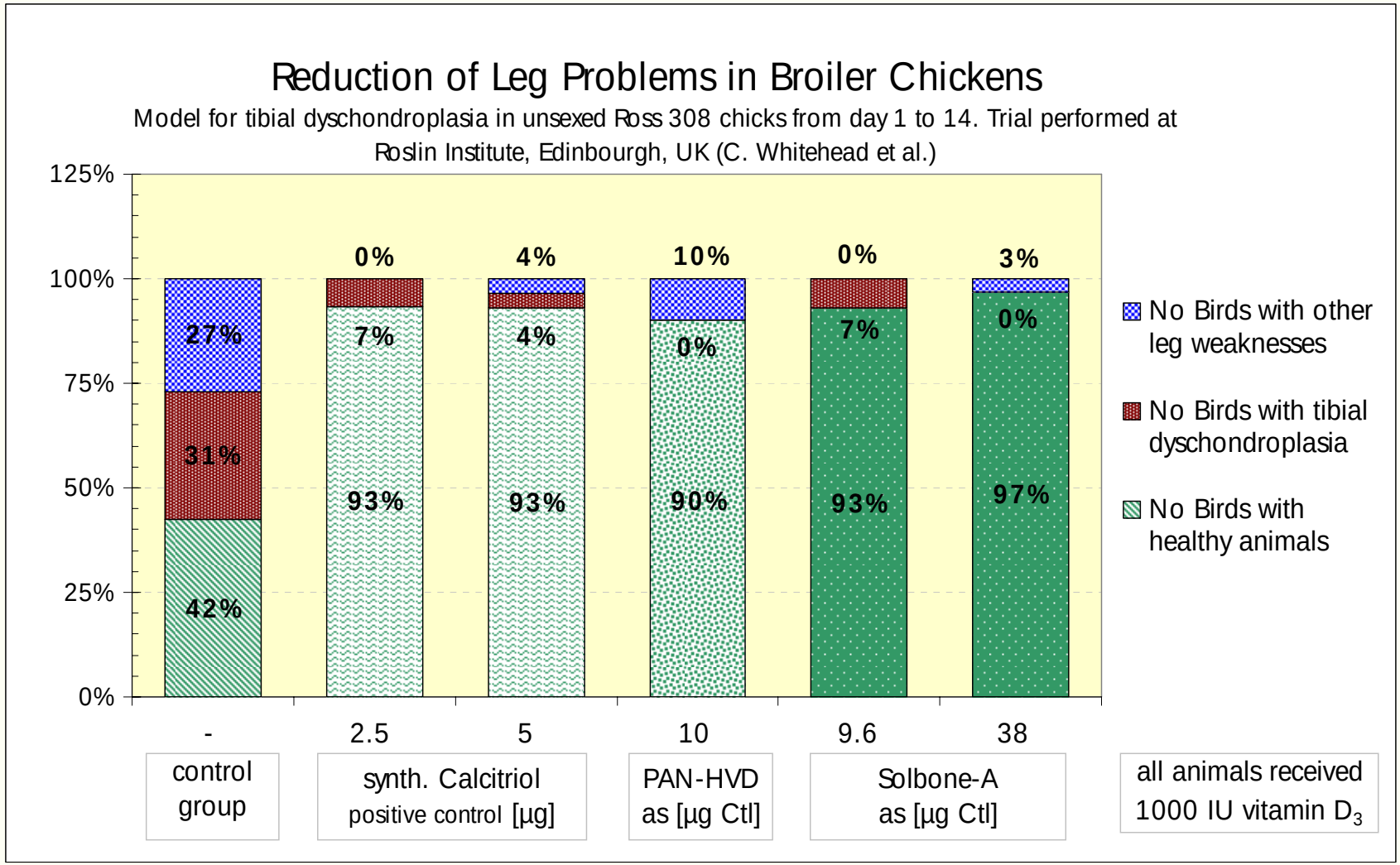



Vitamin D
Solbone A
Liver
25(OH)D3
Kidney
1,25(OH)2D3
Bone
Bone
48 – 72 hours
24 hours

Broiler trial: Preventing leg anomalies

Location:	Roslin Institute, Edinburgh, Scotland, Whitehead C et al.
Title:	Effects of vitamin D metabolites on bone
Objective:	Compare effectiveness of different vitamin D metabolite preparations on bone development
Procedure:	240 male day-old broilers (Ross 308). Basal (control) diet was set on all-vegetable broiler starter diet containing 8 g Ca, 6g available P and 1000 IU vitamin D/kg. Other diets obtained with appropriate supplements. Birds were fed on diets from one day old. At 14 days, proximal tibias were dissected for determination of TD incidence and severity and tibia breaking strength was measured.

effects: leg weaknesses



P and Ca balance trial in broiler chickens. Days 12-17 / 17-22

treatment	Ca % digest	P % digest	Ca % excret	P % excret
Control normal (P_{tot} = 0.66%)	0.51^{a}	0.43^{a}	0.47^{a}	0.40^{a}
Control P_{red} (P_{tot} = 0.50%)	0.37^{b}	0.47^{b}	0.46^{a}	0.22^{b}
P_{red} (P_{tot} = 0.50%)+ Panbonis 75 g/ft	0.43^{c}	0.42^{c}	0.42^{b}	0.20^{b}

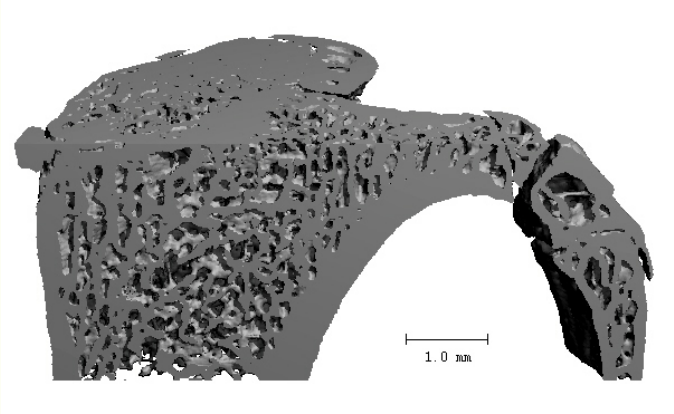
treatment	Ca_{ret} g/kg f	P_{ret} g/kg f	Pyt-P_{ret} g/kg f	diff
Control normal (P_{tot} = 0.66%)	4.55^{a}	2.83^{a}	1.29^{a}	
Control P_{red} (P_{tot} = 0.50%)	3.32^{b}	2.37^{b}	1.46^{a}	-
P_{red} (P_{tot} = 0.50%)+ Panbonis 75 g/ft	3.87^{c}	2.62^{c}	1.52^{b}	11%

Different letters $p<0.05$

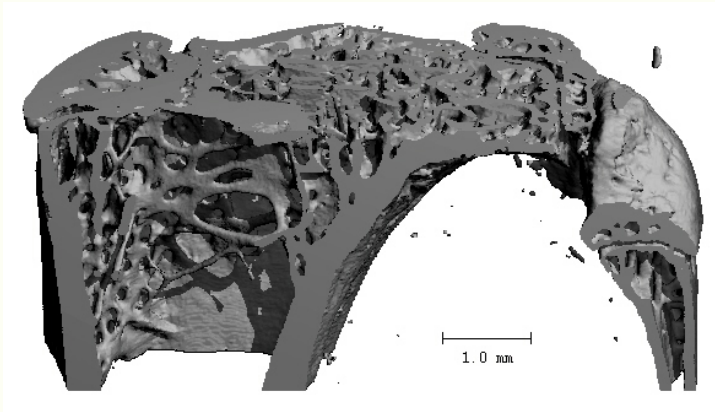
Same effect also published by Cheng et al. 1996

Herbal vitamin D_3 in a rat model for osteoporosis:

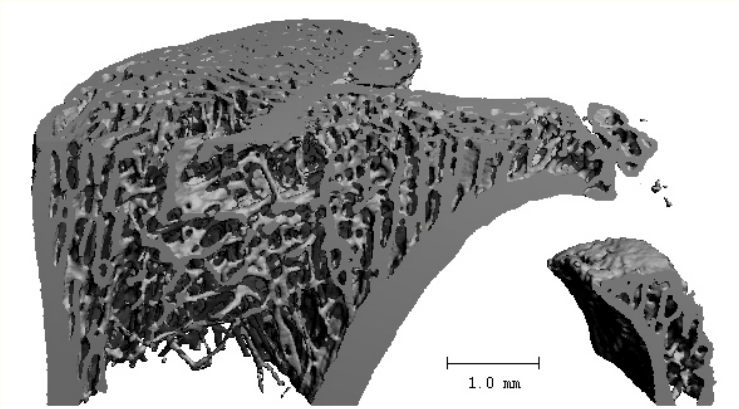
Normal (sham operated)



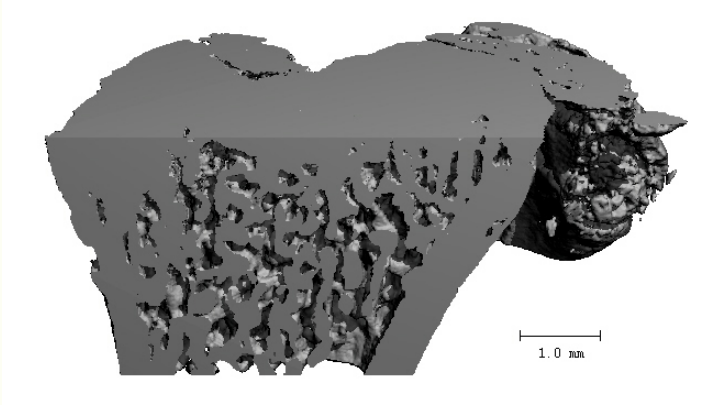
ovariectomized



Fosamax



Solbone



Safety

Herbal Vitamin D_3' safety:

In broilers:

Recommended dose: on top of usual Vitamin D_3:

<2'000 IUD/kg: 0.2 to 0.5 g/kg feed

>2'000 IUD/kg: 0.1 to 0.2 g/kg feed

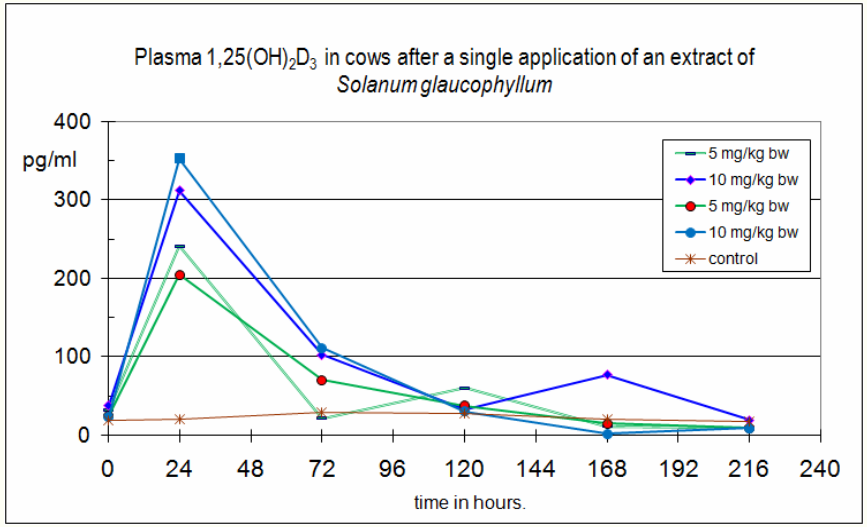
5 g/kg no adverse effect

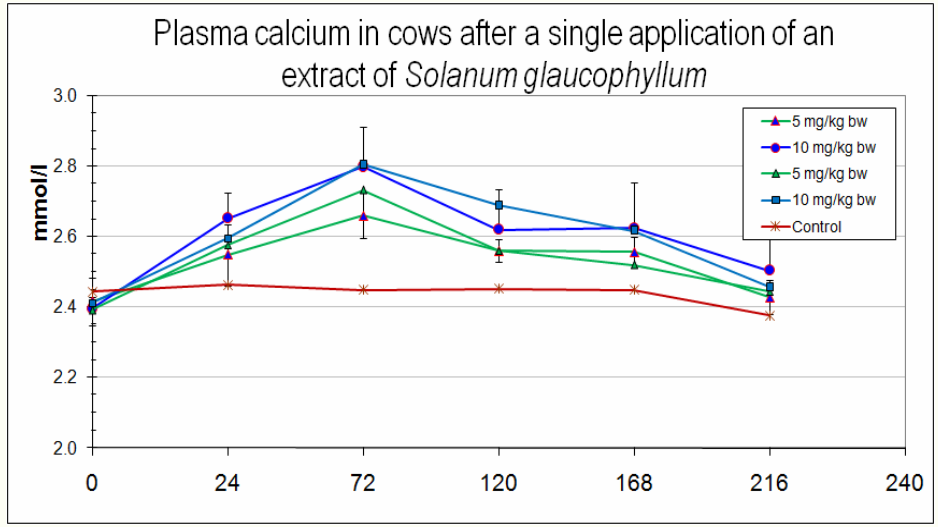
12 g/kg adverse effect level

- after day 14: reduced weight gain in half of animals
- at day 25: hypercalcemia
  blood calcium +38%
  animal weight –36%
  mortality 1.4 ⇨ 5.7%
- at day 38: recovery, normal blood calcium and growth curve after change to normal feed

Plasma kinetics after a single dose of an extract of *Solanum glaucophyllum* to cows

$1,25(OH)_2D_3$ Ca





	Biological actions				Molecular properties				Safety
	VD activity	R	TD[1)]	OP[2)]	Chem stab[6)]	Lipo[3)]	Tissue acc[4)]	Half-life[5)]	Tolerance[7)]
Vitamin D_3	full	Y	-	-	med	high	high	2 mt	20-50x
$25(OH)D_3$	full	Y	-	-	med	med	med	2 wk	5-10x
$1,25(OH)_2D_3$	full	Y	Y	Y	low	low	low	16 hr	5x
Herbal active VD	full	Y	Y	Y	high	low	low	16 hr	10-25x

1) TD: tibial dyschondroplasia
2) OP: osteoporosis
3) Lipophilicity: a measure for the fat-solubility - is the opposite of water-solubility.
4) Tissue accumulation: the tendency of a lipophilic molecule to dissolve in fat-rich tissue and thus accumulates in the body.
5) Half-life: time measure by which half of the applied compound is cleared from the body
6) Chemical stability: determines the storage stability and reactivity with feed components and heat stability at feed processing
7) Tolerance: the factor at which toxicity starts. Based on recommended doses of 2500 IU/kg for VD_3, 69µg/kg for $25(OH)D_3$, 5µg/kg $1,25(OH)_2D_3$ and 250, resp. 100mg/kg feed for Panbonis.)

Herbal active Vitamin D_3

Active agent is1,25-dihydroxyvitamin D_3, the most active natural VDM [1)] in man and animal with proven activity in:

- Bone-related effects
  - Cures vitamin D-deficiency (rickets) faster
  - Prevents leg weakness (tibial dyschondroplasia)
- Other benefits
  - Improves phosphorous absorption
  - Improves performance (1-8 %, weight gain and feed conversion)
  - Improves meat tenderness (in beef, data by Foote et al. 2004)

The present glycosidic form of the active vitamin D_3 shows a better safety profile than free 1,25-dihydroxyvitamin D_3,

The standardized and formulated product has a good stability (up to 3 years)

1) In glycosylated form, a naturally stabilized form

In conclusion, you have the choice of 3 different forms of vitamin D_3 each with it's merits:

Vitamin D_3	cheap; covers normal conditions, rickets
25-Hydroxyvitamin D_3	advantage in specific conditions: performance, mineral supply, rickets
Herbal active vitamin D_3	advantage in specific conditions: calcium uptake, bone health, phosphorus utilization, rickets

Thank you