Nutrition as a tool to modulate immunity in pigs and poultry: the potential of BUTYRATE

Guy Janssens
Nutritional Consultant

Natural ingredients … not exclusively used in (animal) nutrition….

Natural plant extracts for hair care …

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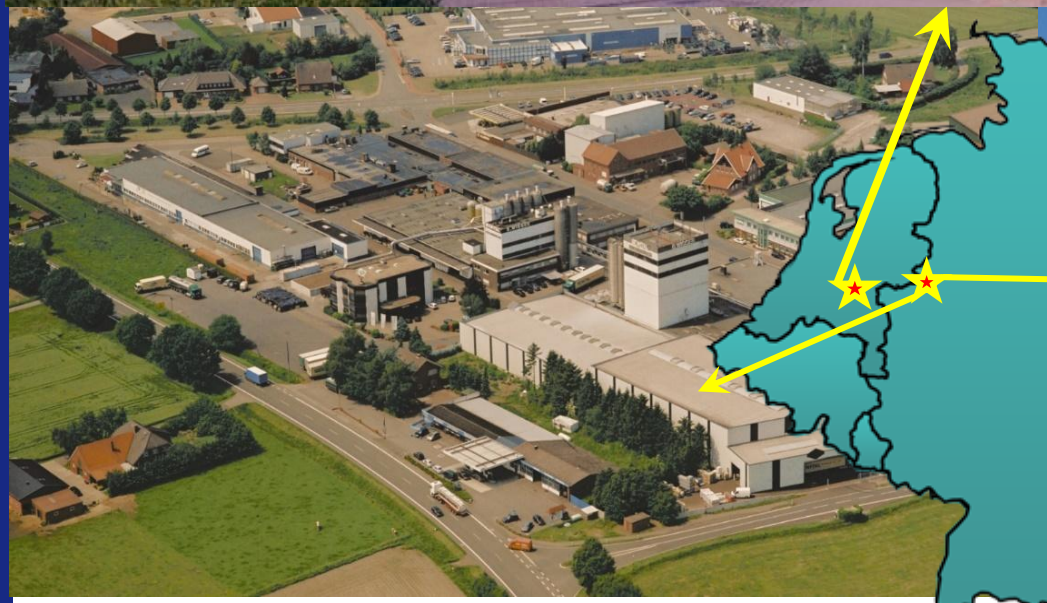
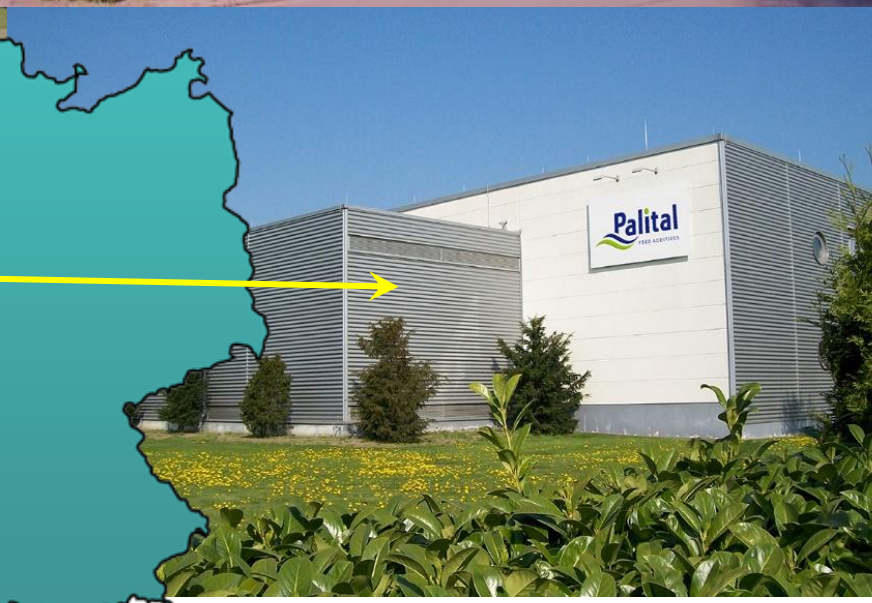
- **Palital Feed Additives**
  - Dutch / German joint venture (Paleon/Bewital)
  - Encapsulation and formulation specialist of feed additives
  - Base manufacturer of
    - Butyrates
    - Gradual release urea
    - Flavours & sweeteners
  - Vast experience and knowledge of the animal feed industry and additives





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Ecofos

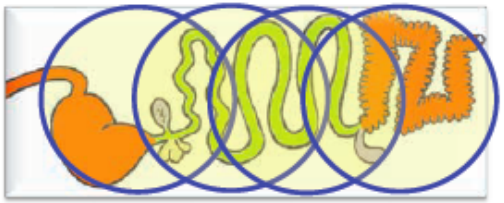
PALITAL partner in Chile

Bluetec SP

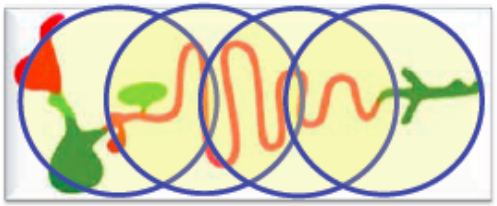
Aditivo Alimenticio

Complejo Inmunoestimulante Natural — Polvo

Efecto Bluetec en Cerdos



Efecto Bluetec en Aves



Bluetec SP es el suplemento alimenticio más completo que existe en el mercado, diseñado para entregar una serie de beneficios a animales monogástricos. Los componentes de **Bluetec SP**, de forma balanceada, actúan como un agente antimicrobiano, fuente de energía, hepatoprotector, inmunomodulador y, adicionalmente, mejorador del apetito.

Su exclusiva composición entrega resultados productivos óptimos: mejora la ganancia de peso, tasa de conversión alimenticia, reduciendo los efectos de infecciones, lo que se traduce en mejores rentabilidades.

Mezcla de aceites esenciales y extractos de plantas con alto efecto antimicrobiano que previene las infecciones por coccidias y reduce el riesgo de enfermedades gástricas.

Promotor de crecimiento, incrementa la palatabilidad de las dietas y mejora el sistema inmunitario.

Modula la microflora intestinal y la inmunidad local de la mucosa del tracto intestinal.

Actúa como precursor de las células epiteliales, mejorando la capacidad de absorción de los nutrientes, biodisponibilidad y permite una mejor salud intestinal.

No tiene período de retiro.

Contiene nucleótidos, levaduras y oligosacáridos que mejoran la inmunidad de los animales.

Permite una menor dependencia de antibióticos e incluso una producción libre de estos.

+Bluetec

Administración

Vía de Administración: Vía Oral, en el Alimento

Dosis: 0,5- 3,0 Kg/Ton de alimento

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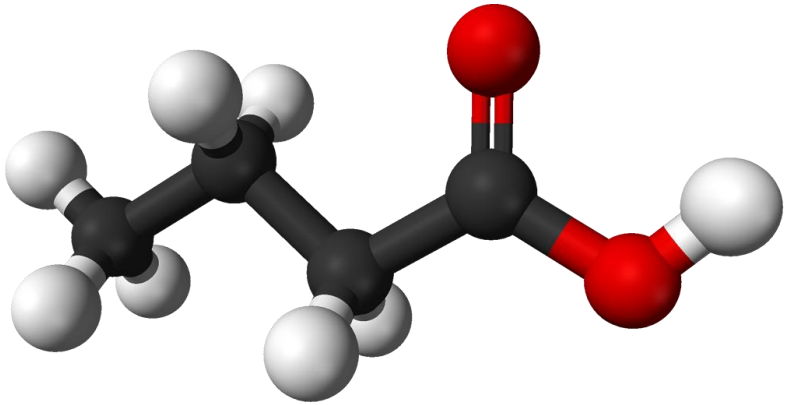
Spain has adopted a five-year plan to combat antimicrobial resistance.

Six strategies are included in this common plan for veterinary and human areas, aimed at promoting appropriate use, ensuring effective surveillance, promoting research and innovation, and the development of a communication and education plan.

www.aemps.gob.es/publicaciones/publica/

Butyrate:
an exceptional fatty acid

- Is the most biologically active short chain fatty acid;
- Is the end product of normal intestinal fermentation (by bacteria);
- Is a natural attractant at low concentration;
- Has an unpleasant smell;



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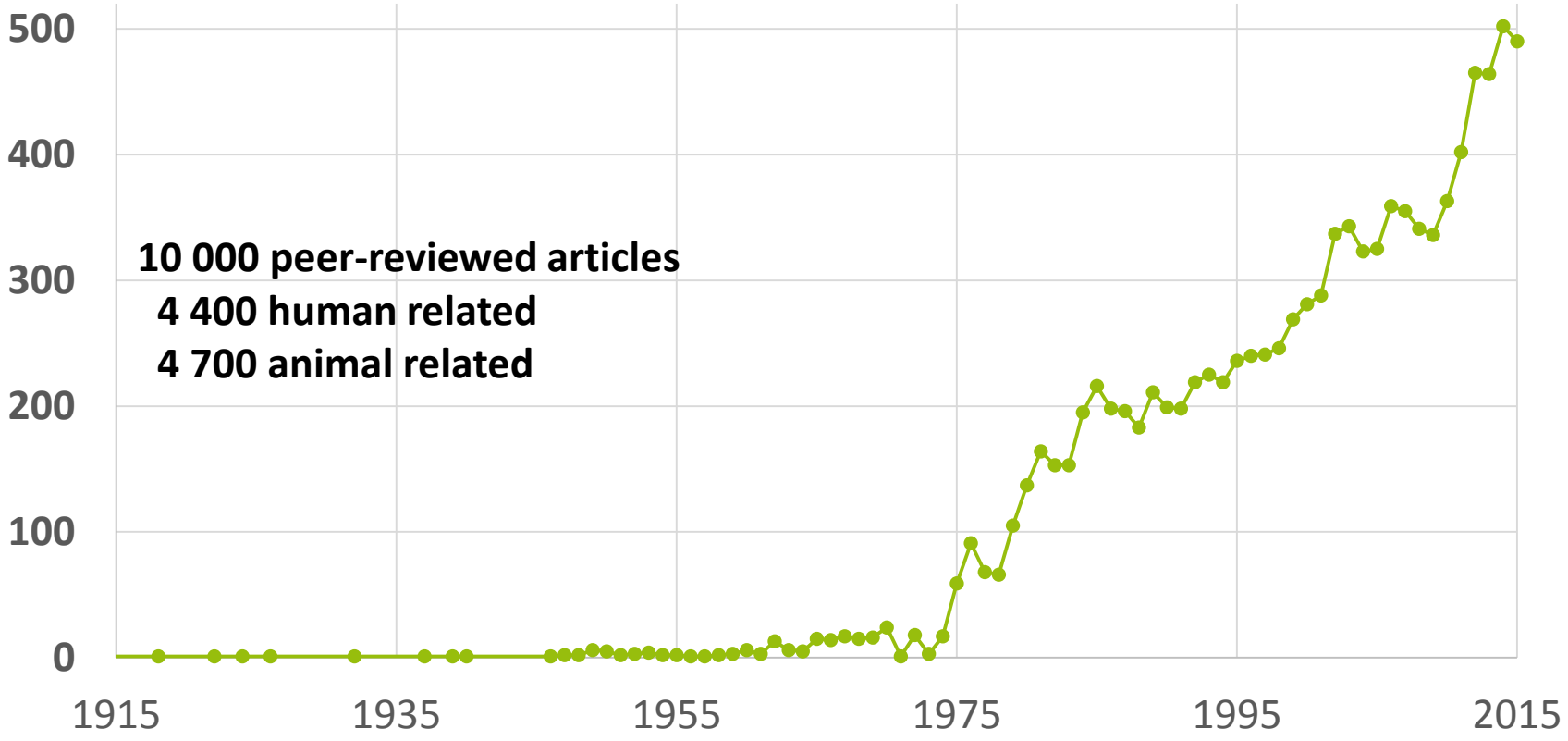
Science behind the benefits of butyrate has grown explosively

Medline publications with Butyrate in title or abstract



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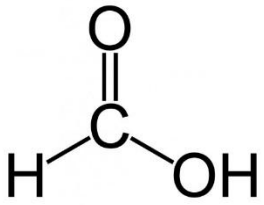
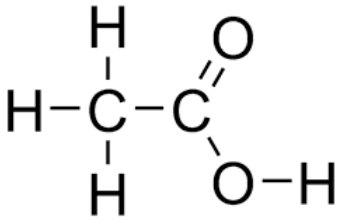
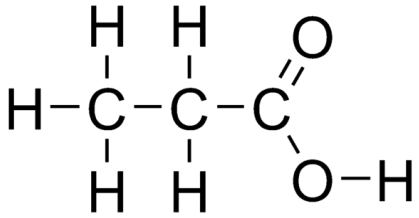
Organic acids



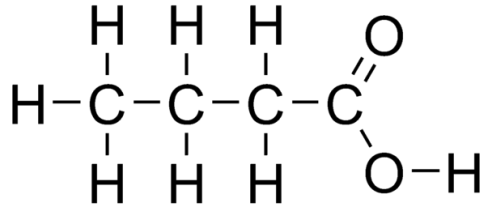
Formic Acid
MW: 46,0
pKA: 3,8



Acetic Acid
MW: 60,1
pKA: 4,8

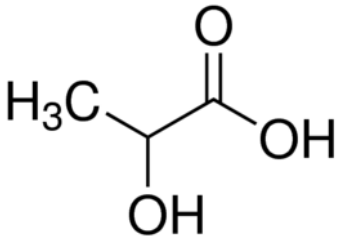


Propionic Acid
MW: 78,1
pKA: 4,9

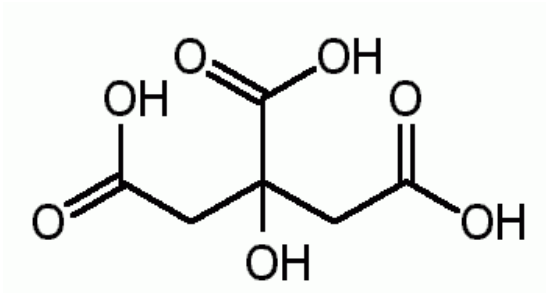


Butyric Acid
MW: 88,1
pKA: 4,8

Butyric acid: *proven health effect (WHO)*



Lactic Acid
MW: 90,0
pKA: 3,8



Citric Acid
MW: 192,0
pKA: 3,1; 4,8; 6,4

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Biological functions of Butyrate

- Energising the epithelium of the colonocytes (colonic barrier function)
  - Preferential source of energy for epithelial cells
  - Stimulates division and development of epithelium cells (Legartova et al 2014) → increases digestive surface
  - Stimulates mucin production (Jung et al 2015)
  - Reduces mucosal permeability and water loss

- Modulating the immune system
  - Moderate butyrate signals the immune system: “all is well with the microflora”
  - Reduces mucosal pro-inflammation signalling
  - Butyrate inhibits inflammation normally induced by LPS (Nastasi et al 2015)

- Modulating the gut microflora
  - Allows adherence of Lactic acid bacteria and repels E.coli (Jung et al 2015)

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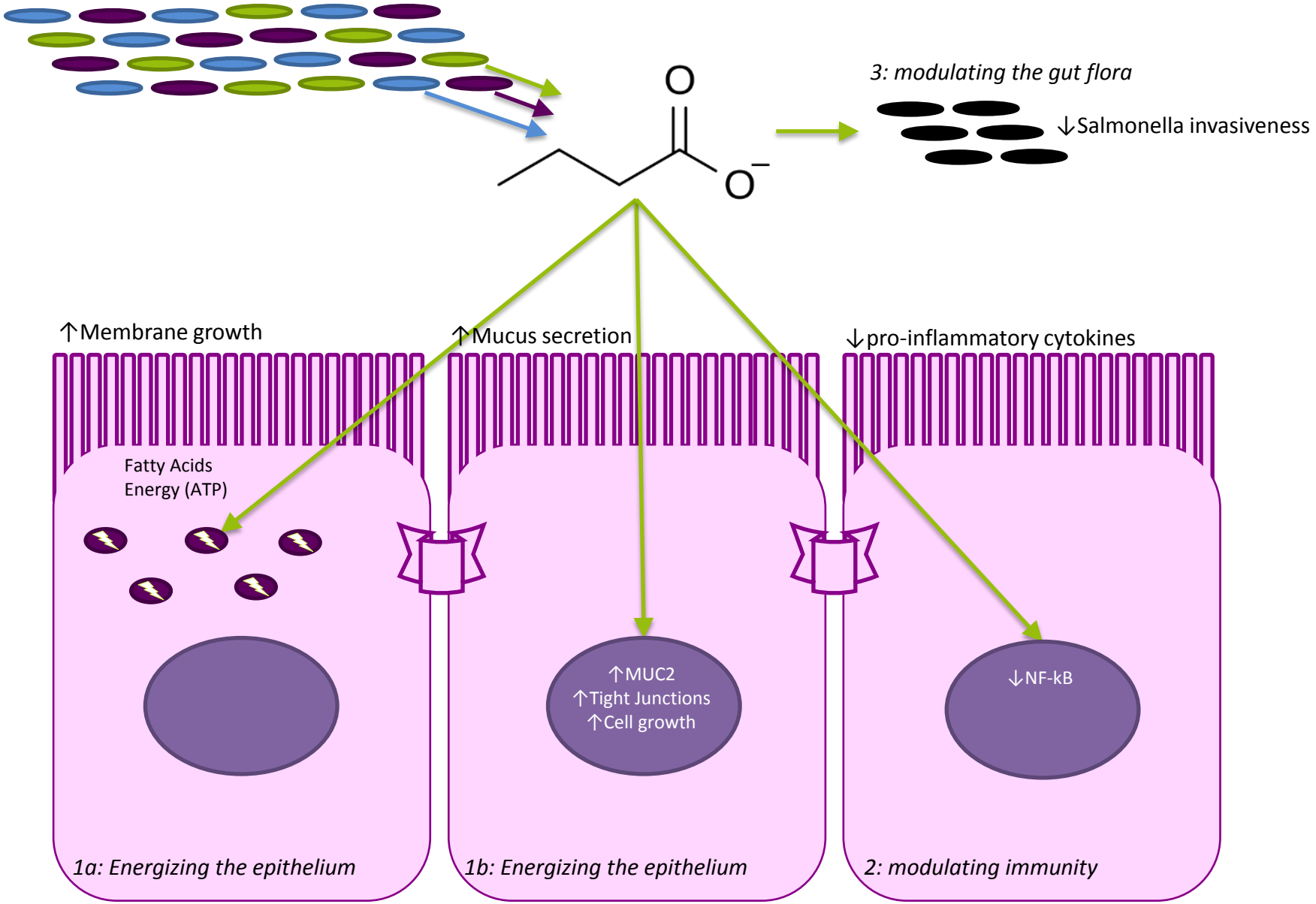

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Immune Network
http://dx.doi.org/10.4110/in.2014.14.6.277
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Gut Microbiota-Derived Short-Chain Fatty Acids, T Cells, and Inflammation

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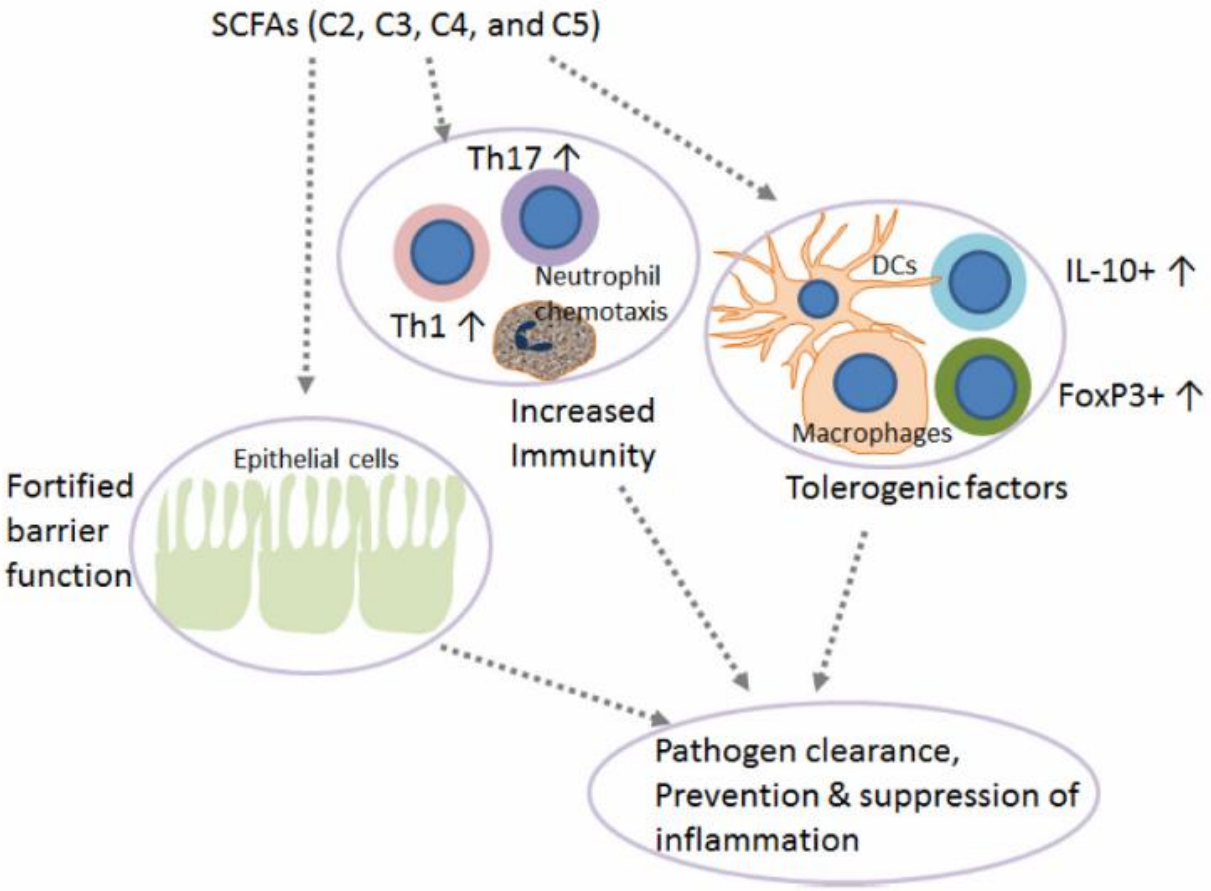
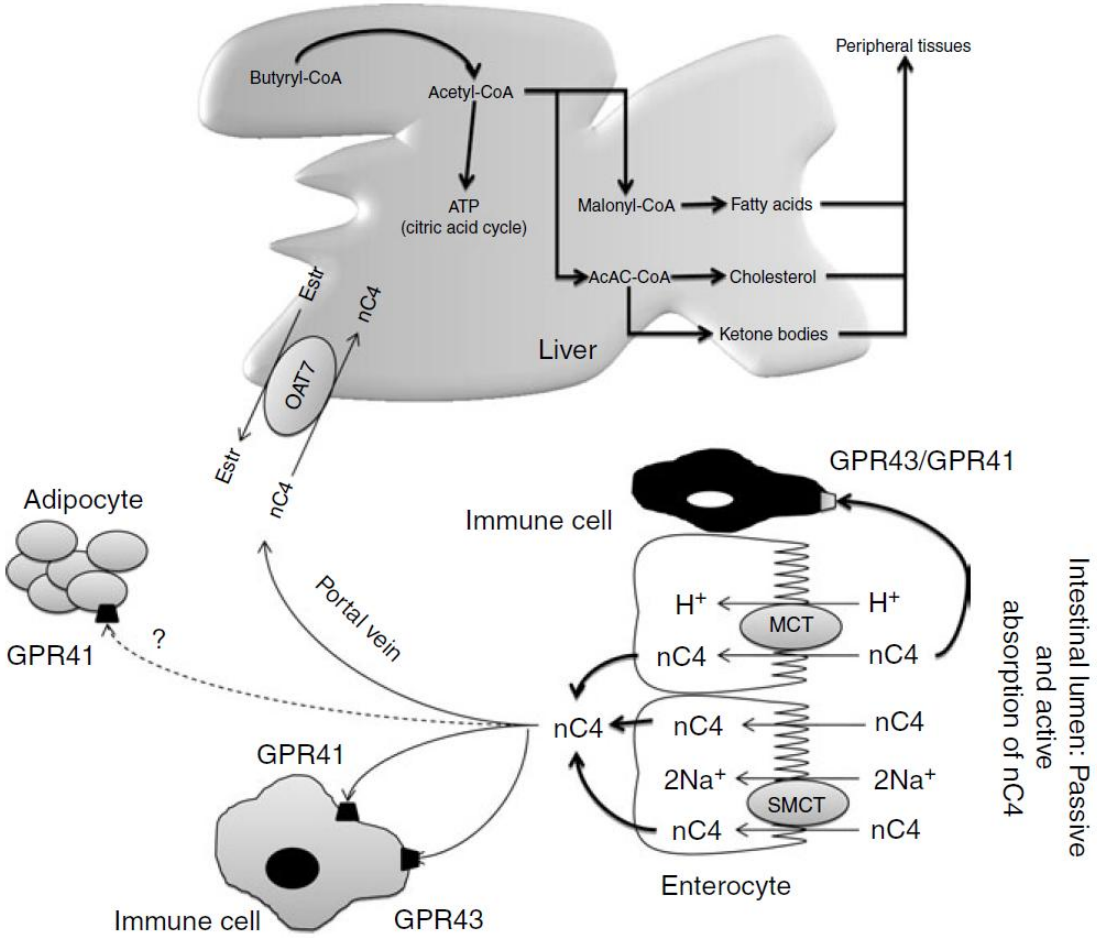
Laboratory of Immunology and Hematopoiesis, Department of Comparative Pathobiology, Purdue Veterinary Medicine; Weldon School of Biomedical Engineering; Center for Cancer Research, Purdue University, West Lafayette, IN 47907, USA



Nutrition Research Reviews (2010), **23**, 366–384
doi:10.1017/S0954422410000247

From the gut to the peripheral tissues: the multiple effects of butyrate

P. Guilloteau[1]*, L. Martin[2,3], V. Eeckhaut[4], R. Ducatelle[4], R. Zabielski[5] and F. Van Immerseel[4]



Am J Physiol Cell Physiol 301: C984–C994, 2011.
First published July 20, 2011; doi:10.1152/ajpcell.00146.2011.

The short-chain fatty acid butyrate is a substrate of breast cancer resistance protein

Pedro Gonçalves, Inês Gregório, and Fátima Martel
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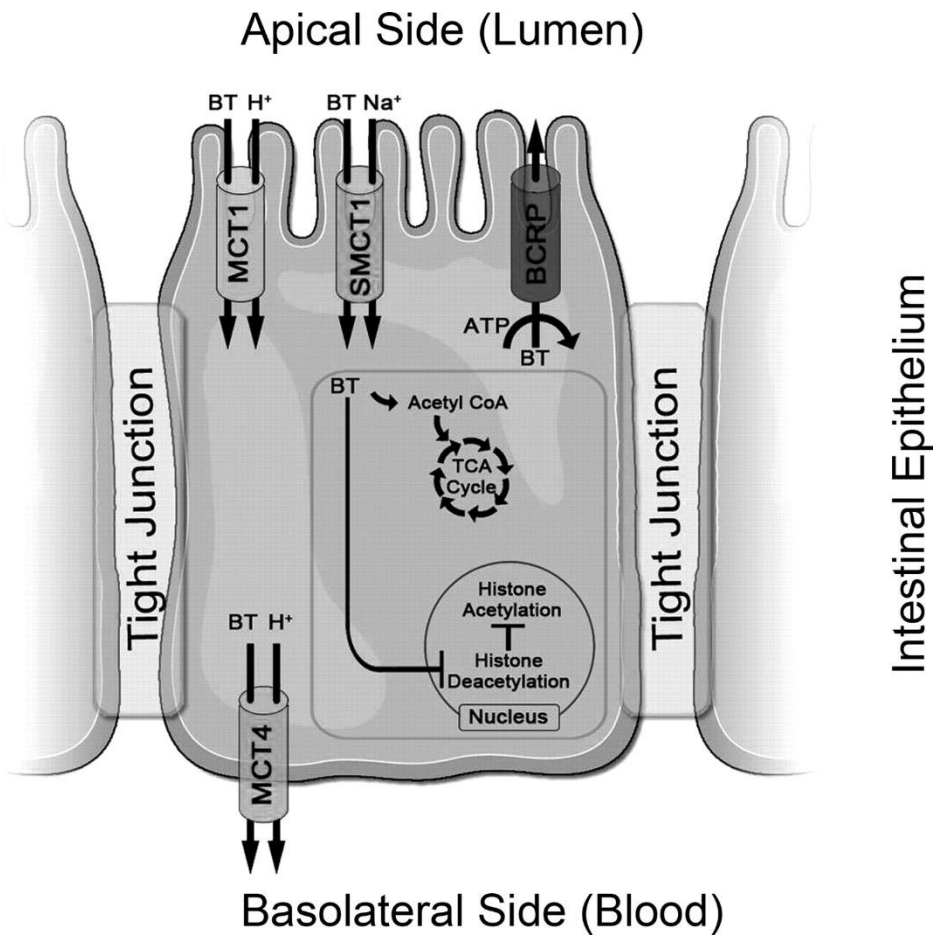
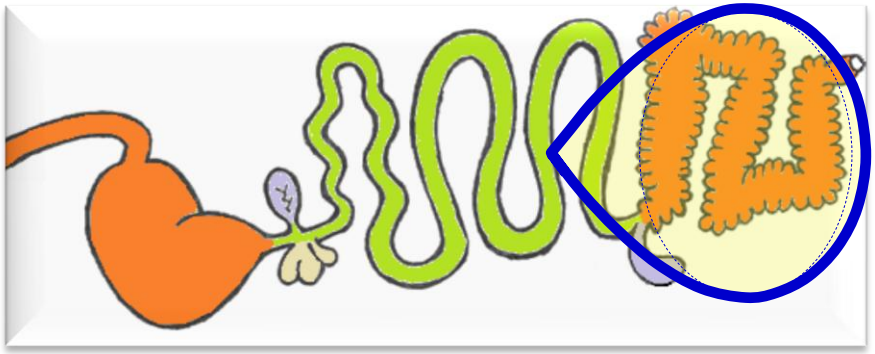


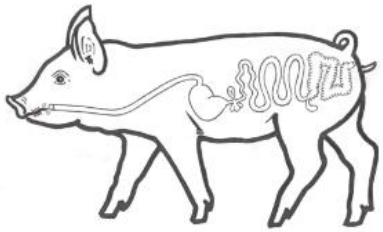
Intest-Plus

Endogenous butyrate production

Pigs (65 kg): (Le Gall et al. 2009), Nielsen et al. 2014)

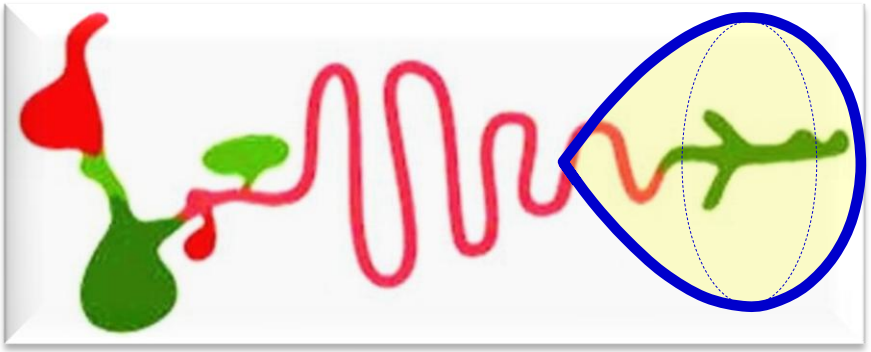
- Ileum 0-3 mMol
- caecum 6-16 mMol
- colon: 6-16 mMol

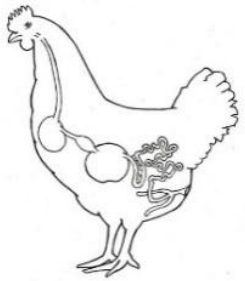




Broiler (42 Day): (Ptak et al. 2015)

- Crop: <1mMol
- Duodenum: <1mMol
- caecum: 5-9mMol





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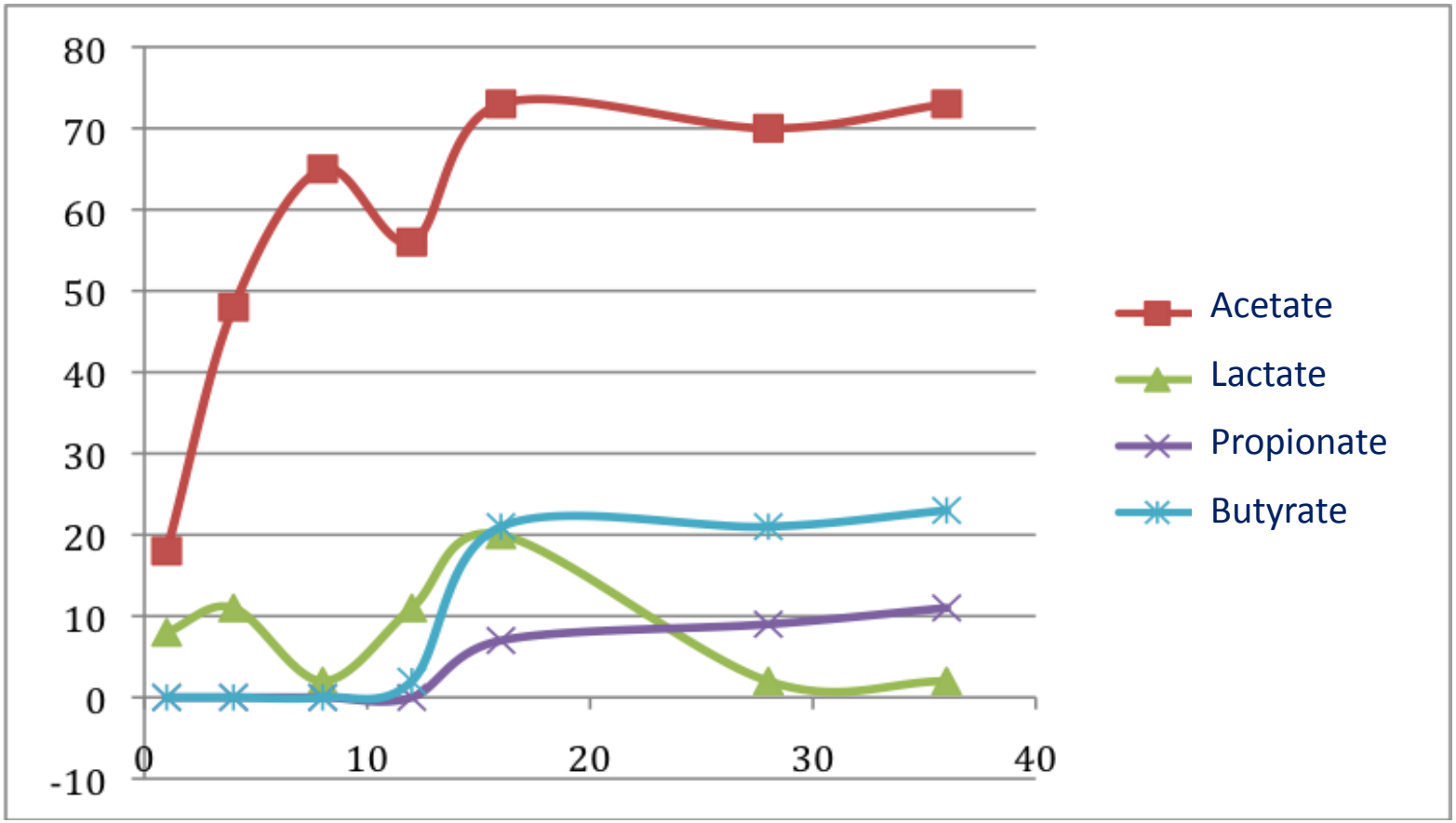
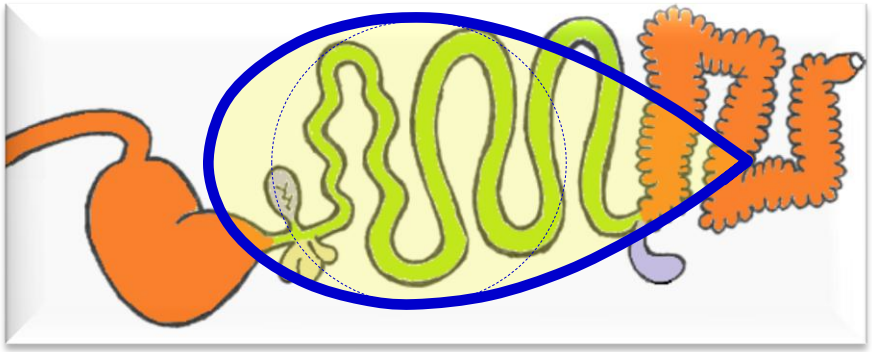
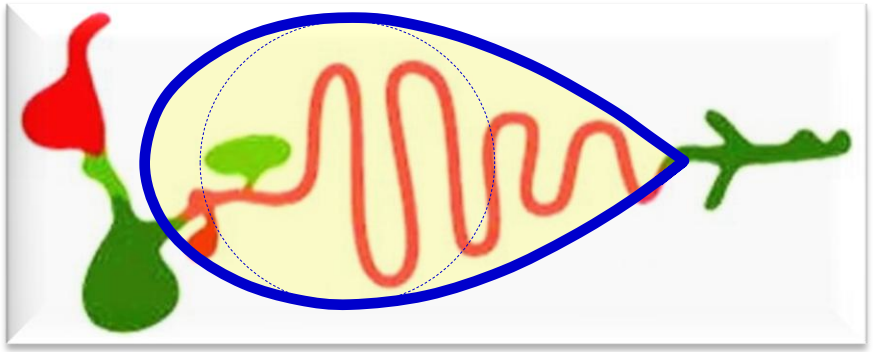
Butyrate production in broilers does not start immediately after hatch

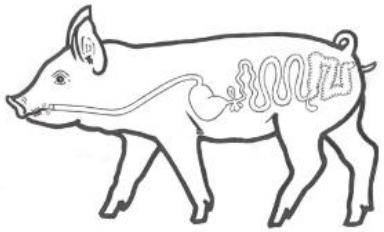


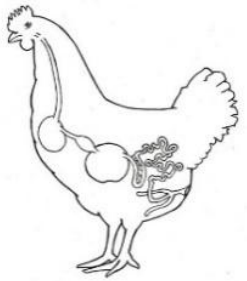
Van der Wielen, 2002

Introducing butyrate in the proximal GIT ?
Is there a benefit for the animal ?









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Butyrate 'in vivo' performance benefits: Review of effects in broilers (Moquet, 2016)

Table 1 Effects of different butyrate derivatives on the growth performance of broiler chickens

Form	References	Experimental set-up	Effects on performance parameters expressed as a percentage of respective controls
Unprotected butyrate	Hu and Guo (2007)	C: Control, T1: 0.5 g/kg B in SGF, T2: 1 g/kg B in SGF, T3: 2 g/kg B in SGF.	BWG was improved in T1 (+4.7%) and T3 (+4.7%) in comparison to C birds during the 0-21 d period. In T3, FCR (+4.6%) was influenced in a positive quadratic fashion during the (-42 d period.
	Panda *et al.* (2009)	C: Control, T1: 0.5 g/kg furazolidone, T2: 2 g/kg B in SGF, T3: 4 g/kg B in SGF, T4: 6 g/kg B in SGF.	T3 (+3.4%) and T4 (+4.0%) had significantly higher BWG than control birds over the whole experimental period. FCR was significantly reduced by B supplementati n (T1: -2.7%; T2: -5.9%; T3: -4.8%).
	Zhang *et al.* (2011b)	Exp. 1: C: Control, T1: 0.25 g/kg B in SGF, T2: 0.50 g/kg B in SGF, T3: 0.75 g/kg B in SGF. Exp. 2: 2 x 2 factorial arrangement with B (none or 1 g/kg in SGF) and challenge status (saline or endotoxin injection) as main factors.	No significant effect of B supplementation o performance parameters in comparison with the control in experiment 1. n experiment 2, B alleviated the reduction in BWG and VFI caused by L PS challenge.
Fat coated butyrate	Smulikowska *et al.* (2009)	2 x 3 factorial arrangement: Enzyme (None or 1 g/kg in SGF) and SCFAs (None, 0.3 g/kg B in SGF, 1 g/kg of a SCFA blend in SGF) as main factors.	B supplementation significantly reduce FCR (-4.6%) n comparison to the control diet.
	Jerzsele *et al.* (2012)	C: Control, T1: 1.05 g/kg B in SGF, T2: 1 g/kg of an essential oils (EO) blend in SGF, T3: T1+T2 in SGF, T4: 10^9 CFU of a probiotic.	No significant effect of B supplementation on BWG of *C. Perfringens* challenged birds in comparison to challenged control.
	Hautekiet *et al.* (2011)	2 x 2 factorial arrangement: Dietary metabolisable energy and amino acid concentration (H: high or L: low) and B (none or 0.75 g/kg in S and 0.5 g/kg in G) as main factors.	B supplementation significantly increa ed VFI (H: +2.4%; L: +1.9%) and BWG (H: +1.5%; L: +3.4 %) n comparison to control over the whole experimental period.
Blend of mono-, di- and tri-butyrins	Leeson *et al.* (2005)	Exp.1: C: Control, T1: 11 pm virginiamycin in SGF, T2: 2 g/kg BB in SGF, T3: 4 g/kg BB in SGF. Exp. 2: C: Control, T1: 50 pm bacitracin in SGF, T2:1 g/kg BB in SGF, T3: 2 g/kg BB in SGF.	Experiment 1: No effect of dietary treatments on BWG. T3 birds showed reduced VFI (-7.7%) compared to control birds. Experiment 2: No effect of dietary treatments on performance parameters

Considerations about ENDOGENEOUS butyrate into the PROXIMAL GIT of pigs

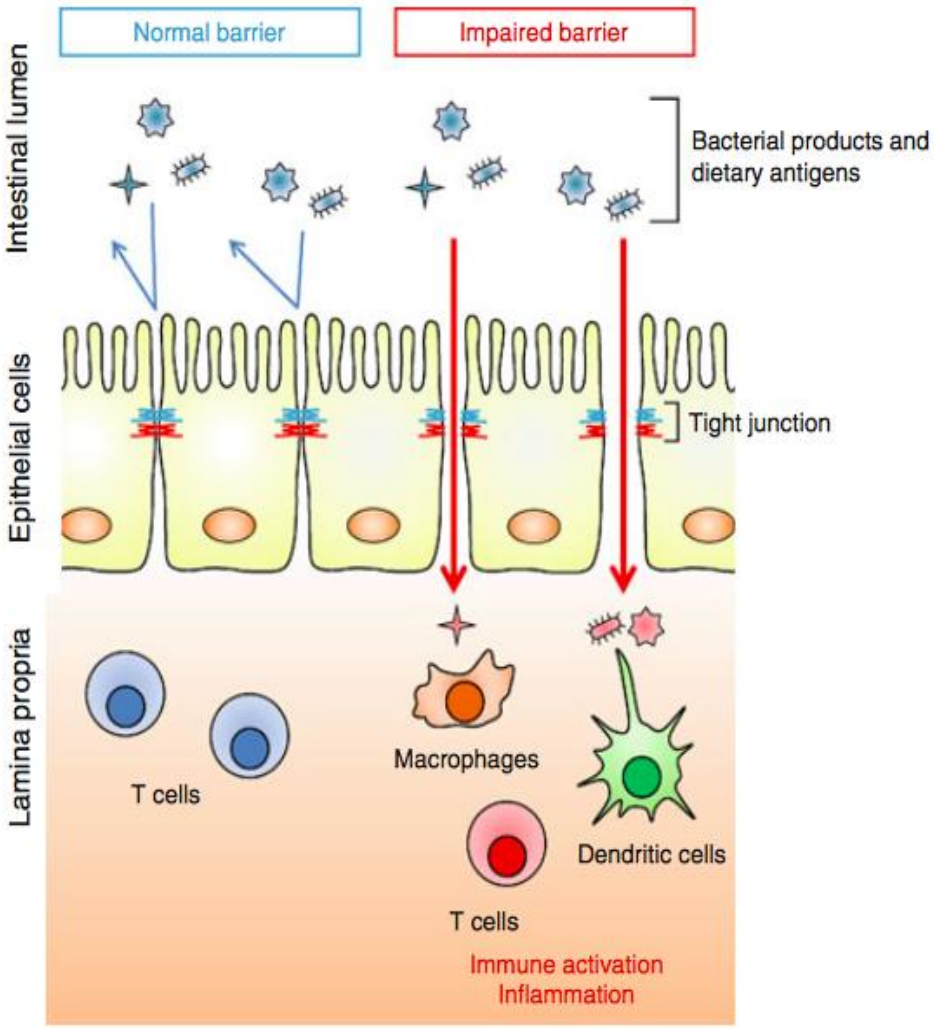
- Production is age related (cfr poultry): piglets < G/F pigs < sows
- SI: site of feed digestion / nutrient absorption process , but hardly any natural butyrate in the stomach and proximal SI
- Evolutionary feeding behaviour
  - From rooting to high performance 'starch' diets
  - More co-products with lower digestibility
  - More enzymatic, less fermentative capacity

- Production performance targets : > 35 piglets /sow /year
- 'Proximal' pathologies

Palital FEED ADDITIVES

Butyric acid and proximal disease
Example: gastric ulcers

- 80% of all pigs slaughtered in UK suffer from oesophago-gastric ulcers or pre-ulcerative changes (Swaby and Gregory, 2012)
- **Helicobacter Pylori** causes targeted disruption of the gastric eptithelial-barrier (tight junctions) and induces chronic gastritis (Wroblewski, 2011)
- Other pathogens can also disrupt the intestinal barrier function (E. Coli, Clostridium, Vibrio..)
- Supplemental Sodium Butyrate stimulates different gastric cells (thickness of gastric mucosa and gene regulation) (Mazzoni et al, 2008)
- Butyric acid decreases and restores intestinal tight junctions permeability (Peng et al., 2009)



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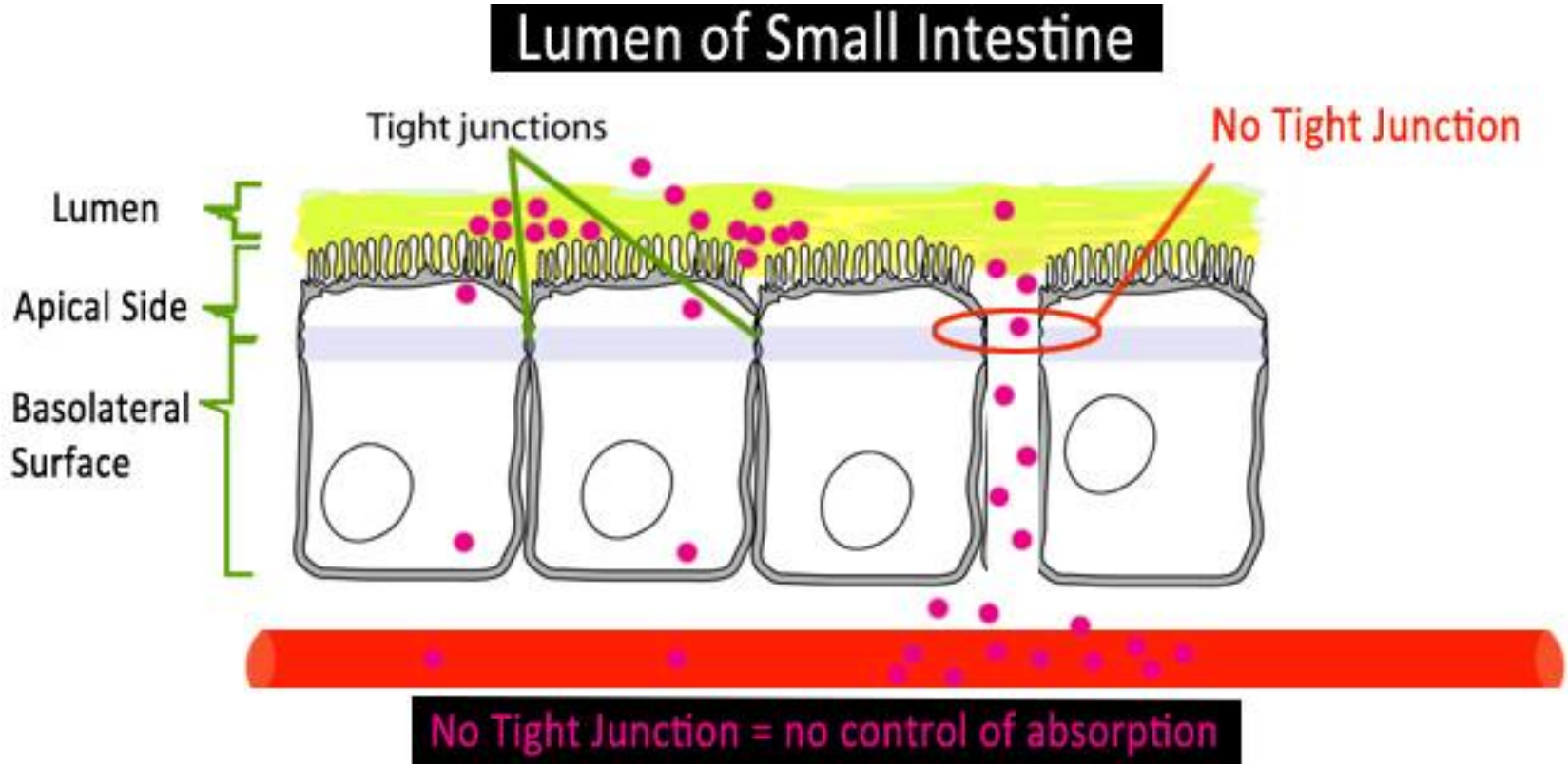
Butyrate promotes the recovering of intestinal wound healing through its positive effect on the tight junctions



Bottom line:
Butyrate treatment of cell cultures scratched to induced wounds, significantly promoted the process of wound healing, indicating the protective effect of butyrate on the intestinal mucosa (maintenance of intestinal barrier function).
In addition, 2 of the main antioxidant enzymes, gluthatione peroxidase and intestinal superoxide dismutase, were significantly enhanced by butyrate treatment.

Ma et al., 2015

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Effect of oral supplementation with 0.3% Sodium Butyrate (NaBut) to gestating (> d 77), lactating sows and pre-weaned piglets on gene expression in adipose tissue and muscles in piglets

Gene	Back fat		LD muscle		Liver	
	X Change	P-value	X Change	P-value	X Change	P-value
PGC-1α	2.53	< 0.05	7.11	< 0.05	1.77	< 0.05
PPARα	1.6	< 0.05	2.52	< 0.05	0.75	> 0.05

PGC-1α: peroxisome proliferator activated receptor gamma coactivator1 alpha
PPARα: peroxisome proliferator activated receptor alpha

Bottom line:
Piglets born to sows that were supplemented with 0.3% butyrate during the last month of gestation, lactation and pre-weaning had a 15% higher body weight at 12 wk than controls.
It may be mediated by increased substrate oxidation in butyrate treated animals, indicating that butyrate favors nutrient partitioning away from adipose tissue through downregulation of genes responsible for fatty acid synthesis and upregulation of genes involved in fatty acid oxidation.

Lu et al., 2012

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Butyrate ‘in vivo’ performance effects in pigs

- **Performance** improvement in **young piglets** (milk fed/prestarter/starter)
  - The pre-weaning NaBut (3kg/T) supplementation was most efficient to stimulate body growth and feed intake after weaning by reducing gastric emptying and by increasing feed digestibility (Le Gall, 2009)
  - Piglets that were orally force fed with 0.3% butyrate from day 4 untill day 21 (weaning) had increased ADG by 13% vs. saline treated controls (Lu, 2012)
  - Butyrate supplementation (0.3% to gestating sows and piglets enhanced postweaning performance, which may be mediated through increased substrate oxidation in butyrate treated animals (Lu, 2012)
  - NaBut added to the pre-weaning diet (0.3%) improved their performance. The difference persisted during the later fattening phase despite feeding the same diets (Hanczakowska, 2014)
  - 0.3% NaBut (DM) to piglets aged between 3 and 10 days of life and fed on a milk formula, increased daily body weight gain significantly versus control (Kotunia, 2004)
  - NaBut (treament 0.1, 0.2 or 0.4%) in weaner diets (> 28 days of age) did not improve animal growth performance (Biagi, 2007)

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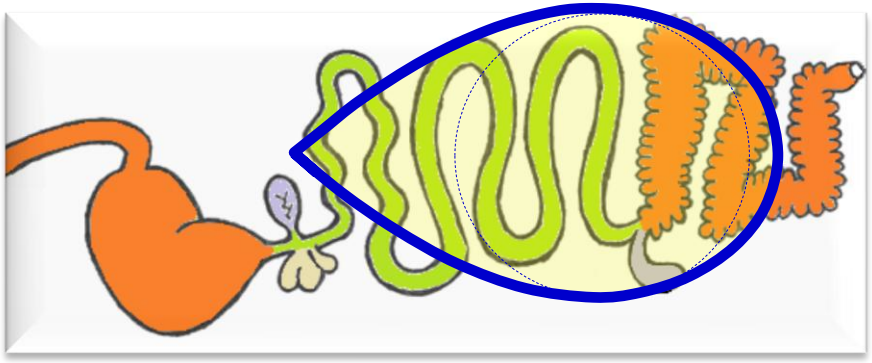
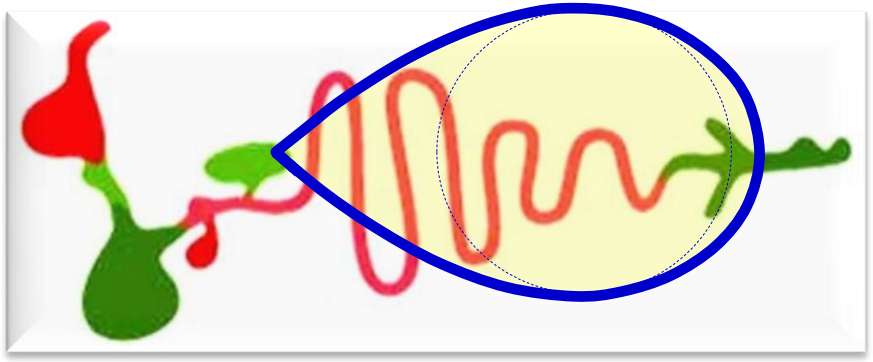
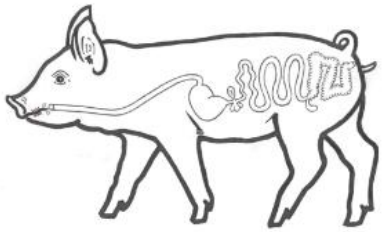
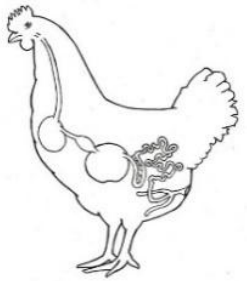
Introducing (additional) butyrate in the distal GIT
Is there a benefit for the animal ?









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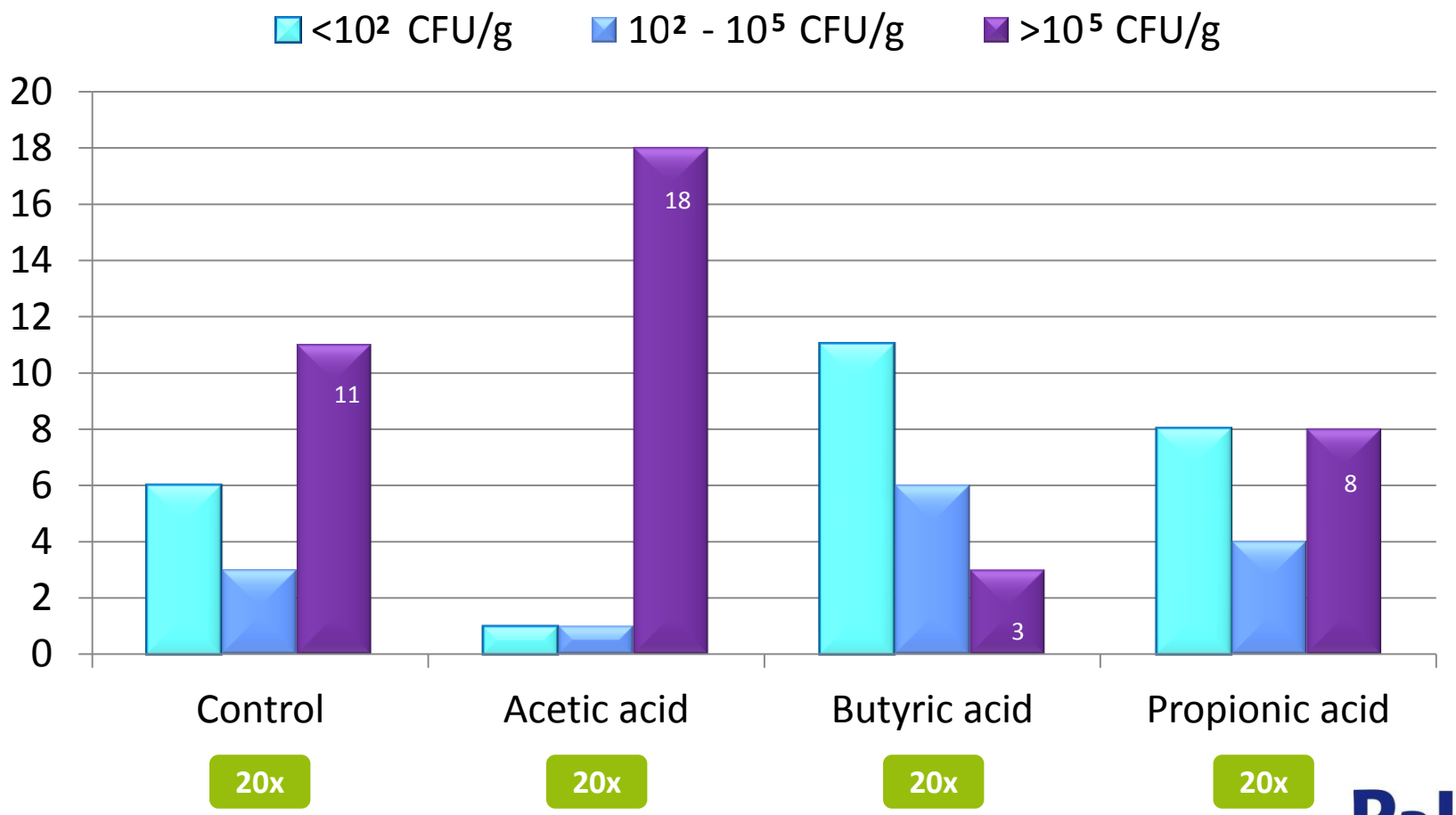
Coated butyric acid reduces caecal Salmonella colonization in broilers

- Broilers orally challenged with Salmonella at day 5-6
- Cloacal swabs tested for degree of colonization on day 8



V Immerseel, Poultry Science 83:69-74 (2004)

Palital FEED ADDITIVES

Butyric acid and distal GIT disease in poultry

- Reduces Salmonella counts in cecum and changes gene expression of Salmonella to prevent invasion (Van Immerseel et al, 2005)
- Reduces effects of necrotic enteritis due to Clostridium perfringens (Timbermont et al, 2010)
- Better resistance to coccidial challenge in birds fed previously butyrate (Leeson, 2005)
- Coated butyrate reduces the concentration of Campylobacter in broilers by 2 log10 CFU/g.

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Dietary fiber and intestinal health in pigs: finding the right balance

Acta Scientiae Veterinariae. 37(Supl 1): s1-s9, 2009.

ISSN 1678-0345 (Print)
ISSN 1679-9216 (Online)

Feed-associated colitis of growing pigs and its interaction with enteric infections

Colite nutricional em suínos de crescimento e sua interação com infecções entéricas

Animal (2015), 9:9, pp 1441–1452
doi:10.1017/S1751731115000919

animal

Review: Dietary fiber utilization and its effects on physiological functions and gut health of swine

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The role of carbohydrates in intestinal health of pigs☆

Knud Erik Bach Knudsen*, Mette Skou Hedemann, Helle Nygaard Lærke

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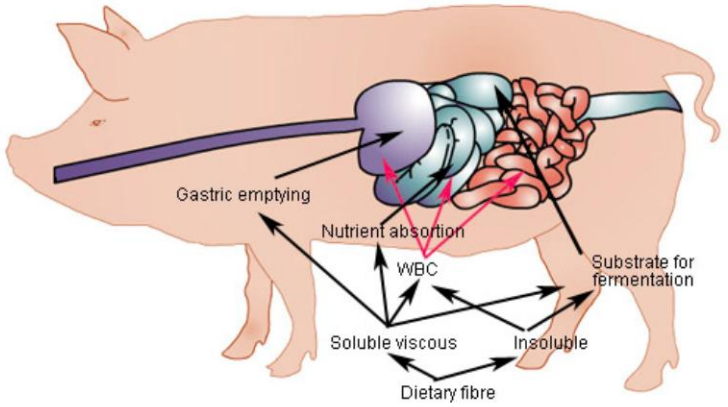
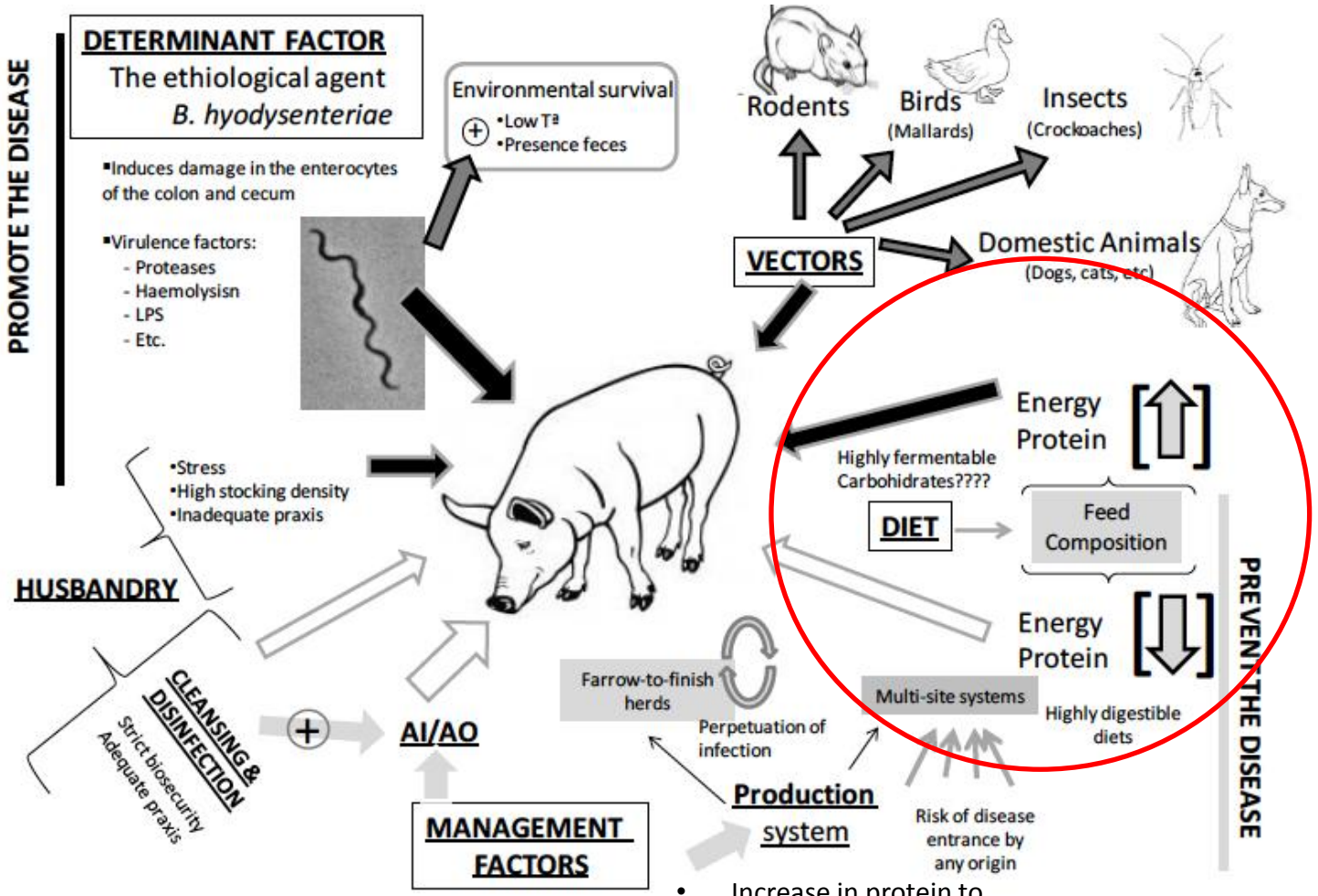
British Journal of Nutrition (2011), **106**, 1506–1513

doi:10.1017/S00071

A high dietary concentration of inulin is necessary to reduce the inci of swine dysentery in pigs experimentally challenged with *Brachyspira hyodysenteriae*



Butyric acid and distal GIT disease: Example: Brachyspira hyodysenteriae



- Increase in protein to carbohydrate ratio
- Highly digestible diets
- Highly fermentable diets (prebiotics),

Alvarez-Oronez et al., 2013
Bach Knudsen et al., 2012t

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Gently Coating

Matrix Coating

Na But

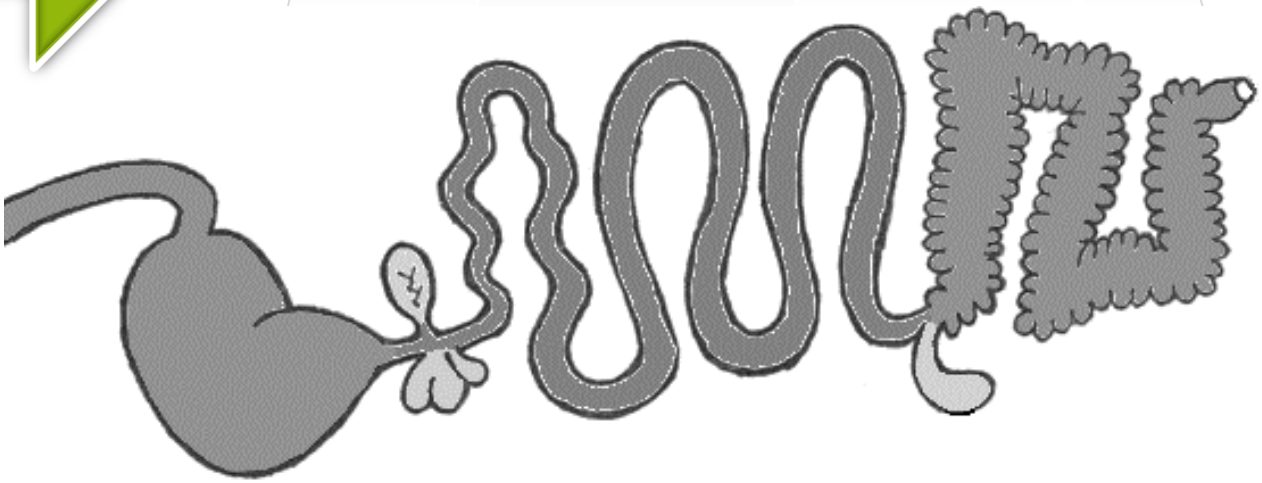
Ca But

Na But

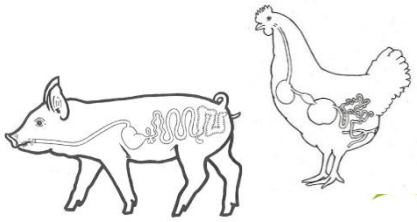
Ca But

Efficacy & Performance

Target-Release & Health



Intest-Plus Quattro



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Conclusions

- The biological role of butyrate, whether is naturally produced or added as a feed additive, is well established.
- The result translates in beneficial systemic effects and improvements in feed efficiency, growth rate and less adiposity.
- In animal production, ingested butyrate allows pathogen control, increased ration digestibility and decreases oxidative stress and cytokine synthesis, even at very low doses.
- The target delivery of butyrate in the GIT is important to achieve the desired effect.

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