GV-SOLAS
Gesellschaft für Versuchstierkunde
Society for Laboratory Animal Science

Specialist information

from the Committee for Hygiene

Implication of infectious agents on results of animal experiments

Status August 2019

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Inhaltsverzeichnis

Introduction

It is generally accepted that rodent pathogens may not only be hazardous for animals (and humans) but can severely influence results of animal experiments. Microbiological standardisation of laboratory animals is therefore of crucial importance (Nicklas 1999).

It has been known for decades that microorganisms may have impact on their hosts in various ways (Bleich and Hansen 2012). Many years ago, influences of microorganisms were detected on development and growth of tumours. It was shown by various authors that germ-free mice develop fewer tumours (lung, liver, mamma, uterus, ovary) after treatment with chemical carcinogens than conventionally housed animals (Burstein et al. 1970, Roe and Grant 1970, Schreiber et al. 1972). The importance of microorganisms as factors that may influence animal experiments has already been described in review articles more than 50 years ago (van der Waaij and van Bekkum 1967, Hanna et al. 1973, Baker et al. 1979, Baker 1998, Baker 2003). A first symposium dealing with this issue was held in 1971, and hitherto known influences of selected microorganisms were published afterwards (Pakes and Benirschke 1971).

Importance of microorganisms

Infectious agents may affect animal populations in various ways. Some are pathogenic and may induce clinical signs with variable morbidity or mortality. However, most microorganisms induce no or only mild disease, at least in cases of endemic infections. Occasionally, loss of animals occurs as a consequence of disease or death. Silent infections are often activated by experimental procedures (stress, immunosuppression, toxic substances, tumours) or environmental influences (transportation, suboptimal humidity or temperature). Frequently, certain strains of a given species are more sensitive to an infection, whereas the same agent may cause milder or different symptoms in other strains, or the infection may be asymptomatic. Clinical signs are usually more serious in immunodeficient animals. Frequently, infections result in a reduced life expectancy in absence of specific disease for some individuals or a whole population. Other agents induce silent infections which are asymptomatic even in the case of experimental inoculation.

Many agents may have impact on physiologic parameters and thus on the results of animal experiments independent from their pathogenic potential. Further, infections may increase interindividual variability. This may result in increased numbers of animals necessary to achieve significant results. Direct effects of infectious agents on experiments may lead to false conclusions or misinterpretation and may be responsible for lacking reproducibility.

The use of laboratory animals that are free from unwanted microorganisms is an important prerequisite to achieve reliable and reproducible results with a minimum of animals and is therefore a significant contribution to animal welfare.

It is obvious that experimental data obtained from diseased animals should, if ever, be used only with maximal precaution. However, the effect of clinically silent infections may also be devastating because they often remain undetected, and thus modified results may be obtained and published.

The absence of clinical manifestations has no diagnostic value. The presence of unwanted microorganisms and the suitability of an animal population for a specific experiment can only be demonstrated by comprehensive health monitoring before and during experimentation.

Health monitoring data are part of the experimental work and have to be considered during interpretation of experimental results by the experimentator and by the reader of a publication. It should, therefore, be self-evident that results of health monitoring are included in scientific publications (Ellery 1985, Kilkenny et al. 2010). Recommendations for health monitoring of laboratory animals have been published repeatedly (Lussier 1991, National Research Council 1991, Kunstyr 1992, Kraft et al. 1994, Nicklas 1996, Rehbinder et al. 1996, Rehbinder et al. 1998, Nicklas et al. 2002, Lipman and Homberger 2003, Mähler et al. 2014, Fahey and Olekszak 2015).

Many agents do not only have impact on animals or animal experiments. Numerous organisms are known to affect experiments conducted with isolated organs or cells. Microorganisms may even persist in cells, tumours or other biological materials for unlimited periods of time and therefore influence in vitro experiments. Furthermore, microorganisms resulting from a natural infection might contaminate biological materials (tumours, sera, cells, viruses, parasites) that originate from or have been passaged in infected animals. They may severely influence experiments conducted with such materials, or may be introduced into animal facilities by contaminated samples (Collins and Parker 1972, Nicklas et al. 1993).

Unfortunately, research complications due to infectious agents are usually considered artefacts and published only rarely. Information on influences of microorganisms on experiments is scattered in diverse scientific journals, and many articles are difficult to detect. This text therefore aims at giving an overview on published influences of selected microorganisms on animals as well as on experiments.

To address the problem, several meetings were held on viral complications on research. The knowledge available was summarised in conference proceedings (Melby and Balk 1983, Bhatt et al. 1986, Hamm 1986) and has later repeatedly been reviewed (Kraft 1985, Lussier 1988, National Research Council 1991, Hansen 1994, Mossmann et al. 1998, Baker 1998, Baker 2003).

Aim of this compilation

After detection of an organism in an animal facility the question frequently arises if and how an animal experiment might be influenced. Experimenters and laboratory animal specialists must in such cases be able to evaluate the importance of an infection on research. It is the purpose of this compilation to aid in evaluating the importance of the most relevant microorganisms for animal experiments. Published influences of microorganisms on physiological parameters of laboratory animals were listed concisely, and the references are cited. In addition, few other questions which often arise together with infections in populations of experimental animals are addressed (e. g., zoonotic potential, host specificity).

Furthermore, it is the aim of this study to support managers of animal facilities in arguing towards improved microbiological standardisation of laboratory animals which will result in better and more reliable results of animal experiments with fewer animals.

The majority of laboratory animals are mice and rats, and most information is available for microorganisms infecting these species. This compilation therefore focuses on rodent microorganisms although there is a general trend towards better microbiological quality also for other animal species (Rehbinder et al. 1998, Rehbinder et al. 2000, Collymore et el. 2016).

Literature

Baker DG. 1998. Natural pathogens of laboratory mice, rats, and rabbits and their effects on research. Clin Microbiol Rev 11(2):231-266.

Baker DG. 2003. Natural pathogens of laboratory animals: Their effects on research. Washington, DC: ASM Press.

Baker HJ, Lindsey JR, Weisbroth SH. 1979. Housing to control research variables. In: Baker HJ, Lindsey JR, Weisbroth SH (eds) The laboratory rat. Vol. 1 Biology and diseases. New York: Academic Press, pp. 167-192.

Bhatt PN, Jacoby RO, Morse HC, New A. 1986. Viral and mycoplasmal infections of laboratory rodents: Effects on biomedical research. New York: Academic Press.

Bleich A, Hansen AK. 2012. Time to include the gut microbiota in the hygienic standardisation of laboratory rodents. Comp Immunol Microbiol Infect Dis 35(2):81-92. https://doi.org/10.1016/j.cimid.2011.12.006.

Burstein NA, McIntire KR and Allison AC. Pulmonary tumors in germfree mice: induction with urethan. J Natl Cancer Inst 1970; 44(1):211-214.

Collins MJ Jr, Parker JC. 1972. Murine virus contaminants of leukemia viruses and transplantable tumors. J Natl Cancer Inst 49(4):1139-1143.

Collymore C, Crim MJ, Lieggi C. 2016. Recommendations for health monitoring and reporting for zebrafish research facilities. Zebrafish 13 Suppl 1:S138-148. https://doi.org/10.1089/zeb.2015.1210.

Ellery AW. 1985. Guidelines for specification of animals and husbandry methods when reporting the results of animal experiments. Working Committee for the Biological Characterization of Laboratory Animals/GV-SOLAS. Lab Anim 19(2):106-108.

Fahey JR, Olekszak H. 2015. An overview of typical infections of research mice: Health monitoring and prevention of infection. Curr Protoc Mouse Biol; 5(3):235-245. https://doi.org/10.1002/9780470942390.mo150023.

Hamm TE. 1986. Complications of viral and mycoplasmal infections in rodents to toxicology research and testing. Washington, DC: Hemisphere Publ Co.

Hanna MG Jr, Nettesheim P, Richter CB, Tennant RW. The variable influence of host microflora and intercurrent infections on immunological competence and carcinogenesis. Isr J Med Sci 1973; 9(3):229-238.

Hansen AK. Health status and the effects of microbial organisms on animal experiments. In: Svendsen P and Hau J (eds.) Handbook of laboratory animal science. Vol. 1. Boca Raton: CRC Press Inc. 1994, pp.125-153.

Kilkenny C, Browne WJ, Cuthill I, Emerson M, Altman DG. 2010. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol; 8(6):e1000412. https://doi.org/10.1371/journal.pbio.1000412.

Kraft V. 1985. Virusinfektionen bei kleinen Versuchstieren. Einflüsse auf die biomedizinische Forschung. Dtsch Tierarztl Wochenschr; 92:484-489.

Kraft V, Deeny AA, Blanchet HM, Boot R. 1994. Recommendations for the health monitoring of mouse, rat, hamster, guineapig and rabbit breeding colonies: Report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Animal Health accepted by the FELASA Board of Management November 1992. Lab Anim 28(1):1-12.

Kunstyr I. 1992. Diagnostic microbiology for laboratory animals. GV-SOLAS. Vol. 11. Stuttgart: Gustav Fischer Verlag.

Lipman NS, Homberger FR. 2003. Rodent quality assurance testing: use of sentinel animal systems. Lab Anim (NY) 32(5):36-43.

Lussier G. 1988. Potential detrimental effects of rodent viral infections on long-term experiments. Vet Res Contrib 12(2-3):199-217.

Lussier G. 1991. Detection methods for the identification of rodent viral and mycoplasmal infections. Subcommittee on Rodent Viral and Mycoplasmal Infections of the American Committee on Laboratory Animal Disease (ACLAD). Lab Anim Sci 41(3):199-225.

Mähler Convenor M, Berard M, Feinstein R, Gallagher A, Illgen-Wilcke B, Pritchett-Corning K, Raspa M. (FELASA working group on revision of guidelines for health monitoring of rodents and rabbits). 2014. FELASA recommendations for the health monitoring of mouse, rat, hamster, guinea pig and rabbit colonies in breeding and experimental units. Lab Anim 48(3):178-192.

Melby EC Jr, Balk MW. 1983. The importance of laboratory animal genetics, health, and the environment in biomedical research. Orlando: Academic Press.

Mossmann H, Nicklas W, Hedrich HJ. 1998. Management of immunocompromised and infected animals. In: Kaufmann SHE (ed). Methods in Microbiology. Vol. 25. London: Academic Press, pp.109-186.

National Research Council. 1991. Committee on Infectious Diseases of Mice and Rats. Infectious diseases of mice and rats. Washington, DC: National Academy Press.

Nicklas W. 1996. Health monitoring of experimental rodent colonies: an overview. Scand J Lab Anim Sci 23:69-75.

Nicklas W. 1999. Microbiological standardization of laboratory animals. Berl Münch Tierärztl Wschr 112(6-7):201-210.

Nicklas W, Kraft V. Meyer B. 1993 Contamination of transplantable tumors, cell lines, and monoclonal antibodies with rodent viruses. Lab Anim Sci 43(4):296-300.

Nicklas W, Baneux P, Boot R, Decelle T, Deeny AA, Fumanelli M, Illgen-Wilcke B. (Federation of European Laboratory Animal Science Associations Working Group on Health Monitoring of Rodent and Rabbit Colonies). 2002. Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units. Lab Anim 36(1):20-42.

Pakes SP, Benirschke K. 1971. Symposium on diseases of laboratory animals complicating biomedical research. Am J Pathol 64:624-769.

Rehbinder C, Baneux P, Forbes D, van Herck H, Nicklas W, Rugaya Z, Winkler G. 1996. FELASA recommendations for the health monitoring of mouse, rat, hamster, gerbil, guinea pig and rabbit experimental units. Report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Animal Health accepted by the FELASA Board of Management, November 1995. Lab Anim 30(3):193-208.

Rehbinder C, Baneux P, Forbes D, van Herck H, Nicklas W, Rugaya Z, Winkler G. 1998. FELASA recommendations for the health monitoring of breeding colonies and experimental units of cats, dogs and pigs. Report of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on Animal Health. Lab Anim 32(1):1-17.

Rehbinder C, Alenius S, Bures J, de las Heras ML, Greko C, Kroon PS, Gutzwiller A. 2000. FELASA recommendations for the health monitoring of experimental units of calves, sheep and goats. Report of the federation of European Laboratory Animal Science Associations (FELASA) Working Group on Animal Health. Lab Anim 34(4):329-350.

Roe FJ, Grant GA. 1970. Inhibition by germ-free status of development of liver and lung tumours in mice exposed neonatally to 7,12-dimethylbenz(a)anthracene: implications in relation to tests for carcinogenicity. Int J Cancer 6(1):133-144.

Schreiber H, Nettesheim P, Lijinsky W, Richter CB, Walburg HE Jr. 1972. Induction of lung cancer in germfree, specific-pathogen-free, and infected rats by N-nitrosoheptamethyleneimine: enhancement by respiratory infection. J Natl Cancer Inst 49(4):1107-1114.

Van der Waaij D, van Bekkum DW. 1967. Resident infection in laboratory animal colonies and their influences on experiments. In: Conalty ML (ed) Husbandry of Laboratory animals. Proceedings of the 3rd international symposium organized by the International Committee on Laboratory Animals. London, New York: Academic Press, pp.373-386.

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