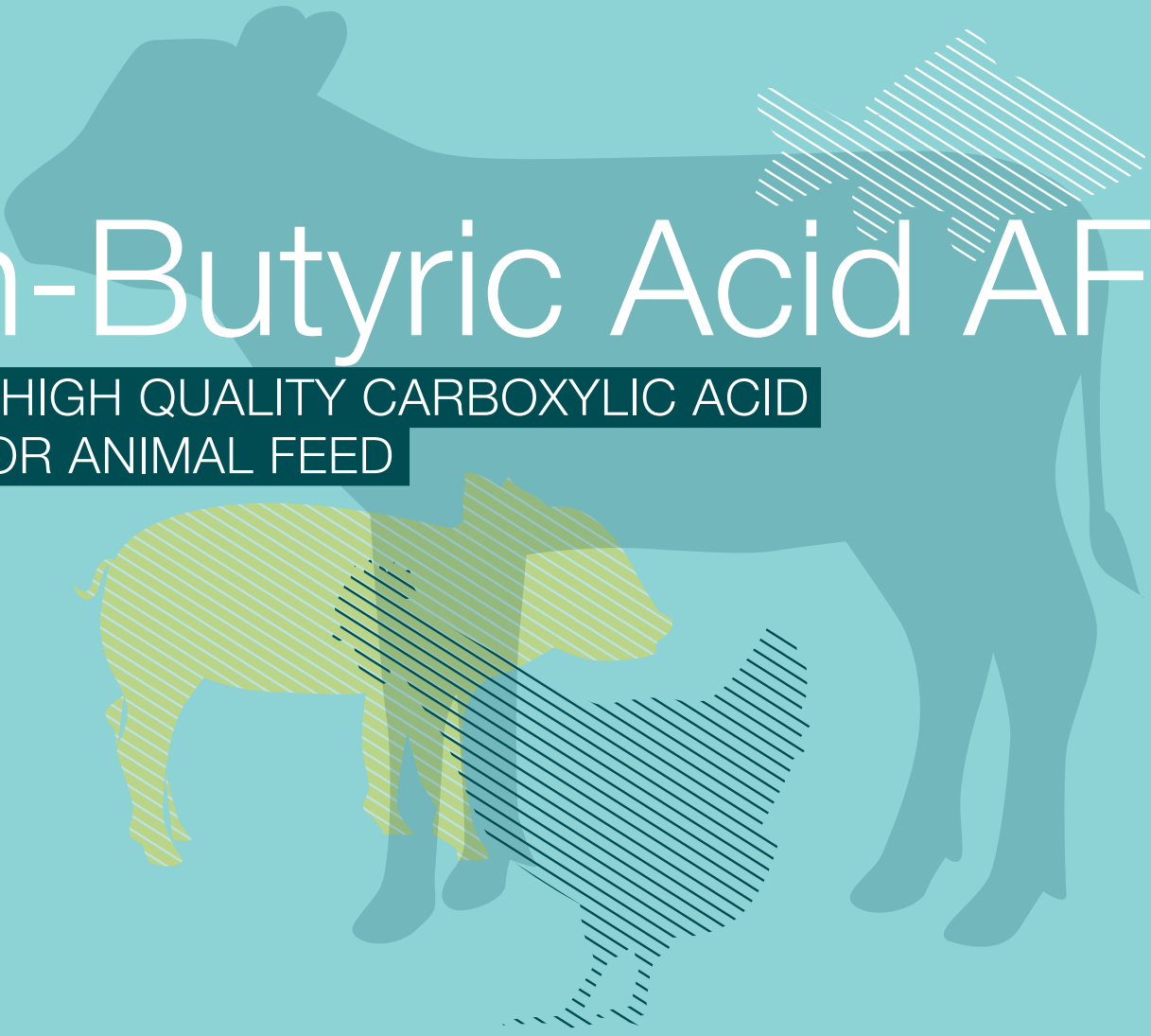
OXEA

n-Butyric Acid AF

A HIGH QUALITY CARBOXYLIC ACID FOR ANIMAL FEED



MATERIAL PROPERTIES

N-BUTYRIC ACID AF – A HIGH QUALITY PRODUCT FOR ANIMAL FEED

Supporting today's trend towards the replacement of antibiotic growth promoters by non-hazardous alternatives, Oxea offers carboxylic acids as special animal feed grades for use as raw material in agricultural industry. This trend started with the ban of antibiotic growth promoters in the European Union and expands to North America and Asia in recent years. Current African swine fever epidemic puts additional pressure on farmers, not only in Asia, to raise animals even more efficiently.

OXEA's n-Butyric Acid AF – animal feed grade – is the key feedstock for different butyrate salts and glycerine esters – so-called butyrins. Salts are incorporated into feed premixes as fat-coated or non-coated administrative forms to channel the active ingredient to the target organs in the animal's intestine. OXEA's n-Butyric Acid AF is produced and handled according to GMP (Good Manufacturing Practice) and HACCP (Hazard Analysis Critical Control Point).

Property	Limit	Unit	Test method
n-Butyric acid	min. 99.5	% (w/w)	gas chromatography
Propionic acid	max. 0.3	% (w/w)	gas chromatography
Isobutyric acid	max. 0.1	% (w/w)	gas chromatography
Water	max. 0.1	% (w/w)	DIN 51 777/ASTM D 1364 (mod. Karl-Fischer-Method)
Platinum/Cobalt color (Hazen/APHA color)	max. 15		DIN EN 1557/DIN ISO 6271/ASTM D 1209

Figure 1: OXEA n-Butyric Acid AF (animal feed grade, CAS 107-92-6)

BUTYRIC ACID AS KEY RAW MATERIAL FOR NON-ANTIBIOTIC FEED ADDITIVES

The increasing awareness of the huge risk to human and animal health of the massive misuse of antibiotics as growth promoters in livestock led to a paradigm shift in Europe, North America, a growing number of countries in Asia and the rest of the world. For several years now, antibiotics consumption on farms in Europe has decreased rapidly.

For example, in Germany, the overall sales of antibiotics used in livestock have been cut in more than half within a 2013 to 2017 timeframe. In other major animal producing countries, such as the US, a similar trend started in the year 2016 by the voluntary action of big food companies. This led to a dramatic drop in antibiotic sales to farmers there.

Development of the sales of antimicrobials for farm animals in the US and in six key countries in Europe

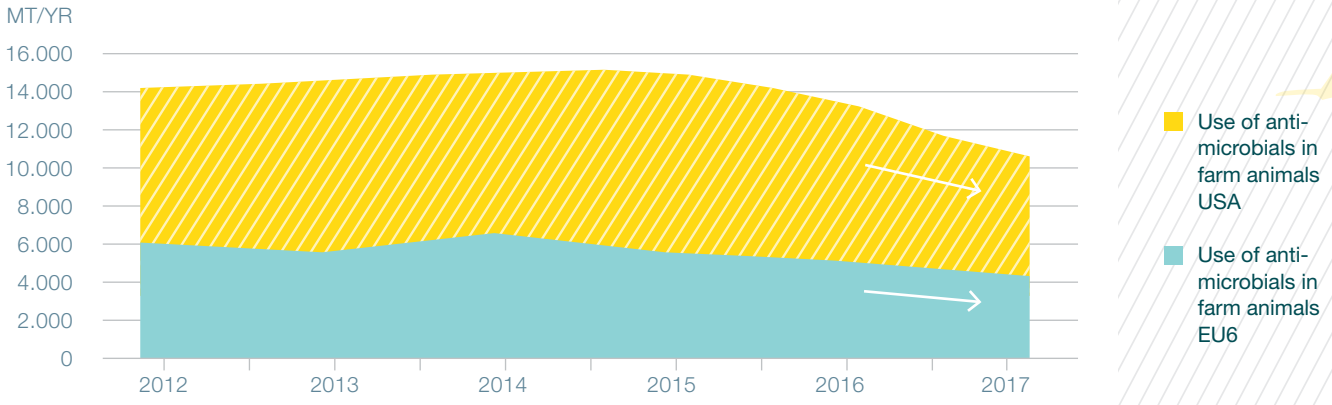


Figure 2: Use of antimicrobials in six European countries (EU6 means: Germany, Spain, Netherlands, France, Denmark and Italy) and in the US. Sources: USDA, FIDIN, ESVAC report.

FEED ADDITIVES CAN COMPENSATE PRODUCTIVITY LOSS BY ANTIBIOTIC REDUCTION

In order to avoid the unfavorable effects seen by the removal of antibiotic growth promoters, farmers try to compensate their losses in livestock productivity by an intensified feeding of special feed additives like n-Butyric Acid derivatives.

Pathogen control, enteritis/diarrhea protection, and other health promoting measures to promote animal welfare in general are another important goal to be achieved by applying non-antibiotic feed additives.

Other effects like higher soy-protein contents in fish diet and improved rumen development in post-weaning calves prove the broad application range of n-Butyric Acid derivatives in many different farm animal species.

Less use of antibiotic growth promoters calls for rebalancing animals' health and performance

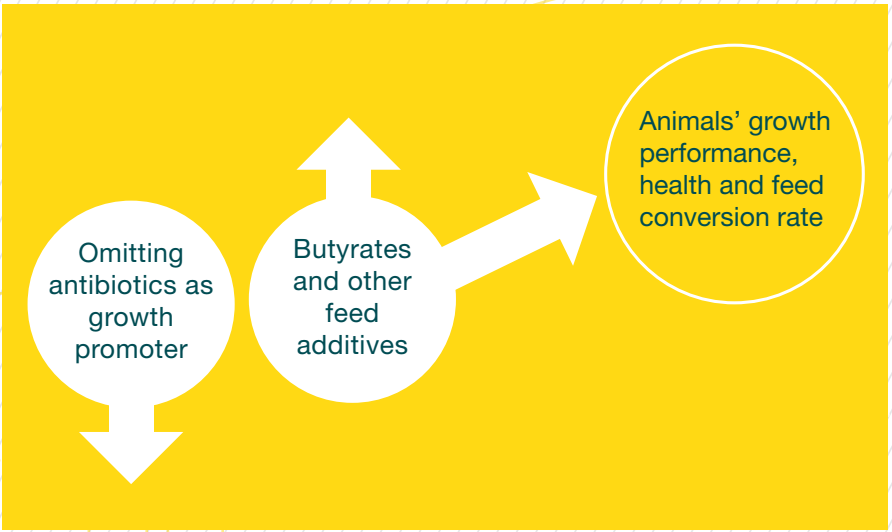


Figure 3: While the use of antibiotic growth promoters is declining, negative impact on performance and health of farm animals has to be compensated by feed additives like n-Butyric Acid derivatives, see also figure 2.

N-BUTYRIC ACID DERIVATIVES ADD VALUE IN ANIMAL HUSBANDRY BY ENHANCING ANIMALS' WELFARE AND PERFORMANCE

One of the most promising precursor molecules for feed additives is n-Butyric Acid in its salt form or as mono-/tri-glyceride ester.

n-Butyric Acid is a natural substance present in biological liquids and tissues. It is naturally produced by the gastro-intestinal microbiota. Ruminants produce up to 1 kg butyrates each day while digesting fibers in the rumen. This endogenously provided breakdown product is directly used as an energy source by the animal's metabolism. Numerous scientific studies reveal that orally ingested n-Butyric Acid derivatives, like butyrates or butyrins*, exert several beneficial effects on different farmed animals. Researchers figured out that n-Butyric Acid derivatives can act directly – e.g. by controlling pathogens, by enlarging villi surfaces or by providing extra energy to enterocytes. But there is also an indirect mode of action e.g. by stimulating immune response. For a review see Bedford A et al, 2018 [43].

n-Butyric Acid derivatives show beneficial effects in poultry, swine, aquaculture and cattle

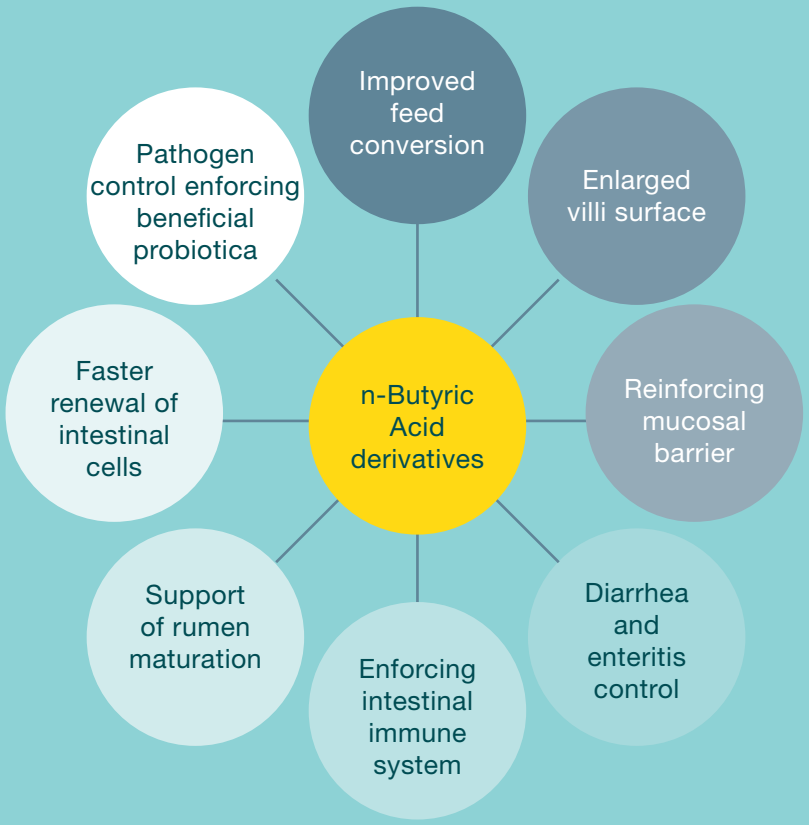


Figure 4: Beneficial effect from using n-Butyric Acid derivatives as in-feed additive in different farm animal species. For references, see below.

SCIENTIFIC STUDIES EMPHASIZE EFFECTIVENESS OF N-BUTYRIC ACID DERIVATIVES AS A BENEFICIAL FEED ADDITIVE

Effectiveness of n-Butyric Acid derivatives is seen for in-feed application for farm animals like swine, poultry, calves and different fish and shrimp species. Dozens of peer-reviewed scientific studies illustrate these beneficial effects when added to livestock diets.

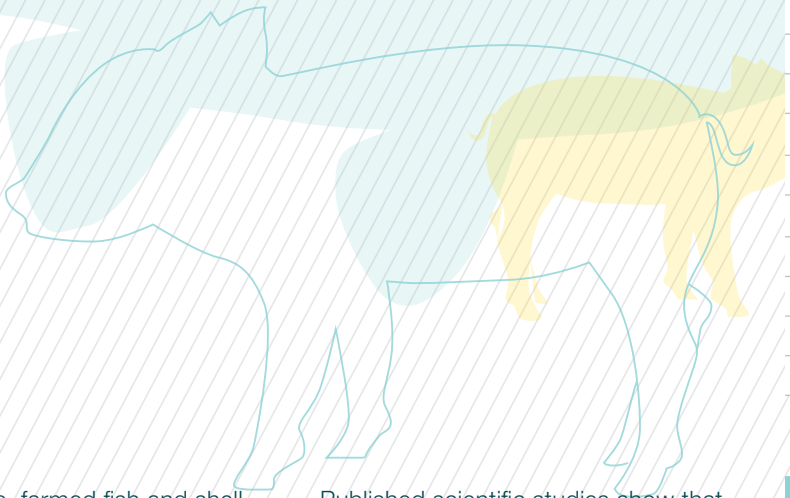
Over the past decades feed conversion and growth rate in chicken production improved dramatically with the consequence that nutrition and health care gained much more relevance. In broiler and hen husbandry improved Salmonella control is one main focus in addition to general productivity improvements by feeding n-Butyric Acid derivatives.

Livestock		n-butyrate				
Poultry species	Animals tested in study	Sodium salt	Calcium salt	Fat coating	Feed conversion	Weight gain
Broiler	480	■		■	✔	
Broiler	200	■		■		✔
Laying hen	288		■	■	✔	
Laying hen	1000		■			
Broiler	480	■				
Broiler	96	■		■		✔
Broiler	2208	■		■		✔
Broiler	288	■			✔	
Yellow broiler	180	■		■		
Broiler	150	■		■		
Breeder rooster	300	■		■		
Broiler	960		■	■	✔	✔
Broiler	720	■		■		
Broiler	240	■			✔	✔

Productivity improvements					Health			Reference
Epithelial surface	Egg quantity/ quality	Repro- duction	Feed digestibility	Pathogen protection	Intestinal health	Benificial microbiota	Carcass state	
				✔		✔		Zou 2010 [1]
✔			✔					Smulikowska 2009 [2]
	✔							Hamme 2013 [3]
	✔							Sengor 2007 [4]
				✔				Cerisuelo 2014 [5]
✔								Czerwinski 2012 [6]
						✔		Bortoluzzi 2017 [7]
			✔					Qaisrani 2015 [8]
					✔	✔		Zou 2019 [9]
				✔				Fernández-Rubio 2009 [10]
		✔						Alhaj 2018 [11]
✔			✔					Kaczmareck 2016 [12]
✔						✔		Wu 2018 [13]
✔				✔			✔	Panda 2009 [14]

In pig fattening and piglet breeding n-Butyric Acid derivatives play an important role not only for increased weight gain. Results from many peer-reviewed scientific studies focus on enhanced feed conversion by better feed digestibility and resorption plus positive health effect like diarrhea protection.

Focus of different n-Butyric Acid administration forms is on young animals in the weaning transition, where the shift from liquid to solid feed plus other factors often results in post-weaning growth lag.



Livestock		n-butyrate	
Swine species	Animals tested in study	Sodium salt	Calcium salt
Weaned piglets	32	■	
Piglets	56		■
Fattening pigs	15		■
Weaned piglets	100	■	
Suckled piglets	32	■	
Weaned piglets	160		
Weaned piglets	528	■	
Weaned piglets	90		
Piglets	90	■	
Weaned piglets	96	■	
Weaned piglets	240		
Piglets	50	■	
Piglets	156	■	
Suckled piglets	16	■	

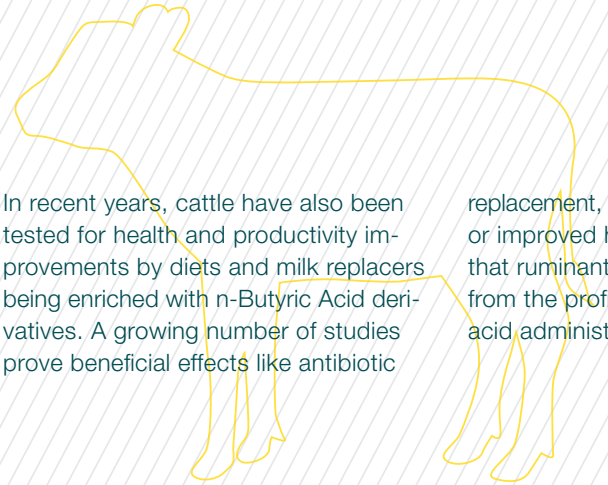
In aquaculture, farmed fish and shellfish are also beneficiaries of positive effects by being fed with n-Butyric-acid-derivatives-containing diets.

Published scientific studies show that beside general productivity improvement by adding n-Butyric Acid derivatives, a higher acceptance of high-soy-protein-containing diets could be noted. This might open the door to more sustainable aquaculture by decreasing the use of fishmeal that runs short.

Livestock		n-butyrate
Marine species	Animals tested in study	Sodium salt
Shrimp	3150	■
Juvenile Sea Bream	120	■
Juvenile Turbot	270	■
Juvenile Gilthead Sea Bream	510	■
Juvenile Gilthead Sea Bream	2200	■
Juvenile common Carp	480	■

Productivity improvements						Health			Reference
Butyrin*	Fat coating	Feed conversion	Weight gain	Epithelial surface	Feed digestibility	Salmonella protection	Diarrhea protection	Immune system	
			✓	✓	✓				Mazzoni 2008 [15]
						✓			de Ridder 2013 [16]
				✓				✓	Claus 2007 [17]
							✓	✓	Fang 2014 [18]
		✓	✓		✓				Le Gall 2009 [19]
		✓	✓	✓	✓				Hou 2006 [20]
			✓						Mallo 2012 [21]
			✓	✓					Piva 2008 [22]
		✓	✓				✓		Huang 2015 [23]
			✓	✓				✓	Wen 2012 [24]
							✓	✓	Gu 2017 [25]
						✓			Lynch 2017 [26]
			✓	✓					Hanczakowska 2014 [27]
			✓	✓	✓				Kotunia 2004 [28]

Productivity improvements						Health		Reference
Fat coating	Feed conversion	Increased weight gain	Epithelial surface	Soybean acceptance	Feed digestibility	Pathogen control	Lower mortality	Enteritis protection	
		✓			✓	✓	✓		da Silva 2014 [29]
	✓	✓			✓				Robles 2013 [30]
		✓	✓	✓				✓	Liu 2019 [31]
				✓					Estensoro 2016 [32]
				✓		✓		✓	Piazzon 2017 [33]
	✓	✓	✓	✓				✓	Liu 2014 [34]



In recent years, cattle have also been tested for health and productivity improvements by diets and milk replacers being enriched with n-Butyric Acid derivatives. A growing number of studies prove beneficial effects like antibiotic replacement, offer better feed conversion or improved health status, showing that ruminants can also participate from the profit of different n-butyric acid administration forms.

Here the focus is clearly on calves with immature rumen where rapid development is needed to fulfill the economic need of an early weaning of calves from milk. The rumen passage in adult animals displays the key hurdle in applying n-Butyric Acid derivatives in beef and milk production.

Livestock		n-butyrate			Productivity improvements						Health			Reference
Cattle species	Animals tested in study	Butyric acid	Sodium salt	Fat coating	Feed conversion	Weight gain	Rumen development	Intestine maturation	Feed digestibility	Cell proliferation	Microbiota modulation	Less apoptosis	Overall health	
Suckling Holstein calves	29		■	■	✔	✔								Roh 2018 [35]
Male Holstein calves	28		■	■			✔	✔		✔		✔		Górka 2014 [36]
Male Holstein calves	21		■									✔		Górka 2011a [37]
Male Holstein calves	28		■	■		✔			✔				✔	Górka 2011b [38]
Male Holstein calves	88	■			✔	✔							✔	Hill 2011 [39]
Holstein calves	88		■		✔	✔		✔						Guilloteau 2009 [40]
Holstein/Frisian calves	16		■		✔	✔					✔			O'Hara 2018 [41]
Male Holstein calves	48	■			✔	✔			✔					Hill 2016 [42]

DISCLAIMER

These scientific studies have not yet been reviewed for effectiveness nor has recommended dosage been established by the FDA.

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* Butyrin means tri-n-butyglyceride or monoglyceride or mixtures thereof

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