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Risk of introducing murine parvoviruses into laboratory animal facilities through animal feed and guidance on irradiation of feed

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Parvoviruses: characteristics and prevalence

Parvoviruses are small, non-enveloped, single-stranded DNA viruses that occur in a large number of different animal species, such as cats, dogs, rabbits, bovines, pigs, poultry and various rodent species, and can cause clinical infections. Parvoviruses of relevance to rodents include Mouse parvovirus (MPV), Minute virus of mice (MVM), Mouse kidney parvovirus (MKPV) (Roediger et al. 2018), Kilham rat virus (KRV), Toolan H-1 virus (H-1 virus), Rat parvovirus (RPV) and Rat minute virus (RMV). Parvoviruses show very high resistance to inactivation by a wide range of pH values (pH 2-11), high temperatures, lipid solvents and chemical detergents and hence possess an extremely high degree of environmental stability (Compton et al. 2012, Mayr and Kaaden 2007). For the inactivation of MVM by heat, for example, a temperature of 86.5°C is required for a period of 10 minutes (Fassolitis et al. 1985). The high level of tenacity shown by murine parvoviruses presents a number of diverse problems when it comes to eradicating them in a laboratory mouse population.

Murine parvoviruses are among the world's most common viral pathogens in mouse populations, although prevalence varies widely (Carty 2008, Janus and Bleich 2012, Marx et al. 2017). In general, MPV is detected more frequently than MVM, so the prevalence of MPV can be assumed to be higher in laboratory mouse populations (Mähler and Köhl 2009, Pritchett-Corning et al. 2009, Schoondermark et al. 2006). An infection with murine parvoviruses usually takes a persistent and clinically silent course in immunocompetent mouse strains (Janus and Bleich 2012). The use of mice infected with parvovirus has a diverse influence on scientific results and particularly affects immunological, oncological and haematopoietic research, as well as transplantation studies. Relevant publications should be consulted for more detailed information (Jacoby et al. 1995, Janus and Bleich 2012, Smith et al. 1993, Implications of infectious agents on results of animal experiments [GV-SOLAS][1]).

Importing mice with an unidentified parvovirus infection into an existing population is the most common cause of infection outbreaks in mouse facilities. Since there are no clinical symptoms present and substantial diagnostic problems exist (e.g., because of the low prevalence within a population and as a result of genetically related differences in the antibody response), a murine parvovirus infection can remain undetected for a long time (Janus and Bleich 2012). The high degree of environmental stability of the viruses and deficiencies in the management of an animal facility can also result in parvoviruses being introduced into a facility. In studies on the transmissibility of MPV, various cage materials with which infected mice come into direct contact were shown to pose a potential source of infection and were related to a spread of murine parvovirus within the facility (Compton et al. 2012). The DNA of murine parvoviruses such as MPV was detected by PCR in the faecal pellets of infected mice and in used bedding material up to four weeks after removal from the cage (Bauer and Riley 2006, Smith et al. 2007). Moreover, mice could be infected using MPV-contaminated bedding material after storing the used bedding for four weeks, but not after eight weeks (Besselsen et al. 2008). In recent years, there have also been repeated reports that laboratory animal feed or also bedding material can be a cause of murine parvovirus infection in the animal population. It is assumed that feed which was inadequately or not autoclaved at all and whose components were already contaminated with murine parvoviruses before the handling process (e.g., by wild rodents) or packaging material contaminated with parvoviruses could be the cause of infection

[1] http://www.gv-solas.de/fileadmin/user_upload/pdf_publikation/Hygiene/Infektionserreger/Parvovirus.pdf

with MPV in the mouse population (Reuter et al. 2011, Schoondermark et al. 2013, Watson 2013, Adams et al. 2019). PCR analysis of the feed to detect contamination of this kind, however, is of little value, because a positive result does not indicate an infectious pathogen. Analysing a sample from the feed is also not very reliable because of the dilution effect (De Bruin 2016). It is therefore recommended to autoclave food before use (various programmes are possible; procedures [a frequently used option is e.g., 20 min. at 121°C] should be validated in every facility) or, if this is not possible, to use irradiated feed (Reuter et al. 2011, Watson 2013)

Irradiation of laboratory animal feed: does and sterility

As regards the radiation dose needed for the irradiation of feed, due account should be taken of the high degree of resistance and stability of parvoviruses in the environment, which also includes a high level of resistance to radiation. The sterility of a product is determined with reference to the *Sterility Assurance Level* (SAL). Since absolute sterility is hardly possible to achieve or, at least, cannot realistically be verified, the SAL is used to describe the degree to which a pathogen is reduced by the sterilization process. The necessary SAL for a product (medical supplies or pharmaceuticals) is usually specified as 10^{-6} by general convention. On this basis, the following formula is used for sterilization by irradiation according to Gazsó et al. (2005): the required sterilization dose (SD) depends on the microbial contamination (N), the radiosensitivity of the microorganism (D10, i.e., the dose necessary to reduce the population of the microorganism by 90% or by 1 $\log_{10}$- step) and the required SAL: i.e.: $SD = D_{10} (\log_{10}N – \log_{10}SAL)$. Using this formula, the dose of 25 kGy that for about four decades has been judged to be adequate in many fields (e.g., medical supplies) was also determined according to Ponta (2005) with data on what at the time was known to be the most radioresistant microorganism, namely *Bacillus pumilus* (SD = 3.1 x (2 – (–6)) corresponding to 25 kGy). This dose is also frequently used in the irradiation of feed for laboratory animals. However, other more radioresistant microorganisms that require a higher SD have since become known. In addition, radiosensitivity can also be influenced by many environmental factors. It is increased, for example, by a low oxygen content (two to fourfold increase in resistance), by low temperatures, by reducing substances, alcohols and organic substrate (i.e., a high protein content) (Gazsó 2005, Hewitt and Leelawardana 2014).

These results, which were obtained for the quality assurance of human tissue transplants and biological materials, should certainly serve as a reference when assessing a suitable radiation dose for rodent feed. For standardized, pelleted rodent feed, a minimum radiation dose of 20-25kGy is generally used (Tobin et al. 2007). However, Suckow et al. (2006) and others call for an effective dose of 30-50 kGy, while the upper dose of 50 kGy should not be exceeded (FDA 2001). For feed under gnotobiotic conditions, a radiation dose of 40-50 kGy is generally used (Tobin et al. 2007). A publication in a British journal describes doses between 28.9 and 34.3 kGy as “typical” for laboratory animal feed and doses between 38.4 and 48.7 kGy, which are used for feed under gnotobiotic conditions, as “high end” (Caulfield et al. 2008). The authors’ experiences, in which an MPV infection occurred in mouse populations after the use of feed irradiated with a dose of 20 kGy (Leblanc, personal communication), suggest that a radiation dose of 20 kGy is insufficient for reliable inactivation of MPV. A comparable observation has also been made in a recent study, where even a dose of 25 kGy was not sufficient to prevent the experimental infection of a mouse fed on contaminated feed (1 out of

6 mice was infected) (Adams et al. 2019). The possibility cannot therefore be ruled out that, when it comes to feed based rather on empirical data from the feed producer for inactivating a bacterial contamination, the customary radiation dose of 25 kGy might not be sufficient to reduce the viral load of parvovirus in the feed to a level that is no longer infectious. For the technique of the irradiation procedure, it should be noted that, at the producer's minimum dose, it is guaranteed that this dose is reached in the middle of the packaging or container (e.g., pallet), i.e., the outsides or outer edges of the packaging have then been irradiated with a higher dose (depending also on the density of the material). The producers "fortify" the fed to be irradiated in order to compensate for vitamin/nutrient losses. Assessment of the radiation doses required should also consider that short-term heat treatments in the pellet manufacturing process likewise lead to a reduction of possible infectious pathogens. To date, no reliable test results are available to indicate what radiation dose is actually suitable in order to rule out the introduction of infectious murine parvoviruses in the feed altogether.

Irradiation of laboratory animal feed: effects on nutrients

What is important when assessing the irradiation of feed, however, is not only the question of how effectively it inactivates pathogens. The potentially harmful effects of irradiation on the nutrients must also be considered.

The following publications describe some results in this regard, albeit from studies under sharply differing conditions: Caulfield et al. (2008) studied the effect of conventional radiation doses between 28.9 and 34.3 kGy for laboratory animal feed and doses between 38.4 and 48.7 kGy that are used for gnotobiotic animal feed compared with heat treatment (107°C for 15 min). They found more marked reducing effects in the high radiation dose group of 38.4-48.7 kGy than in the heat treatment group only in respect of vitamin A content (reduction to 67% vs 80% with heat sterilization) and of vitamin B6 content (reduction to 65% vs 73% with heat sterilization). But they also found a marked increase in peroxides (expression of oxidative fat rancidity) to 1150% (at a dose of 38.4 kGy) and 2488% (at 48.7 kGy) versus an increase to 175% with heat sterilization. Minami et al. (2012) report that irradiation (40 kGy) under anaerobic conditions could prevent the degradation and peroxidation of fatty acids, whereas a degradation of this kind occurred under aerobic conditions. Extrapolated to laboratory animal feed, this suggests that the conventional technique of irradiating feed in vacuum packs (anaerobic conditions) protects fatty acids.

Other sources report a dose-dependent loss of vitamins C, B1, E, K, and beta-carotene; this loss increased with storage time more markedly in irradiated feed than in non-irradiated feed (review article by Da Silva Aquino 2012). As regards growth, reproduction, haematological and biochemical blood, and urine parameters, as well as histopathological parameters, however, a Dutch study observed no differences either in rats or pigs that received either irradiated feed (50 kGy) or autoclaved feed over a period of 2.5 years (Strik 1986). Other studies likewise found no changes with regard to general health parameters, growth or reproduction in mice that received feed irradiated with 50 kGy over a period of 18 months or in a rat colony given feed irradiated with 25 kGy over a period of five years (Ley et al. 1969). In more than 50 carcinogenicity studies with mice and rats, in which not only 25 kGy but frequently also high radiation doses (55, 60, 74 and 93 kGy) were applied to the feed, no significant toxicological changes and no increased tumour rates were found during observation periods of up to 3 years (European Commission 2003).

In the food industry, total doses of <10 kGy are used (EFSA 1) and considered safe for human health. It is also known from food testing that the breakdown of longer chain molecules and the formation of radicals may be a consequence of irradiation. The irradiation of fatty foods also gives rise to 2-alkylcyclobutanones, which may have toxic potential, and to hydrocarbons, cholesterol oxides and furans (potentially carcinogenic) (WHO 1999, EFSA 2). This must be borne in mind with laboratory animals especially when it comes to experimental fatty diets. Many of these substances are also generated, however, with other stability treatments, e.g., heat (EFSA 3). In this regard, 2-alkylcyclobutanones (2-ACBs) are the only substances for which toxicity in animals is known. In cats, the occurrence of leukoencephalomyelopathy (LEM) has been attributed to 2-ACBs with a concurrent vitamin A deficit in irradiated feed, and LEM was also experimentally reproduced with radiation doses of 25.7 to 53.6 kGy (Caulfield et al. 2009). The administration of 2-ACBs to rats in acute and chronic studies did not result in an unequivocally damaging effect, but an increased colon tumour rate may be associated with this treatment (Raul et al. 2002).

Summary

In summary, it can be said that parvoviruses pose a particular challenge in a laboratory animal facility, because their physicochemical characteristics and the high degree of environmental stability require special measures in the operation of an animal facility. However, the risk of introducing murine parvoviruses can be kept largely to a minimum by complying with strict rules on importing animals, using pre-treated feed, and making sure to use meticulous procedures in the care and husbandry of mice. In view of the uncertain data as regards the effective radiation dose, it is currently recommended in particular to autoclave the feed to rule out the possibility of a food-borne infection or to select a radiation dose of at least 25 kGy for irradiating the feed and make absolutely sure this dose penetrates the entire feed. The user should pay attention to terms in the producer's labels such as "minimum" or ">" 25kGy which, unlike the term "average", confirm that the required radiation dose was achieved at each point. The producer should also be able to provide information on the irradiation process and irradiation certificates for each batch. It must be borne in mind, however, that a high radiation dose and also heat treatment can have a negative influence on the quality of the feed and could compromise the nutritional value of the feed. Fortified feed should therefore be used in these cases.

In general, there is a much greater risk of introducing murine parvoviruses when importing infected mice than by using contaminated feed. It is therefore more important to prevent the important of mice infected with parvoviruses, which includes sanitation measures by embryo transfer, as well as the systematic testing of biological materials before use to avoid unintentionally introducing murine parvoviruses into a mouse population (see GV-SOLAS: "Infection risk with biological materials" and "Hygiene risk when importing mice and rats – sanitation strategies"). In view of the characteristics of parvoviruses and diagnostic problems, however, there is always a residual risk even with the diligent application of all these preventive measures.

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