Bacteriophages FAQs

BfR FAQ of 6 November 2019

Bacteriophages (phages) are viruses that exclusively infect bacteria. The term phage is derived from Greek and means “bacteria-eater”. Phages generally possess a narrow host range so that they can often only infect and kill few strains of a species (for example, *E. coli*). Two types are distinguished: virulent (lytic) phages and temperate phages. The process for virulent phages sees them multiplying in the infected bacteria, causing the bacteria to disintegrate. Newly formed phages are then released as part of this. In contrast, temperate phages can integrate their genome into that of the bacteria. The bacteria continue to live and then propagate with the genome of the phage.

The German Federal Institute for Risk Assessment (BfR) has put together an FAQ on the topic of bacteriophages.

What do phages consist of?

Phages consist of a head containing the genome of the phage which is enclosed by a protein shell (capsid). The genome is usually double-stranded DNA. In addition to the capsid, the most frequently occurring phages have a tail segment which can take various forms and sizes.

Where are phages present?

Phages are present wherever their host bacteria live: worldwide. Since there are about ten times as many phages as bacteria, very large numbers of phages often develop. This means that up to 100 million phages per milliliter are found in the water of lakes. In soils, there may even be up to 1 billion phages per gram.

Are phages poisonous when taken orally?

No, there is no evidence of this. Phages are absorbed in large numbers daily when food is eaten; up to around 10 billion phages may be contained in 100 grams of meat.

Are there also phages which may pose a hazard to humans?

Yes, in rare cases temperate phages contain virulence or resistance genes in their genome and may indirectly transfer this to people through bacteria. Examples of this are cholera and diphtheria toxins, which can be located in the genome of temperate phages. After a bacteria cell becomes infected, these phages are able to integrate themselves into the genome of the host and are passed on by cell division in the daughter cells (in a lysogenic life cycle). At this stage, the integrated phage is called a prophage. If the prophage contains virulence or resistance genes, the infected bacterium may develop new properties so that it forms toxins or becomes resistant to antibiotics. Under stress conditions, such as UV light, temperate phages can go back into the virulent cycle.

How do phages pass on foreign DNA from bacteria to bacteria (horizontal gene transfer)?
In principle, temperate as well as virulent phages are able to integrate non-specific parts of the bacterial genome from infected bacteria into phage heads (transduction). This ability essentially depends on the structure of the phage's genome and on the phage species. Temperate phages are usually more suited to horizontal gene transfer since they linger in the bacterial genome and exchange is therefore possible.

Prophages can also be cut out of the bacterial genome. However this may be done in an imprecise way, whereby the phage may be linked to adjoining bacterial sequences. Transfer to other bacteria could therefore be possible.

How can phages be used?
Phages can be used for a variety of applications. In addition to the phage therapies, i.e. use to combat bacterial infections in people or animals, phages can be used against pathogens occurring throughout the food chain. This can take place in the animal or in the field *(pre-harvest*) or during processing of the food (*post-harvest*). Furthermore, phages can be used as a decontamination agent, as a probiotic, for diagnostic purposes, to clean water and can be used for vaccine manufacture.

Are there any phage preparations that have been approved in Germany?
No, there are currently no phage preparations authorised in Germany or EU-wide, neither for phage therapy nor for use in the food sector. The EU commission has received an application for approval of a preparation to fight listeria in food and production facilities, but no decision has been made on this yet.

Which conditions must phages fulfil so that they can be used in phage preparations?
Phages intended for therapeutic treatment in people or animals or to fight bacterial pathogens within food production must be characterised in detail in terms of biology and in relation to their genome. Only virulent phages, which can be propagated using non-pathogenic bacteria (which do not cause sickness) are considered for such applications. The phages should be able to intensively propagate in the infected bacteria, which should release many newly formed phages. Moreover, phages should also have a wide host range within the bacteria species to be fought. In addition, the phages should demonstrate high stability to environmental influences and cause as little resistance development in the target bacteria as possible. Their genome must be free from characteristics that encourage the bacteria to become pathogenic or develop resistance. The ability to transfer parts of the bacterial chromosome into other bacteria should only be low. Finally, the phages should not encourage allergies and should be toxocologically safe.

How stable are phages in the environment?
The most frequently occurring phages are characterised by very high stability to environmental factors. This means that they can be stable over longer periods, from a few weeks to years, as well as when exposed to dryness, higher temperatures at around 60 º Celsius, pH values between 5 and 9 and salts. Phages can, however, be damaged by UV light. In addition, it should be noted that there can be big differences

between phages in terms of stability and that the stability and activity depend on various factors. Phages which are sprayed on food, for example, usually attach themselves to this so that they are no longer mobile and their activity is therefore limited.

Can bacteria become resistant to phages?
Yes, there are various possibilities for bacteria to develop resistance to phages. Resistance via mutations is the most common, resulting in the bacterial receptors changing so that the phages can no longer bind. However, this often reduces the fitness or the pathogenic potential of the bacteria. What’s more, the injection and replication of the phage genome can be prevented and bacterial resistances can be caused by “restriction enzymes” and CRISPR/Cas systems, which cut the injected phage genome and therefore render it ineffective. The mechanisms represent natural bacterial defence mechanisms to combat phages. Even they are now better known for the production of genetically modified organisms, these mechanisms have their origin in bacteria where they help to defend against foreign DNA, from phages for example.

In principle, however, it should be noted the ongoing development of bacteria and phages is quasi mutual. This means that if bacteria develop resistance, the phages can easily counteract this by changing their genome to combat this resistance.

Do phages also affect antimicrobial-resistant pathogens?
Yes, phages can also destroy antimicrobial-resistant bacteria.

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