

# Safety

REFERENCE	STUDY OBJECTIVES	STUDY DESIGN*	SUBJECTS AND (DAILY DOSE)	RESULTS
Papagaroufalis K, 2014	To assess the safety of starter infant formula containing <i>L. reuteri</i> DSM 17938 during the first month of life, with special reference to D-lactic acid, in comparison to infants fed a control starter formula. Other outcomes were GI tolerance, sleeping and crying behaviour, growth and occurrence of adverse events.	R, DB, controlled 28 days  Follow-up on days 112 and 168	<i>L. reuteri</i> : 36 (6.6 x 10 <sup>8</sup> CFU) Control: 35  31 infants in each group took part in the follow-up on days 112 and 168	<ul style="list-style-type: none"> <li>Median urinary D-lactate levels were higher in the <i>L. reuteri</i> group than in the control group at 7 and 14 days, but lower at 28 days. Results were consistent with normal ranges of D-lactate previously reported for healthy infants, and far below pathological ranges described in adults.</li> <li>The occurrence of serious and non-serious AEs was comparable between the two groups. Non-serious AEs were reported in 20% of infants in the probiotics group and 23% of infants in the control group. In both groups, most of these (5 in the probiotics group and 6 in the control group) were respiratory system disorders. None was related to the study products.</li> <li>In all, 5% of infants in each group had a serious AE during the study</li> <li>Growth was normal, without differences between groups</li> <li>There were no differences in the duration of crying or night time sleep</li> </ul>
Ceratto S, 2014 (abstract, sub-study of Savino 2010)	If probiotic treatment for infantile colic may prevent atopic diseases (cow's milk allergy and atopic dermatitis), asthma and migraine at the age of five, and effects on growth.	Original study: R, DB, PC	<i>L. reuteri</i> : 25 (1x10 <sup>8</sup> CFU). Placebo: 23 In 2010 50 were randomised at baseline and 46 analysed	Growth was similar in the two groups, measured as BMI Z-score.
Abrahamsson TR, 2013 Substudy of Abrahamsson 2007	In a study on prevention of allergy in newborns, <i>L. reuteri</i> ATCC 55730 reduced the incidence of IgE-associated allergic disease in infancy. This treatment might therefore also reduce the risk of asthma and allergic rhino conjunctivitis in school age, which this follow-up study set out to investigate. It also evaluated whether this supplementation was associated with any long-term side effects.	Original study: R, DB, PC	<i>L. reuteri</i> : 94 (1x10 <sup>8</sup> CFU) Placebo: 90 In the 2007 trial 232 infants were randomised and 188 completed	<ul style="list-style-type: none"> <li>Growth indices and gastrointestinal symptoms were similar in the two groups</li> <li>No severe adverse events were reported</li> </ul>
Lee LY, 2012 (abstract)	To establish safety in healthy, full term infants of starter infant formulae containing <i>L. reuteri</i> , and <i>L. reuteri</i> plus prebiotics FOS/GOS as assessed against WHO Growth Standards (CGS), and between the two test groups. GI tolerance and urinary L- and D-lactate were also investigated.	R, DB, controlled 6 months  Follow-up at 2 and 4 mo	<i>L. reuteri</i> : 68 <i>L. reuteri</i> + FOS/GOS: 72  No dose information	<ul style="list-style-type: none"> <li>Both groups gained weight in accordance with WHO CGS. Other growth parameters were similar in the two groups.</li> <li>Excretion of urinary L- and D-lactate were similar in the groups</li> <li>GI tolerance and morbidity were similar in the two groups</li> </ul>
Savino F, 2010	To study the effect of <i>L. reuteri</i> DSM 17938 on infantile colic in infants 2-16 weeks old, and investigate changes in the faecal microbiota.	R, DB, PC 21 days	<i>L. reuteri</i> : 25 (1x10 <sup>8</sup> CFU) Placebo: 21	<ul style="list-style-type: none"> <li>Infants in both groups increased their growth parameters significantly during the 3-week study, with no statistical differences between groups.</li> <li>The study products were well tolerated. 5 adverse events were reported, whereof one in the probiotic group. All were evaluated as unrelated to the study product.</li> </ul>
Abrahamsson T, 2007	Prevention of atopic eczema in infants 0-2 years old.	R, DB, PC 12 months	<i>L. reuteri</i> : 95 (1x10 <sup>8</sup> CFU) Placebo: 93	No clinical tolerance problems during the 12 months supplementation or at follow-up at 2 years of age
Weizman Z, 2006	Safety in healthy infants 3-65 days old.	R, DB, PC 4 weeks	<i>L. reuteri</i> : 20 (1.2x10 <sup>9</sup> CFU) Bb-12: 20 (1.2x10 <sup>9</sup> CFU) Control: 19	Infant formulas with added probiotics were safe, well tolerated and did not negatively affect growth, defecation habits or infant behaviour.
Connolly E, 2005	To investigate if levels of D(-)-lactic acid levels in the blood is a safety issue in infants who get <i>L. reuteri</i> as a long-term daily supplement from birth.	R, DB, PC 12 months	<i>L. reuteri</i> : 14 (1x10 <sup>8</sup> CFU) Placebo: 10	<ul style="list-style-type: none"> <li>All infants had very low levels of D(-)-lactic acid (20-130mM) as measured after 6 and 12 months, i.e. far below levels associated with D(-)-lactic acidosis</li> <li>This D(-)-lactic acid producing probiotic can be safely given to infants</li> </ul>
Karvonen A, 2001 (abstract)	Safety and colonisation in newborn term infants.	R, DB, PC 30 days	<i>L. reuteri</i> : 12 (10 <sup>5</sup> CFU) <i>L. reuteri</i> : 25 (10 <sup>7</sup> CFU) <i>L. reuteri</i> : 25 (10 <sup>9</sup> CFU) Placebo: 28	<ul style="list-style-type: none"> <li>No clinical tolerance problems</li> <li>Reduction in frequency of watery stools compared to placebo</li> </ul>

\* R= randomized, DB= double blind, PC= placebo controlled.  A video presentation of this study is available on [www.biogaia.com](http://www.biogaia.com)

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