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Risk assessment of *Lactococcus lactis* W58 used as "other substances"

Opinion of the Panel for Biological Hazards of the Norwegian Scientific Committee for Food Safety

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Risk assessment of *Lactococcus lactis* W58 used as "other substances".

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Assessed and approved

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements sold in Norway. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC *as substances other than vitamins or minerals that have a nutritional and/or physiological effect*. It is added mainly to food supplements, but also to other foods. VKM has not in this series of risk assessments of "other substances" evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of *Lactococcus lactis* W58, and it is based on previous risk assessments and articles retrieved from a literature search.

The risk of *L. lactis* W58 was assessed for the general population. However, in previous assessments of "probiotics" published by VKM, concerns have been identified for specific groups. Therefore, the risk was assessed for the age group with immature gastro-intestinal microbiota (age group 0-36 months), population with mature gastro-intestinal microbiota (>3 years) and vulnerable groups independent of age. VKM has also assessed the risk of *L. lactis* W58 in food supplements independent of the dose and have assessed exposure in general terms.

Other sources of *L. lactis* W58, such as foods, have not been included in the present risk assessment.

VKM concludes that it is unlikely that *L. lactis* W58 causes adverse health effects in the general healthy population with mature gastro-intestinal tract.

However, no data on long-term adverse effects on infants and young children were identified. As evidence is accruing that the early microbial composition of the neonatal gut is important for the development of the gut microbiota and the immune system of the growing child, it is not possible to exclude that a daily supply of a single particular bacterial strain over a prolonged period of time to an immature gastro-intestinal tract may have long-term, although still unknown, adverse effects on that development.

Key words: Adverse health effect, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM, *Lactococcus lactis* W58, food supplement

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetning av «andre stoffer» i kosttilskudd som selges i Norge. Disse risikovurderingene vil gi Mattilsynet vitenskapelig grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som stoffer som har en ernæringsmessig og/eller fysiologisk effekt, og som ikke er vitaminer og mineraler. VKMs oppgave er å utføre risikovurderinger av mulige negative helseeffekter av «andre stoffer». VKM vurderer ikke påståtte gunstige helseeffekter av «andre stoffer».

Denne rapporten er en risikovurdering av *Lactococcus lactis* W58 og er basert på tidligere risikovurderinger og artikler hentet fra litteratursøk.

Risiko for negative helseeffekter av *L. lactis* W58 er vurdert med tanke på hele befolkningen. Mulige uheldige virkninger for bestemte befolkningsgrupper er imidlertid blitt identifisert i tidligere risikovurderinger av probiotika utført av VKM. Risiko er derfor spesielt vurdert for aldersgruppen med umoden tarmflora (aldersgruppe 0-36 måneder), befolkning med moden tarmflora (> 3 år) og sårbare grupper uavhengig av alder. VKM har også vurdert risikoen for negative helseeffekter av *L. lactis* W58 i kosttilskudd uavhengig av dose og eksponering på generelt grunnlag.

Risikovurderingen inkluderer ikke andre kilder til *L. lactis* W58 enn kosttilskudd (som for eksempel mat).

VKM konkluderer med at det er usannsynlig at *L. lactis* W58 forårsaker negative helseeffekter i den generelle friske befolkningen med moden tarmflora.

Det er imidlertid mangel på data om uønskede langtidsvirkninger for spebarn og små barn (0-36 måneder). Det er økende vitenskapelig dokumentasjon som viser at den mikrobielle sammensetningen i neonatal tarm er viktig for utviklingen av en funksjonell tarmflora og et godt fungerende immunsystem hos det voksende barn. Det kan derfor ikke utelukkes at daglig tilførsel av en enkelt spesifikk bakteriestamme over en lengre tidsperiode til barn med en umoden tarmflora, kan ha langvarige negative effekter på utviklingen av en funksjonell tarmflora.

Abbreviations and glossary

Abbreviations

CFU	- Colony Forming Units
EFSA	- European Food Safety Authority
FAO	- Food and Agriculture Organization of the United Nations
GRAS	- Generally Recognized As Safe
ISAPP	- International Scientific Association for Probiotics and Prebiotics
NFSA	- Norwegian Food Safety Authority [Norw.: Mattilsynet]
SCF	- Scientific Committee on Food
QPS	- Qualified Presumption of Safety
VKM	- Norwegian Scientific Committee for Food Safety [Norw.: Vitenskapskomiteen for Mattrygghet]
WHO	- World Health Organization

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (REF).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition established by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences .

Probiotics¹

¹ The International Scientific Association for Probiotics and Prebiotics, ISAPP, proposed that when combined with the specifications outlined by the FAO/WHO Working Group for the Evaluation of

In 2001, the Food and Agriculture Organisation (FAO) of the United Nations and the World Health Organisation (WHO) defined probiotics as: Live microorganisms, which when administered in adequate amounts confer a health benefit on the host (FAO & WHO, 2002).

Alternative term to “probiotic”:

Currently, there are no approved health claims for probiotics. Applications for health claims on probiotics have been submitted for evaluation to EFSA and no application has received a positive opinion. For this reason, the term ‘probiotic’, when used on a food label, is considered to be a health claim (<http://ec.europa.eu/nuhclaims/>) and should not be used and should be replaced by “microorganism”.

No claims on probiotics are listed on the EU register as authorised for use. The probiotic claims that have been fully evaluated and rejected are listed as non-authorised on the EU register.

Probiotics in Food (2002), the key aspects of this definition should be more precise and in addition include the following aspects:

- A probiotic must be alive when administered,
- A probiotic must have undergone controlled evaluation to document health benefits in the target host,
- A probiotic must be a taxonomically defined microbe or combination of microbes (genus, species and strain level),
- A probiotic must be safe for its intended use.

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

While at the EU level, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods.

The Norwegian Food Safety Authority (NFSA) has recommended the Norwegian Ministry for Health and Care Services to regulate the addition of "other substances" to food supplements and other foods at a national level. NFSA has suggested using the Danish regulation as a model while establishing a national regulatory framework in Norway. NFSA has further suggested that the establishment of a list of substances with permitted maximal doses should be based on the products and substances found on the Norwegian market.

In preparation for a regulation, NFSA has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, after consultation with the industry, has compiled a list of "other substances" added to food supplements and foods marketed in Norway. NFSA requests VKM to carry out safety assessments for the microorganisms on the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to:

Phase 1

Since risk/safety assessments for some of the substances on the list have already been carried out by competent authorities (such as the European Food Safety Authority, Institute of Medicine - USA and Norwegian Scientific Committee for Food Safety), in phase 1 of the assignment, VKM has been requested to:

- make an overview of existing risk/safety assessments for «other substances» enlisted by NFSA, prepared by a competent risk assessment authority.

If assessments for some of these substances exist, then, VKM is requested to:

- describe data on upper limits (UL), guidance limits (GL) or other safe limits established for the substances in these assessments.

Phase 2:

Prepare a guidance document outlining the methodology to be used for the safety assessments of microorganisms.

Phase 3:

Assess the safety of microorganisms in accordance to the guidance document developed in Phase 2.

Safety assessments of microorganisms added to food supplements and other foods shall be carried out for the general population.

The NFSA requests the VKM to describe risks for vulnerable groups such as, infants and babies, pregnant and breast feeding women or those suffering from certain illnesses, in each of these assessments.

Attachment:

The list of microorganisms to be assessed.

1 Introduction

This risk assessment addresses the microorganism *Lactococcus lactis* W58.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any claimed beneficial effects from these substances.

According to information from the Norwegian Food Safety Authority (NFSA), *L. lactis* W58 is an ingredient in food supplements purchased in Norway. The total exposure to *L. lactis* W58 from other sources than food supplements, such as food products, is not included in the risk assessment.

The risk of adverse effects from exposure to *L. lactis* W58 was assessed for the general population. However, in previous assessments of probiotics published by VKM concerns in specific groups have been identified. Therefore, the risk was estimated for the age group with immature gastro-intestinal microbiota (age group 0-36 months), population with mature gastro-intestinal microbiota (>3 years) and vulnerable groups with mature gastro-intestinal tract. VKM has also assessed the risk of *L. lactis* W58 independent of the dose and possible matrix effect and have assessed exposure in general terms.

The present report is based on previous risk assessments and articles retrieved from a literature search.

2 Literature

The present risk assessment is based on articles retrieved from a literature search.

2.1 Previous risk assessments

As the recommendation for the QPS status is based on broad criteria, extensive literature search and transparent expert judgement, VKM has decided to accept the safety status as given by EFSA in the most up-to-date list (EFSA 2015) including possible qualification criteria. Therefore, the literature search for this assessment has been limited to the reports and articles published in 2015-2016.

2.2 Literature search

Following literature search was performed in the PUBMED:

1. ("Lactococcus lactis W58"[MeSH Terms])

The search returned 3 results. Two of these articles are published in period 2015-2016.

Other relevant articles, including reports from EFSA (QPS) and FDA (GRAS) are listed in the reference section.

2.3 Relevance screening

The titles of all results were scanned by project group, and for those that were of potential relevance, the abstracts were also inspected. The members of the project group performed the relevance screening, independently. Citations were excluded if they did not relate to the terms of reference. The reference lists in selected citations were scrutinized to identify additional articles or reports, not identified by the PubMed searches.

3 Hazard identification and characterisation

3.1 Hazard identification

L. lactis is a mesophilic Gram-positive bacteria used in the manufacture of a variety fermented dairy products. It is a lactic acid-producing bacteria which contributes to the characterisation development of flavour and texture, while protecting the product from spoilage microorganisms (de Ruyter, Kuipers, Meijer, & de Vos, 1997).

L. lactis is mainly isolated in the natural environment, including products of spontaneously fermented milk, the environment or plant material (Zycka-Krzesinska, Boguslawska, Aleksandrzyk-Piekarczyk, Jopek, & Bardowski, 2015).

Origin of the strain and the culture collection for deposition were not identified in the literature.

3.2 Hazard characterisation

3.2.1 QPS/GRAS

QPS

A wide variety of microbial species are used in food and feed production. Some have a long history of apparent safe use, while others are less well understood and their use may represent a risk for consumers. Experience has shown that there is a need for a tool for setting priorities within the risk assessment of those microorganisms used in food/feed production referred to EFSA and consequently the subject of a formal assessment of safety. To meet this need a system was proposed for a pre-market safety assessment of selected groups of microorganisms leading to a "Qualified Presumption of Safety (QPS)". In essence

this proposed that a safety assessment of a defined taxonomic group (e.g. genus or group of related species) could be made based on four pillars (establishing identity, body of knowledge, possible pathogenicity and end use). If the taxonomic group did not raise safety concerns or, if safety concerns existed, but could be defined and excluded (the qualification) the grouping could be granted QPS status. Thereafter, any strain of microorganism the identity of which could be unambiguously established and assigned to a QPS group would be freed from the need for further safety assessment other than satisfying any qualifications specified. Microorganisms not considered suitable for QPS would remain subject to a full safety assessment (EFSA, 2007).

The list of the microorganisms have been (and will be) regularly updated by EFSA.

GRAS

Any substance that is intentionally added to food is regarded as a food additive and is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excluded from the definition of a food additive. The use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food (FDA, 2016).

3.2.2 Influence of live microorganisms on the development of gut microbiota

It is now generally recognised that the establishment of the gut microbiota very early in life is a critical stage of development and probably has far-reaching effects on the health of the individual at all ages, including the development of some so-called life-style diseases later in life. Gut colonization begins very early and may in fact even have started before birth (Greenhalgh, Meyer, Aagaard, & Wilmes, 2016). Immediately after birth a beneficial microbiota develops following transfer of bacteria from the mother during birth, from the birth canal. There follows a further transfer of the mother's own microbiota during breast-feeding from bacteria resident in the breastmilk-producing glands and canals. Human milk contains components that stimulate the growth of these bacteria and therefore further influences and encourages the establishment of a beneficial microbiota. There is also evidence that both oral and faecal microorganisms may be transferred from mother to child at a very early stage (Greenhalgh et al., 2016).

Colonization of the infant gut mucosa is important in the establishment of the gut mucosal barrier and for maturation of the gut immune system. It is known that infants born by Caesarean section develop a gut microbiota that is more reflective of environmental bacteria. However, several factors can affect this natural progression, including Caesarean delivery, prematurity, use of formula feeds and treatment with antibiotics (Wang, Monaco, & Donovan, 2016).

The use of antibiotics, both to the neonate and to the mother before parturition, has been shown to change the types and/or the comparative ratios of bacteria in the gut of the neonate. It has been suggested that even a temporary diversion from the establishment of a healthy gut microbiota at this point may cause alterations in the establishment of the adaptive immune system and that this may have many far-reaching effects later in life, such as allergy and autoimmune diseases.

A disturbance in microbiota from what is presently regarded as “normal” is called dysbiosis. However there is at present no “Gold standard” for the composition of the gut microbiota in neonates and very young children. The human host and its gut microbiota have an important relationship whereby the host recognizes members of the gut microbiota and adjusts the immune response to their presence. Thus the intestinal microbiota of the neonate guides the development of the immune system and a tolerance to the host commensal bacteria. It has been suggested that dysbiosis may be the cause of many conditions, including necrotizing enterocolitis, inflammatory bowel disease, irritable bowel syndrome, atopic and allergic disease and metabolic diseases including obesity and diabetes 1. However, dysbiosis may influence these diseases in different ways – by affecting the immune system or by a direct result of the changed microbiota (Wang et al., 2016). Dysbiosis at an early age can predispose to obesity at any age in life. This may be due to the establishment of a different balance of microorganisms in the gut microbiota which are able to extract energy from multiple sources and thus predispose the host to obesity.

Studies of the role of the neonates GIT microbiota indicate a diversity of microorganisms that include, but not exclusively, such bacteria as lactobacilli and bifidobacteria. Present opinion suggests that this diversity in itself is an important factor. The inclusion of large numbers of one particular strain of probiotic bacteria in the diet of a neonate can therefore be questioned. Indeed, Berstad et al (2016) voiced concern that ingestion of probiotics could negatively affect the resident commensal flora and leave an empty ecological niche following cessation of treatment. Some probiotic strains have been shown to have a number of effects on neonate conditions that can be attributed to the gut microbiota. However, long-term studies of the effects of consumption of probiotic cultures have not been done and therefore it has not been possible to evaluate the long-term effects of manipulating the gut microbiota in neonates and very young children. Similarly, it has not been possible to evaluate the safety of the establishment of a less diverse microbiota as a consequence of feeding probiotics to very young children.

3.2.3 Antimicrobial resistance properties of *L. lactis* W58

Data regarding antimicrobial resistance in *L. lactis* W58 is lacking.

Dairy lactococci are in general sensitive to most clinical antibiotics and therefore can antibiotic residues in milk can cause starter failures. They are however known to contain plasmids and to exchange genetic material by intra- and intergeneric conjugation and

therefore the potential for the spread of transferable antibiotic resistances exists (Leuschner et al., 2010).

Under this selective pressure, *Lactococcus* may acquire antibiotic resistance and survive antimicrobial treatments, and subsequently also act as reservoir for antibiotic resistance genes for other bacteria. While the antibiotic resistance situation of *Lactococcus* directly isolated from milk is not well documented, resistant strains have been reported to be present in raw milk cheese (Florez, Ammor, & Mayo, 2008; Teuber, Meile, & Schwarz, 1999). One of these strains, *L. lactis* K214, harbored a multidrug resistance plasmid pK214 which contains the tetracycline resistance gene *tet(S)*, the chloramphenicol resistance acetyltransferase gene *cat_{pc223}*, the streptomycin adenylyl transferase gene *str* and the multidrug transporter gene *mdt(A)* (Perreten et al., 1997). Mdt(A) was shown to confer resistance to macrolides, lincosamides, streptogramins and tetracycline in *L. lactis* (Perreten, Schwarz, Teuber, & Levy, 2001) and has not been detected in other species to date.

L. lactis produces two distinct multidrug transporters, designated LmrA and LmrP, that both confer resistance to a wide variety of cationic lipophilic cytotoxic compounds as well as to many clinically relevant antibiotics (Poelarends, Mazurkiewicz, & Konings, 2002). The broad antibiotic specificity of LmrP and LmrA, the possible transfer of the *ImrP* and *ImrA* genes to other bacteria in food or the digestive tract, and the presence of homologues in pathogenic microorganisms, provide a serious threat to the efficacy of valuable antibiotics. In addition, LmrA is able to complement the human MDR P-glycoprotein, supporting the clinical and academic value of studying these bacterial proteins.

3.2.4 Safety concerns

Lactococcus lactis subsp. *lactis* and *Lactococcus lactis* subsp. *cremoris* are common starter organisms in dairy industry and have been included in the QPS list, despite of isolated human and animal clinical cases involving *L. lactis* that have been reported (EFSA, 2011). A search in PubMed revealed new human cases of neonatal meningitis and septicaemia (Uchida et al., 2011). Two reported cases of brain abscesses in children were reported whereby the details of the species identification were not described in the first (Topcu, Akinci, Bayram, Hiz, & Turkmen, 2011) and in a second case study the child was immunocompromised without an individualized diet or nutrition (Feierabend, Reichart, Romeike, Kalff, & Walter, 2013). The authors did not describe the method of species identification.

The species *L. lactis*, is considered by the EFSA to be suitable for QPS approach to safety. Therefore, the strain does not require any specific demonstration of safety other than confirming the absence of any determinants of resistance to antibiotics of human and veterinary clinical significance. EFSA concludes that further studies on both human and veterinary clinical isolates could be considered to find out any possible strain specific factors that might contribute to the pathogenicity (EFSA, 2012).

An occasional association with extremely rare individual cases of infections such as endocarditis, septicaemia, necrotising pneumonitis and liver abscess should not be regarded as an indication of human pathogenicity taking into account the extent of exposure to these microorganisms (Leuschner et al., 2010).

The recent findings do not warrant a reconsideration of the QPS recommendation of *L. lactis* which is maintained.

L. lactis is widely used in food- and biotechnological processes because the American Food and Drug Administration (FDA) classified it as GRAS in the Food Additives Amendment of 1958. Industrially, it is used in dairy starter cultures and there have been several attempts to use lactococci as cell factories for the production of various compounds (flavors, bacteriocins, vitamins etc.) (Adamberg, Seiman, & Vilu, 2012).

3.2.5 Possible infectivity in vulnerable groups

Previously published assessments have identified vulnerable groups as; pregnant women, children, elderly people, immunocompromised and critically ill patients (VKM, 2014, 2016).

However, no studies on long-term effects on infants and young children were identified in the literature search. Due to mesophilic property of *Lactococcus* spp. and relatively low growth temperature optima make even opportunistic infections unlikely. As evidence is accruing that the early microbial composition of the neonatal gut is important for the development of the gut microbiota and the immune system of the growing child, it is not possible to exclude that a daily supply of a single particular bacterial strain over a prolonged period of time to an immature gastro-intestinal tract may have long-term, although still unknown, adverse effects on that development.

4 Exposure assessment

As this assessment is concerned with general safety of the *L. lactis* W58 and is not related to a specific product or dose, the exposure assessment is given in general terms.

The dose ingested in the portion of the product usually recommended for daily consumption contains log 9 of at least one strain among those present in the product. The use of different number of microorganism may be allowed when its rationale has been demonstrated by significant scientific studies. The number of cells must be specified on the product label, and moreover, this number has to be guaranteed until the end of the product shelf-life, at the specified storage conditions, with uncertainty of 0.5 log units. It is emphasized that the analytical method of quantification of living bacterial cells may differ from species to species (Ministero, 2013).

Regarding consumption by infants, Fernandez et al. (2003) extrapolated from the results of several authors that an infant would consume between log 5 and log 7 bacteria daily along

with the consumption of 800 ml breast milk. As a comparison, a 100 g serving of commercial probiotic yoghurt would contain approximately log 9-10 CFU. Thus the amount of cells consumed in a serving of yoghurt would be considerably higher than natural milk levels, in fact up to 10 000 x greater (difference between log 5 and log 9).

5 Risk characterisation

According to FAO/WHO, integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties.

The safety aspects of *L. lactis* W58 give no reason for concern and it has been granted QPS status by EFSA and GRAS status by EFSA. However, no data on long-term adverse effects on infants and young children were identified. As evidence is accruing that the early microbial composition of the neonatal gut is important for the development of the gut microbiota and the immune system of the growing child, it is not possible to exclude that a daily supply of a single particular bacterial strain over a prolonged period of time to an immature gastrointestinal tract may have long-term, although still unknown, adverse effects on that development. An occasional association with extremely rare individual cases of infections may occur. It should not be regarded as an indication of human pathogenicity taking into account the extent of human exposure to these microorganisms.

The safety aspects of *L. lactis* W58 for vulnerable groups other than the one with immature gastrointestinal tract give no reason for concern.

6 Uncertainties

Consumption of microorganism *L. lactis* W58 in a "normal" dose is considered safe in an adult (> 3 years) "normal" population. In this assessment, some uncertainties have been identified. Many of these uncertainties may overlap with the data gaps (Section 8).

The uncertainties identified are as follows:

- Long-term effects on infants and young children
- Consumption by vulnerable groups other than the group with immature gastrointestinal tract
- Antimicrobial resistance property of *L. lactis* W58

7 Conclusions with answers to the terms of reference

VKM concludes that it is unlikely that *L. lactis* W58 causes adverse health effects in the population with mature gastro-intestinal tract. However, it is not possible to exclude that a daily supply of a single particular bacterial strain over a prolonged period of time to an immature gastro-intestinal tract may have long-term, although still unknown, adverse effects on that development.

There is also lack of data regarding consumption of *L. lactis* in vulnerable groups (e.g. elderly, immunocompromised patients, critically ill patients and pregnant) other than the one with immature gastrointestinal tract.

8 Data gaps

- Studies on adverse effects in children and vulnerable groups are lacking.
- Data regarding human studies on adverse effects after long-term oral exposure to *L. lactis* W58 are lacking.
- Antimicrobial resistance profile
- Data regarding multidrug transporter LmrA and LmrP in *L. lactis* W58

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