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Allulose, sugar substitute: More data is required for a health assessment as a food ingredient

BfR opinion No. 001/2020 of 8 January 2020


D-allulose is a rare sugar belonging to the monosaccharides. The sweetness of D-allulose corresponds to about 70 % of the sweetness of household sugar (saccharose). However, a significantly lower calorie intake is associated with the consumption of D-allulose. D-allulose is therefore one of the sugar substitutes listed in the National Reduction and Innovation Strategy for Sugars, Fats and Salts in Ready-Made Products by the Federal Ministry of Food and Agriculture (BMEL). No opinion on the safety of D-allulose as a novel food has been adopted by the European Food Safety Authority (EFSA) as yet.

The German Federal Institute for Risk Assessment (BfR) has evaluated whether the use of D-allulose as a food ingredient could pose a health risk. Against the background that the rare sugar trehalose has caused an increase of hospital infections with the highly virulent bacteria *Clostridium difficile* in the USA, the BfR assessed the possibility that a comparable risk is associated with the consumption of D-allulose. However, based on currently available data, it is not yet possible to draw definitive conclusions on this question.

The BfR concludes the following in its risk assessment:

- The use of D-allulose as a food ingredient may selectively favour the growth of bacteria in the species *Klebsiella*, such as *K. pneumoniae*, within the human body. While healthy people do not show any symptoms of illness during colonisation with *Klebsiella*, which are one of the five most frequent causes of hospital-borne infections (especially sepsis and lung inflammation). Health risks caused by regular consumption of food to which D-allulose has been added would therefore initially be most relevant in hospitals.
- In the case of the addition of D-allulose to foods, *Klebsiella* spp. may require monitoring as part of the microbiological food monitoring.
- From a risk assessment perspective, scientific clarification is still needed as to the extent to which regular consumption of unusual quantities of D-allulose thus far, as a novel food, increases the concentration of this sugar in certain areas of the human body, has an unwanted influence on the occurrence and characteristics of *Klebsiella* spp. in the human intestinal flora and/or changes the infectiousness of virulent *Klebsiella* spp. (esp. *K. pneumoniae*).

The specific risk of favourable conditions for human pathogenic bacteria within the human body caused by food ingredients - as with trehalose - can be considered as a possibly 'emerging risk'. It has not been considered in previous safety assessments carried out, especially those which have authorised the use of D-allulose as a food ingredient in various Asian countries and in the USA.

BfR		BfR risk profile: [Allulose] (Opinion No. [001/2020])			
A Affected persons	General population Persons with weakened immune systems				
B Probability of an impairment to health from the use of D-allulose as a food ingredient	Practically impossible	Unlikely	Possible	Probable	Certain
C Severity of an impairment to health from the use of D-allulose as a food ingredient	A conclusive assessment of possible health risks cannot be made from the data which is currently available.				
D Validity of available data	High: The most important data is available and there are no contradictions	Medium: Some important data is missing or contradictory		Low: Much important data is missing or contradictory	
E Controllability by the consumer	Controls not needed	Controllable through precautionary measures	Controllable through avoidance	Not controllable	

Fields marked in dark blue indicate the properties of the risk assessed in this opinion (for further details, see the text of Opinion No. 001/2020 of the BfR issued 8 January 2020)

Explanations

The risk profile is intended to visualise the risk outlined in the BfR opinion. The profile is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding opinion.

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)

1 Subject of the assessment

The BfR carried out a risk assessment of the monosaccharide D-allulose, which is listed as a possible sugar substitute in the National Reduction and Innovation Strategy. The background for the BfR assessment is a rise in infections with highly virulent *Clostridium difficile* in the USA, which has occurred in connection to the use of another rate sugar, the disaccharide trehalose, as a food ingredient. It has to be clarified whether there may be a possibility of such a problem also occurring due to the increased use of D-allulose.

The BfR has dealt with the following questions:

- Does the use of allulose favour the growth and infectiousness of human pathogenic bacteria (e. g. *Clostridium difficile*)?
- Which bacteria may be affected by this?
- Does the use of D-allulose as a food ingredient pose a risk to health?

2 Results

The BfR states the following results:

- A case control study has indicated that the D-allulose operon may be an independent pathogenicity factor in *Klebsiella pneumoniae*.
- Over two-thirds of the available isolates from the species *Klebsiella* in the database, which also includes multi-resistant and/or hypervirulent strains of *K. pneumoniae*, contain the identified D-allulose operon in their genome. Based on available sequence data no statement on the functionality of this operon can be made. A connection between the D-allulose operon and the pathogenicity and/or resistance of bacteria to anti-microbial

substances also cannot be derived from the analyses of the publicly available *K. pneumoniae* genomic data.

- The use of D-allulose as a food ingredient may be associated with a selective advantage for the growth of bacteria in the species *Klebsiella*, such as *K. pneumoniae*, within the compartments of the human body.
- A selection advantage for growth could become most relevant in hospitals, due to the infection biology characteristics of *K. pneumoniae*.
- If D-allulose would be added to foods, *Klebsiella spp.* may require monitoring from a microbiological food monitoring perspective.

Furthermore, scientific clarification is still needed as to the extent of which regular consumption of thus far unusual quantities of D-allulose, as a novel food

- a) increases the concentration of this sugar in certain human body segments,
- b) undesirably affects occurrence and properties of *Klebsiella spp.* in the human intestinal flora and/or
- c) changes the infectiousness of virulent *Klebsiella* (esp. *K. pneumoniae*).

The BfR points out that in previous safety assessments, which have authorised the use of D-allulose as a food ingredient in various Asian countries and in the USA, have not considered the potential selection advantage for human pathogenic bacteria within the human body. This specific risk was first evident in 2018 in the USA, by the example of the disaccharide trehalose, and has to be considered as a possible 'new emerging risk'.

3 Rationale

3.1 Background

The carbohydrates trehalose (a disaccharide from fungi with cold protection characteristics) and D-allulose (an almost indigestible, but sweet-tasting C3-epimer of fructose) naturally occur only in small quantities. In recent years, both sugars have become available in large quantities and at reasonable prices by means of suitable technological procedures. Trehalose has been used as a food ingredient in the USA since the 2000s. In the EU, a marketing authorisation for trehalose under the *Novel Food* Regulation (Regulation (EC) No 258/97) was also granted with decision 2001/721/EC.

Along to the increased use of trehalose in foods, a rise of severe colitis cases caused by *Clostridium difficile* was registered in the USA. Three *C. difficile* types with increased virulence were identified to be responsible for the increase of the infections. Interestingly, all *Clostridium difficile* strains had newly acquired but independent mutations which increased their ability to use trehalose (Collins et al., 2018 a and b).

D-allulose (D-ribo-2-hexulose, or psicose) has been used as a sweetener in foods in Asia (Japan, China, Korea) since 2010. In the USA, the Food and Drug Administration (FDA) granted GRAS (*generally recognized as safe*) status for D-allulose several times in 2016 and 2017 (GRAS No. 647, No. 693 and No. 755). In Europe, several *Novel Food* requests have been submitted to EFSA for D-allulose and are currently being processed.

In Germany, the use of D-allulose to replace saccharose is a central part of the 'National Reduction and Innovation Strategy for Sugars, Fats and Salts'. The Federal Ministry of Food and Agriculture (BMEL) is funding technological research for exploring the conditions of use for D-allulose in the period from 2018 to 2021.

3. 2 D-allulose intake, metabolism and excretion

The sweetness of D-allulose corresponds to about 70 % of the sweetness of saccharose (household sugar). However, a significantly lower caloric intake is associated with the consumption of D-allulose (Chung et al., 2012; Chattopadhyay et al., 2014; Mooradian et al., 2017). D-Allulose occurs naturally in small quantities in foods and drinks. In the Japanese population, intake quantities of 206 mg per day or 3.5 mg/kg body weight (BW) and day were estimated to be from natural sources. However, there is no existing data for the intake of D-allulose from natural sources in Germany.

Studies of rats and humans show that D-allulose is quickly absorbed in the gastrointestinal tract, and the maximum blood level is reached about an hour after consumption. D-allulose competes with fructose and glucose in the human small intestine for binding to the fructose transporter GLUT5 (Hishiike et al., 2013; Kishida et al., 2019). Therefore, D-allulose (depending on the intake quantities) is not completely absorbed in the small intestine, but enters the colon. The human body is not able to metabolize D-allulose. Also, D-allulose using bacteria are rare among the human gut bacteria (Iida et al., 2010). Therefore, D-allulose passes unchanged the human body and is excreted in the urine via the kidneys. Non-absorbed D-allulose is excreted with the faeces. After oral intake the maximum D-allulose concentrations have been found in the bowel, the liver, the kidneys and the bladder of rats (Tsukamoto et al., 2014). Comparable distribution data for humans are lacking. However, humans to whom D-allulose was administered as a bolus for up to 0.17 g/kg BW (approx. 12 g at a BW of 70 kg) excreted around 80 % of the sugar unchanged via the urine within 48 hours. If higher doses were administered, the portion excreted after 48 hours fell below 80 % (Iida et al., 2010).

3. 3 D-allulose - potential influence on human pathogens

In a case control study, the ability to use D-allulose was identified as a pathogenicity factor in the genome of clinical *K. pneumoniae* isolates (Martin et al., 2018).

In this study, the pathogen was isolated and sequenced from 38 patients who developed *K. pneumoniae*-specific clinical symptoms during a hospital stay. For comparison, *K. pneumoniae* was also isolated and sequenced from 76 control patients with a similar demographic background (age and sex), who were colonised with *K. pneumoniae*, but did not show any clinical symptoms. A gene cluster coding enzymes for sugar utilization was identified as a potential pathogenicity factor in *K. pneumoniae* isolates, using bioinformatic sequence analysis and logistic regression methods.

The sugar D-allulose was experimentally identified as the relevant substrate of the enzymes coded by the identified gene locus. Furthermore, the authors demonstrated that genetic elimination of the D-allulose metabolism gene locus significantly reduced the pathogenicity of the hypervirulent *K. pneumoniae* pathotype NTUH-K2044 in a mouse infection model.

The results from the mouse infection model suggest that the gene locus of the *K. pneumoniae* isolates could be relevant for their pathogenicity. However, this suggestion needs to be verified by additional experiments.

K. pneumoniae represents an aerobic (facultatively anaerobic), gram-negative, immovable, enclosed rod-shaped bacteria which belongs to the enterobacteria family (Enterobacteriaceae). It is ubiquitously distributed in the soil and in water, and is also known as an asymptomatic coloniser of the respiratory and intestinal tract of healthy humans.

In hospitals, *K. pneumoniae* causes 6.7 % to 10.1 % of the sepsis and pneumonia cases among patients with nosocomially infections. However, *K. pneumoniae* can also cause urinary tract infections, liver abscesses and meningitis. Therefore, *Klebsiella* spp. were assigned to the 26 top priority nosocomial infectious agents by the Robert Koch Institute (RKI) (Epidemiological Bulletin No. 44 from the RKI on 7 November 2011).

3. 3. 1 Distribution and significance of the gene cluster coding D-allulose metabolism enzymes in *Klebsiella* spp. isolates

The BfR has performed bioinformatic sequence analysis to investigate the distribution and significance of the gene cluster in publicly available, bacterial genome sequences. The analysis is based on the D-allulose metabolism gene cluster of the *K. pneumoniae* isolate NTUH-K2044, which is representative for this gene cluster. It includes five genes, four of which (KP1_RS12820-KP1_RS12835) are arranged in an operon structure, and one of which (KP1_RS12840) is localised inverse to the operon.

An initial overview of a nucleotide comparison (Blastn) with sequences from the NCBI Refseq database (database version of 16/01/2019) shows that only a few bacteria species that contained all genes of the D-allulose usage system were found. A complete D-allulose usage system was most frequently detected in the species *Klebsiella* (5025 *K. pneumoniae*, 107 *K. oxytoca*, 68 *K. michiganensis*, 15 *Klebsiella* spp., 6 *K. quasipneumoniae*, 2 *K. grimontii*, 1 *K. quasivariicola*).

Moreover, sporadically conserved sequences from all genes in *Proteus* spp. (n=1), *Enterobacter* spp. (n=1), *Serratia* spp. (n=3), *Cedecea* spp. (n=3), *Gibbsiella quercinecans* (n=4) and *Escherichia coli* (n=2) were identified.

3. 3. 2 Further analyses of sequence data from complete *Klebsiella* spp. genomes from the nucleotide databases

Detailed analyses were exclusively performed with complete *Klebsiella* spp. genomes from the nucleotide databases (n=304). The frequency of the D-allulose utilization gene cluster in *Klebsiella* spp. was investigated as a whole, and by country of origin and isolation period. Furthermore, an association of the D-allulose utilization gene cluster with known virulence factors and antibiotic resistance genes was tested, and the localisation of the cluster in the genome of the bacteria determined, which in turn meant that information could be gained about the likelihood of the D-allulose utilization gene cluster being transmitted to other bacteria.

The validity of all analyses is subsequently limited by the available sequences mainly coming from isolates from clinical samples, as clinical isolates were generally sequenced more frequently than isolates from environmental and waste water samples. It can also be observed that many antimicrobial-resistant pathotypes could also be disproportionately found among the sequences from clinical isolates, as these are also disproportionately sequences because of their clinical significance. Databases only contain for some of the sequences information about the origin of the isolates, and the period of isolation.

Investigation of the complete genomes includes 246 *K. pneumoniae*, 14 *K. oxytoca*, 12 *K. aerogenes*, 12 *K. variicola*, 9 *K. quasipneumoniae*, 8 *K. michiganensis*, 1 *K. quasivariicola* and 2 *Klebsiella* spp. isolates. With regards to all genomes investigated, a complete D-allulose usage system was detected in 71.5 % of analysed sequences. 3.5 % of the ge-

nomes only demonstrated part of the genes. The other 23.6 % of genomes did not demonstrate any genes from the D-allulose utilization gene cluster. Certainly, there has only been limited genome data available in the nucleotide databases thus far for most *Klebsiella* species (exceptions: *K. pneumoniae*, *K. oxytoca*).

The majority of the *Klebsiella* spp. genomes, for which there is information about their origins, originate from clinical material. Most clinical isolates, albeit not all, contain the genes of the D-allulose utilization gene cluster, while the genes of this cluster can only be found in a few isolates from the environment and waste water. Nevertheless, an association between the occurrence of the D-allulose utilization gene cluster and clinical isolates using existing results is not unequivocally possible, as there was only information about the isolation origins of the bacteria for around 50 % (145 out of 304) of the genomes analysed.

The distribution of the genomes with and without D-allulose utilization gene cluster from different years shows that this cluster was originally found in isolates which were acquired in 2004. However, this statement was also qualified by the uncertainty that the information about the year of isolation was only provided in the metadata for 115 out of 304 genomes.

It has become evident from detailed investigations that several sequenced isolates of *K. pneumoniae*, which code the allulose utilization gene cluster, belong to clinically significant, multi-resistant *K. pneumoniae* clones (e.g. ST-11, ST-528) (Ning Dong et al., 2018; Venditti et al., 2016) and that the strains occur worldwide. A statistical evaluation of the origins of the isolates has currently not proved to be practical, due to the lack of information in several metadata, and the unequal distribution of the number of sequenced isolates over different countries.

No differences have been found in the frequencies of virulence factors between genomes with and without the D-allulose utilization gene cluster. For comparison, 16-21 and 28-35 virulence factors were respectively identified in both genome types. The comparative genome analyses could not determine any difference between genomes with and without D-allulose utilization gene cluster related to the frequency of resistance genes. Certainly, the diversity of the genomes analysed is low, as clinical isolates with multiple resistances were predominantly sequenced and present in databases.

The localisation of the D-allulose utilization gene cluster in bacteria genomes was investigated in the example of selected *Klebsiella* spp. genomes (~30 %). The genes were exclusively available in the chromosome of the bacteria in the analysed genomes. No mobile genetic elements (e.g. transposases, integrases) could be identified 20 kb upstream or downstream of the sequence range analysed. This information suggests that the D-allulose utilization gene cluster is firmly anchored in the *Klebsiella* chromosome. Therefore, a transmission of the gene cluster to other species via a horizontal gene transfer is unlikely.

3. 3. 3 Can the growth and infectiousness of *Klebsiella* species, especially *K. pneumoniae*, be favoured by the use of D-allulose as a food ingredient?

The maximum D-allulose concentrations in rats have been found in the bowel, the liver, the kidneys and the bladder after oral intake (Tsukamoto et al., 2014). Humans to whom D-allulose was administered as a bolus also excreted around 80 % of the sugar unchanged via the urine within 48 hours (Ilda et al., 2010). *Klebsiella* spp., especially *K. pneumoniae*, mainly colonise the digestive tract in humans, but can also infect the upper respiratory tract, the liver and the urinary tract. Therefore, the colonisation sites of *K. pneumoniae* in humans partially

correspond with the organs of rats where the maximum D-allulose concentrations were found after oral intake. If humans regularly consume foods which introduce new amounts of D-allulose in the human body, a growth advantage may be expected for allulose utilizers among the species *K. pneumoniae* in human carriers.

The D-allulose utilization gene cluster has been identified in the genome of over two-thirds of isolates of *Klebsiella* spp. which are available in public databases, including antibiotic-resistant and virulent strains. Colonisation with classic *Klebsiella* remains asymptomatic in healthy humans. However, the species is one of the five most frequent originators of infections acquired in hospitals (especially sepsis and lung inflammation). Favourable conditions for *Klebsiella*-related disease symptoms, caused by regular consumption of food to which D-allulose has been added, could therefore initially occur in hospitals.

An worldwide spreading of hypervirulent *K. pneumoniae* pathotypes originating from Asia, which trigger both nosocomial as well as community-based infections (e.g. liver abscesses and meningitis) has been registered since the mid 1980s (Marr et al., 2019). Indeed, the classic *K. pneumoniae* pathotypes do dominate in Germany (Becker et al., 2018). However, a first report about a case of a liver abscess outside hospitals caused by a hypervirulent *K. pneumoniae* type occurred in 2016 (Pichler et al., 2017).

Regular consumption of foods containing new amounts of D-allulose could therefore also favour the spread of *K. pneumoniae* strains, including hypervirulent strains as well, outside hospitals in the long term.

There are experimental indications, albeit no proof, from a control case study (Martin et al., 2018) that the D-allulose utilization gene cluster could be an independent pathogenicity factor in *K. pneumoniae* strains. However, the question of whether the pathogenicity of *K. pneumoniae* may also be directly increased by the consumption of D-allulose can only be answered after more research has been done.

Foods to which D-allulose is added offer bacteria from the species *Klebsiella* a carbon source which has rarely been available before, in new quantities. It is therefore possible that *Klebsiella* may develop into a food-borne pathogen which requires monitoring in the long term. *Klebsiella* in foods are already publicly monitored today in China (Zhang et al., 2018).

3. 4 Other comments and open questions about the risk assessment of D-allulose

D-allulose has been used as a sweetener in foods in Asia (Japan, China, Korea) since 2010. In the US, the FDA granted D-allulose GRAS (*generally recognized as safe*) status several times in 2016 and 2017 (GRAS No. 647, No. 693 and No. 755). From an inspection of the GRAS documents available on the FDA website (e. g. <https://www.fda.gov/media/106159/download>), and a Japanese internet publication on the safety of D-allulose (https://www.kagawa-isf.jp/glycobio/english/pdf/foods_06.pdf), it can be seen that the problems of potential selection and favourable growth conditions for human pathogens within the human body have not been considered in the assessments. However, D-allulose was authorised as a food ingredient in both regions before the problem of trehalose first emerged.

Furthermore, scientific clarification is still needed as to the extent of which regular consumption of thus far unusual quantities of D-allulose, as a novel food
a) increases the concentration of this sugar in certain human body segments,

- b) undesirably affects occurrence and properties of *Klebsiella* spp. in the human intestinal flora and/or
- c) changes the infectiousness of virulent *Klebsiella* (esp. *K. pneumoniae*).

The few human studies, in which D-allulose was administered to healthy persons (Iida et al., 2008; Iida et al., 2010; Kimura et al., 2017; Braunstein et al., 2018; Han et al., 2018a) and/or persons with metabolic disorders (Hayashi et al., 2010; Han et al., 2018b; Norhona et al., 2018), mainly investigated the gastrointestinal compatibility of D-allulose, their intestinal re-sorption, their urinary excretion as well as their effects on weight gain, body composition and glucose metabolism. However, data about the distribution of D-allulose in different compartments of the human body which are predominantly colonised by *K. pneumoniae* spp., such as the gastrointestinal tract, the urogenital tract (exception: excretion of D-allulose in urine) and the respiratory tract were not generated in these studies.

Furthermore, with regards to the human intestinal flora, there is only one publication which states that four of 35 selected species (*Bacterioides thetaiotaomicron*, *Bacterioides uniformis*, *Bifidobacterium dentium* and *Ruminococcus productus*) from the human intestinal flora were identified as moderate D-allulose users (Iida et al., 2010). Whether the regular consumption of new amounts of D-allulose increases the frequency and percentage of *Klebsiella* in the human colon could not be gained from this publication. Furthermore, research on the effects of an increased consumption of D-allulose on the composition of the *Klebsiella* population in the human colon is also required.

In addition to their case control study, Martin et al. (2018) demonstrated that genetic elimination of the D-allulose utilization gene cluster significantly reduced the pathogenicity of the hypervirulent *K. pneumoniae* pathotypes NTUH-K2044 used in a mouse infection model. However, it was not investigated whether feeding rats with increased quantities of D-allulose also increased the infectiousness of *K. pneumoniae* pathotypes. Experimental clarification of this question is needed also before D-allulose is used as a food ingredient.

Further information on the BfR website

Novel foods

https://www.bfr.bund.de/en/a-z_index/novel_foods-130348.html

Sweeteners

https://www.bfr.bund.de/en/a-z_index/sweeteners-130251.html



BfR "Opinions app"

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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 German federal government and German federal states ("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.

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