

DOI 10.17590/20190606-133224

## **New pathogens in beef and cow's milk products: More research required**

BfR Opinion No 014/2019 of 18 April 2019, updated on 19 September 2019

In February 2019, the German Cancer Research Centre (DKFZ) presented findings on new infectious agents referred to as “Bovine Milk and Meat Factors” (BMMFs). According to these findings, the previously unknown pathogens can cause inflammation. According to the DKFZ, they have been detected thus far in cow's milk, cow's milk products and the blood serum of healthy cattle. From the scientific findings made to date, it seems possible that an indirect connection could be interpreted between the consumption of various foods originating from cattle and the occurrence of several cancer types in humans. The DKFZ is assuming that infants whose immune system has not yet fully matured become infected with BMMF during their first year of life through supplementary feeding with cow's milk. They therefore conclude that infants should not be given cow's milk too early.

According to the DKFZ, BMMFs are new pathogens similar in type to both viruses and bacteria. Because they are related to plasmids, they are currently being called “plasmidomes”. As far as can be established by the DKFZ researchers, the BMMF do not occur as “naked” genetic material but rather together with proteins.

The German Federal Institute for Risk Assessment (BfR) and Max Rubner-Institut (MRI) jointly conclude that an assessment of the possible risks posed by so-called BMMFs as possible cancer risk factors has not yet been possible due to insufficient data. The presumed connection between the BMMFs and the incidence of cancer in humans should be examined further.

In line with the latest available information regarding nutrition, the BfR and MRI agree with the following recommendation: On the basis of currently published epidemiological studies on the connection between the consumption of red and processed meat and an increased risk of colon cancer and in concurrence with the German Nutrition Society (DGE), it is recommended that meat consumption be limited to a maximum of 600 grams per week. However, the consumption of cow's milk without any restriction is still recommended in compliance with the latest available knowledge and is still advocated in the first year of life in accordance with the recommendations of the *Gesund ins Leben* Network. Breastfeeding in order to prevent various diseases is also fundamentally advocated.

The German Federal Institute for Risk Assessment (BfR) and Max Rubner-Institut (MRI) have assessed a press release on an event held at the German Cancer Research Centre (DKFZ) in Heidelberg on “new infection pathogens from milk and meat as cancer risk factors” and state their joint position on this in the following paragraphs.

### **Background of the DKFZ press release**

In the opinion of the DKFZ, a certain class of pathogens in beef and milk, the so-called “Bovine Meat and Milk Factors” (BMMFs), could be the cause of chronic inflammations which could form the basis for a malignant degeneration of cells in the breast and colon. According to the DKFZ (2019) and zur Hausen et al. (2017), the geographical distribution pattern of the incidence rates of colon and breast cancer indicates a close connection with the consumption of milk and meat products from European cattle (*Bos taurus*).

According to the documents provided at the DKFZ press conference (2019), BMMFs are single-stranded, ring-shaped DNA elements which bear a great similarity to the sequences of specific bacterial plasmids. All BMMFs known to date possess a gene for the “rep” protein (replication initiator protein) required for their own replication, irrespective of other genes which may exist. According to Eilebrecht et al. (2018), most BMMFs show a similarity to plasmids of the species *Acinetobacter baumannii*, although several BMMFs also have similarities with certain viruses having small, circular, single-strand genomes (DKFZ, 2019). Furthermore, they probably do not occur in nature as naked DNA but rather in association with proteins. BMMFs constitute, according to the DKFZ, a new class of pathogens whose characteristics lie between viruses and bacteria. Due to their relationship with plasmids, they are therefore currently being referred to as “plasmidomes”. The DKFZ points out that it has not yet been possible to clearly define the nature of these pathogens.

Over 120 different types of BMMF DNA have been isolated until now from commercially available cow’s milk, cow’s milk products and from serum samples from healthy cattle (Whitley et al., 2014; Falida et al., 2017; DKFZ, 2019). A replication of various BMMFs in human cells was proven (Eilebrecht et al., 2018), whereby the pathogens depend on cellular proteins which have not yet been determined. Furthermore, serum antibodies against BMMF were detected in a total of 350 individuals (healthy people and cancer patients), thus proving exposure to the pathogen. According to the DKFZ, BMMF proteins have been so far found in the colon, prostate gland and brain, whereas BMMF DNA was detected in the human colon.

Areas of tissue infected with BMMFs show increased levels of reactive oxygen compounds, which are a typical characteristic of inflammation and which favour the development of genetic changes. Due to these observations, particularly the epidemiological ones, the DKFZ is assuming that an infection with BMMFs can result from the consumption of dairy products and/or beef, especially among infants whose immune system has not yet fully developed. No indications of a possible time of infection are to be found in the literature. The immune system is not fully developed at birth, or rather works at a reduced level, according to the latest findings (Ulas et al., 2017), and develops itself further step by step through exposure to antigens during childhood (Simon et al., 2015). However, infection at a later stage of life with a fully developed immune system cannot be excluded at present.

After infection, the pathogens are said to induce a chronic-inflammatory reaction in certain tissues (colon, breast) which can promote the development of cancer in the surrounding tissue (especially colon cancer, possibly also breast and prostate cancer). The outbreak of the disease is not expected to occur until decades after the actual infection (zur Hausen et al., 2019). BMMFs are thereby thought to have an indirect carcinogenic effect, meaning that they are not involved directly in the cancer-promoting molecular processes of the cells but create a – usually inflammatory – carcinogenic environment. For these reasons, the DKFZ concludes that there is no direct causality between an infection with BMMFs and colon cancer, for example, but that the BMMFs share a portion of the risk for colon cancer which cannot be exactly quantified (DKFZ, 2019).

The DKFZ mentions breastfeeding over a longer period (over 6 months) as a possible preventive measure against infection with BMMFs. Breast milk contains numerous substances with antipathogenic properties (Peterson et al., 2013). These often contain glycan structures, i.e. sugars, which occur either as free oligosaccharides (human milk oligosaccharides) or bound as macromolecules in the form of glycoconjugates (glycoproteins and glycolipids) (Peterson et al., 2013; Morozov et al., 2018). Human milk glycans are capable of mimicking the recognition points for some pathogens, binding themselves to them and hindering the pathogens from adhering to cell surfaces, thus preventing infections (Newburg et al., 2009; Peter-

son et al., 2013; Morozov et al., 2018). Breastfeeding goes hand in hand with a reduced risk of infection by various pathogens (e.g. rotaviruses), especially if infants are exclusively breastfed over the first 6 months (Krawczyk et al., 2016; Quigley et al., 2016). It cannot therefore be ruled out, and it is generally conceivable as a hypothesis, that human milk glycans could also protect against infections with BMMFs. This hypothesis cannot be substantiated at the moment, however, due to a lack of data.

The evidence of a connection between early feeding with breast milk and the risk of cancer of the progeny in adulthood is limited. The most extensive research has been conducted on the association with breast cancer, but the results are inconsistent (Ekbom et al., 1993; Freudenheim et al., 1994; Weiss et al., 1997; Titus-Ernsthoff et al., 1998; Martin et al., 2005; Wise et al., 2009).

## Assessment

As explained above, it is currently not possible to determine or define the exact nature of BMMFs. The above-mentioned observations – especially the epidemiological ones – can be interpreted as preliminary indications of a possibly indirect connection between the consumption of various foods of bovine origin and the incidence of certain types of cancer in humans, but they do not as yet show a causal connection.

Valid, evidence-based examinations for estimating the potential risk are currently lacking. There is no data, for example, on the occurrence of BMMFs in other foods of non-bovine origin, on the occurrence of BMMFs in healthy people compared to cancer patients, on the mechanism of inflammation and cancer induction through BMMFs, and on the infectivity and inactivation of BMMFs in foods. The estimation of a connection between the consumption of bovine foods containing BMMFs and the incidence of tumour diseases seems hardly possible at the moment, since BMMFs are only supposed to act as indirect carcinogens and only after a very long latency period.

Moreover, the epidemiological studies published to date must be seen in a critical light. In the case of intestinal tumours, the studies published to date indicate that the consumption of red and processed meat correlates with the occurrence of colon cancer (WCRF, 2007; Huxley et al., 2009; Chan et al., 2011; Corpet, 2011), but that a high consumption of milk and dairy produce is accompanied by a reduced risk of colon cancer (WCRF, 2007). According to the WCRF (2018), neither the consumption of red meat nor of cow's milk results in increased incidence of breast cancer.

## Conclusion

An assessment of the hazards posed by so-called “Bovine Meat and Milk Factors” (BMMFs) as possible cancer risk factors is currently not possible due to insufficient data.

On the basis of the epidemiological studies published to date with regard to the connection between the consumption of red and processed meat and increased risk of colon cancer, and in concurrence with the German Nutrition Society (DGE) it is recommended limiting meat consumption to a maximum of 600 g/week. However, the consumption of cow's milk without any restriction is still recommended in compliance with the latest available knowledge and, in accordance with the recommendations of the *Gesund ins Leben* Network is still advocated in the first year of life. The network *Gesund ins Leben* is headquartered at the Federal Centre

for Nutrition (BZfE), the competence and communication centre for nutrition issues in Germany.

Breastfeeding as a preventive measure against the occurrence of various diseases is fundamentally to be advocated. With regard to the prevention of an infection with BMMFs, however, the current lack of valid data precludes any conclusion.

### More information on the topic of viruses in food at the BfR website

Viruses

[https://www.bfr.bund.de/en/a-z\\_index/viruses-130212.html](https://www.bfr.bund.de/en/a-z_index/viruses-130212.html)

Scientific publication on polyomaviruses in beef

[https://www.bfr.bund.de/en/detection\\_and\\_genome\\_characterization\\_of\\_bovine\\_polyomaviruses\\_in\\_beef\\_muscle\\_and\\_ground\\_beef\\_samples\\_from\\_germany-240042.html](https://www.bfr.bund.de/en/detection_and_genome_characterization_of_bovine_polyomaviruses_in_beef_muscle_and_ground_beef_samples_from_germany-240042.html)



BfR "Opinions App"

### References

Chan D.S. et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *Plos One* 8, e20456 (2011).

Corpet DE. Red meat and colon cancer: should we become vegetarians, or can we make meat safer? *Meat Sci* 89, 310-316 (2011).

Deutsches Krebsforschungszentrum (DKFZ). Pressekonferenz „Neuartige Infektionserreger als Krebsrisikofaktoren“. Heidelberg, 26.02.2019. verfügbar unter: [https://www.dkfz.de/de/presse/download/Hintergrund-PK-Plasmidome\\_final.pdf](https://www.dkfz.de/de/presse/download/Hintergrund-PK-Plasmidome_final.pdf).

Eilebrecht, S., Hotz-Wagenblatt, A., Sarachaga, V., Burk, A., Falida, K., Chakraborty, D., Nikitina, E., Tessmer, C., Whitley, C., Sauerland, C., Gunst, K., Grewe, I., Bund, T. Expression and replication of virus-like circular DNA in human cells. *Sci Rep.* 12;8(1):2851 (2018). <https://doi.org/10.1038/s41598-018-21317-w>.

Ekbom A, Hsieh CC, Trichopoulos D, Yen YY, Petridou E, Adami HO. Breast-feeding and breast cancer in the offspring. *Br J Cancer.* 1993;67(4):842-5.

Falida, K., Eilebrecht, S., Gunst, K., zur Hausen, H., de Villiers, EM. Isolation of two virus-like circular DNAs from commercially available milk samples. *Genome Announc* 5:e00266-17 (2017). <https://doi.org/10.1128/genomeA.00266-17>.

Freudenheim JL, Marshall JR, Graham S, Laughlin R, Vena JE, Bandera E, et al. Exposure to breastmilk in infancy and the risk of breast cancer. *Epidemiology.* 1994;5(3):324-31.

Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int. J. Cancer* 125, 171-180 (2009).

- Krawczyk A, Lewis MG, Venkatesh BT, Nair SN. Effect of Exclusive Breastfeeding on Rotavirus Infection among Children. *Indian J Pediatr.* 2016;83(3):220-5.
- Martin RM, Middleton N, Gunnell D, Owen CG, Smith GD. Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. *J Natl Cancer Inst.* 2005;97(19):1446-57.
- Morozov V, Hansman G, Hanisch FG, Schroten H, Kunz C. Human Milk Oligosaccharides as Promising Antivirals. *Mol Nutr Food Res.* 2018;62(6):e1700679.
- Netzwerk Gesund ins Leben. Milch und Milchprodukte in der Beikostzeit. <https://www.gesund-ins-leben.de/inhalt/milch-und-milchprodukte-in-der-beikostzeit-29754.html> (retrieved on 12 August 2019)
- Newburg DS. Neonatal protection by an innate immune system of human milk consisting of oligosaccharides and glycans. *J Anim Sci.* 2009;87(13 Suppl):26-34.
- Peterson R, Cheah WY, Grinyer J, Packer N. Glycoconjugates in human milk: protecting infants from disease. *Glycobiology.* 2013;23(12):1425-38.
- Quigley MA, Carson C, Sacker A, Kelly Y. Exclusive breastfeeding duration and infant infection. *Eur J Clin Nutr.* 2016; 70(12):1420-7.
- Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci.* 2015;282(1821):20143085.
- Titus-Ernstoff L, Egan KM, Newcomb PA, Baron JA, Stampfer M, Greenberg ER, et al. Exposure to breast milk in infancy and adult breast cancer risk. *J Natl Cancer Inst.* 1998;90(12):921-4.
- Ulas, T., Pirr, S., Fehlhaber, B., Bickes, MS., Loof, TG., Vogl, T, Mellinger, L., Heinemann, AS., Burgmann, J., Schöning, J., Schreek, S., Pfeifer, S., Reuner, F., Völlger, L., Stanulla, M., von Köckritz-Blickwede, M., Glander, S., Barczyk-Kahlert, K., von Kaisenberg, C., Friesenhagen, J., Fischer-Riepe, L., Zenker, S., Schultze, JL., Roth, J., Viemann, D. S100-alarmin-induced innate immune programming protects newborn infants from sepsis. *Nat Immunol.* 2017 Jun;18(6):622-632. doi: 10.1038/ni.3745.
- WCRF World Cancer Research Fund. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR (2007).
- WCRF World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective . Continuous Update Project Expert Report 2018. Available at [dietandcancerreport.org](http://dietandcancerreport.org).
- Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, et al. Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology.* 1997;8(2):181-7.
- Whitley C., Gunst, K., Müller, H., Funk, M., zur Hausen, H., de Villiers, EM. Novel replication-competent circular DNA molecules from healthy cattle serum and milk and multiple sclerosis-affected human brain tissue. *Genome Announc.* 2(4):e00849-14 (2014). <https://doi.org/10.1128/genomeA.00849-14>.
- Wise LA, Titus-Ernstoff L, Newcomb PA, Trentham-Dietz A, Trichopoulos D, Hampton JM, et al. Exposure to breast milk in infancy and risk of breast cancer. *Cancer Causes Control.* 2009;20(7):1083-90.
- zur Hausen, H., Bund, T., de Villiers, EM. Infectious agents in bovine meat and milk and their potential role in cancer and other chronic diseases. *Curr. Top. Microbiol. Immunol.* 407:83-116 (2017). [https://doi.org/10.1007/82\\_2017\\_3](https://doi.org/10.1007/82_2017_3).

zur Hausen, H., Bund, T., de Villiers, EM. Specific nutritional infections early in life as risk factors for human colon and breast cancers several decades later. *Int. J. Cancer*: 144, 1574–1583 (2019) <https://doi.org/10.1002/ijc.31882>.

### **About the BfR**

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the Federal Government and Federal Laender on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

*This text version is a translation of the original German text which is the only legally binding version.*