Infectious diseases in laboratory animals

Standards for care and storage of experimental animals and alleviation of suffering

Ministry of the Environment Notification No. 88, 2006 Final revision: 2013 Ministry of the Environment Notification No. 84

3rd Common Criteria

- 1. Maintaining animal health and safety
- (1) Feeding and storage methods

Laboratory animal managers, experimenters, and caretakers should take note of the following:

Strive to maintain the health and safety of experimental animals. (Omitted)

b. Perform necessary health management, such as preventing the Experimental Animals from being injured or contracting diseases other than those related to the purpose of the Experiment, etc. In addition, if an experimental animal is injured or afflicted with a disease, appropriate treatment, etc. should be provided to the extent that it does not interfere with the achievement of the purpose of the experiment, etc.

(Omitted)



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Problems when infectious diseases occur in experimental animals

1. Zoonotic diseases (infection to humans, infection from humans)

2. Impact on the health of experimental animals, decrease in reproductive efficiency, and spread of infection within the facility

3. Impact on the accuracy of animal experiments



Microbial monitoring

Purpose: Rapid detection of infections

Overview of monitoring: The number of animals subject to inspection, breeding period, inspection items, inspection methods, inspection frequency, and commissioned inspection organizations are determined by each animal testing organization.



Microbial monitoring test method

Extracted animals/monitoring animals:

Conventional methods: culture, antibody titer, microscopy, PCR from biomaterials Exhaust dust(Exhaust Air Dust: EDA):Array(high-density PCR array)



Pathogenicity-Based Microbial Categories (Criteria for Small Animal Monitoring Microorganisms)

A Zoonotic disease

Hantavirus, lymphocytic choriomeningitis virus, salmonella, etc.

- B It is a highly pathogenic microbe that can kill animals and is highly contagious. Sendai virus, mouse hepatitis virus, lung mycoplasma, etc.
- C It does not have the power to kill animals, but it can cause disease. Alters physiological functions Salivary gland lacrimal virus, Tyzer bacteria, etc.
- D Experimental procedures may induce disease.
 - Pulmonary Pasteurella, Staphylococcus aureus, Pseudomonas aeruginosa, etc.
- E Nonpathogenic. It is useful as an index for judging the quality of microbial control in the rearing environment.
 - Rat cecal pinworm, unidentified protozoa, etc.

Current Status of Microbial Monitoring (Europe and America) about 500,000 about 80,000

		Pathogenic	Symptoms		mouse		ət
	lymphocytic choriomeningitis virus	А	invisibility	\bigcirc	0%		
Virus	hantavirus	А	invisibility			0	0.07%
	Sendai virus	В	bronchitis	\bigcirc	0%	\bigcirc	0.02%
	mouse hepatitis virus	В	Invisibility, hepatitis, enteritis	\bigcirc	<mark>0.80%</mark>		
	ectromere virus	В	smallpox, crusting	\bigcirc	0.02%		
	Salivary dacryodenitis virus	С	Submandibular gland hypertrophy, bloody discharge on eyes and nose			0	0.29%
	<mark>mouse norovirus</mark>	С	invisibility	\bigcirc	<mark>32.37%</mark>		
Bacteria Parasite							
	salmonella	А	sepsis, fever, diarrhea	0	0%	0	0%
	lung mycoplasma	В	Nasal noise, pneumonia	\bigcirc	<mark>0.10%</mark>	\bigcirc	<mark>0.23%</mark>
	teaser fungus	С	Invisibility, emaciation, diarrhea	\bigcirc	(NT)	\bigcirc	(NT)
	corynebacterium murineus	С	Invisibility, emaciation, diarrhea	\bigcirc	0%	\bigcirc	0%
	bronchiseptica	С	invisibility			\bigcirc	0%
	<mark>Pneumocystis</mark>	С	chronic pneumonia	\bigcirc	(NT)	\bigcirc	<mark>6.36%</mark>
	Pasteurella	D	invisibility	\bigcirc	<mark>12.90%</mark>	\bigcirc	0%
	gastrointestinal protozoa	C,E	invisibility	\bigcirc	<mark>≒8.88%</mark>	\bigcirc	<mark>≒4.60%</mark>
	pinworm	C,E	Intestinal thickening (immunocompromised animals)	\bigcirc	<mark>0.25%</mark>	0	<mark>1.10%</mark>
	<mark>Ectoparasite</mark>	C,E	hair loss, itching	\bigcirc	<mark>0.12%</mark>	\bigcirc	0%

Laboratory Animals, 2009; 43: 165-173 Charles River

Pathogens to be detected are roughly determined

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Mouse hepatitis virus : Mouse hepatitis virus Coronavirus single-stranded(+)RNA (Laboratory Animals, 2009; 43: 165-173 : Infection rate: 0.8%) Category B Polytropic: Infected from the respiratory system, hepatitis, encephalitis Enterotropic: Infection from the intestinal tract Treatment: culling, disinfection, cleaning



The current epidemic strain is an asymptomatic infection in infants and parents

Establishment of subclinical infection in coloniesIncreased antibody titer and experimental variation

Experimental variability was due to infection



T-cell-deficient mice

weakness, emaciation, diarrhea Comparative Medicine.2004,54:29

Mouse hepatitis virus: impact on diabetes development

Diabetologia. 1991 Jan;34(1):2-5.

Persistent MHV (mouse hepatitis virus) infection reduces the incidence of diabetes mellitus in non-obese diabetic mice.

Wilberz S, Partke HJ, Dagnaes-Hansen F, Herberg L.

Diabetes Forschungsinstitut, Universität Düsseldorf, FRG.



Pollution accident occurred

Mouse norovirus : Caliciviridae, single-stranded(+)RNA

(Laboratory Animals,2009; 43: 165-173 : Infection rate: 32.3%, Category C) Treatment: culling, disinfection, cleaning

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Original Research

Murine Norovirus Infection Variably Alters Atherosclerosis in Mice Lacking Apolipoprotein E

Charlie C Hsu,¹⁴¹ Jisun Paik,¹¹ Thea L Brabb,¹ Kevin D O'Brien,³ Jinkyu Kim,³ Brittany G Sullivan,³ Kelly L Hudkins, Audrey Seamons,¹ Jennifer C Finley,¹ Stacey M Meeker,¹ and Lillian Maggio-Price¹



Atherosclerosis model mouse Increased plaque Accumulation of virus-infected macrophages Need to be careful because it infects macrophages.

uninfected

norovirus

Movat pentachrome staining

Murine Norovirus Infection: Effects on Immunodeficient Mice

Norovirus triggered microbiota-driven mucosal inflammation in interleukin 10-deficient mice. Basic M, Keubler LM, Buettner M, Achard M, Breves G, Schröder B, et al. *Inflamm Bowel Dis.* (2014) 20:431–43.

4 weeks after experimental infection



C3H-IL10 KO mice Mild hyperplasia, edema, accumulation of inflammatory cells in the lamina propria and submucosa

Wild

Immunodeficient mice are more susceptible to infections



Pneumocystis carinii : Rat interstitial pneumonia, a special fungus Former name: rat respiratory virus

P.Carinii experimental infection

Filtrate

Pasteurella :

Mice, usually subclinical infection, lung lesions in immunocompromised animals

(Laboratory Animals,2009; 43: 165-173 : Infection rate: 12.9%, Category ${\sf D}$)

Treatment: can be eradicated with enrofloxacin

Pathogenicity of *Pasteurella pneumotropica* in Immunodeficient NOD/ShiJic-*scid*/Jcl and Immunocompetent Crlj:CD1 (ICR) Mice

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Exp. Anim. 60(5), 463-470, 2011



It is asymptomatic in healthy mice, but symptoms appear in immunocompromised animals.



NOD/scid 70 days post-infection pulmonary lesions Arrow indicates abscess

Murine large intestine pinworm :

Usually inapparent infection, occasionally intestinal thickening

(Laboratory Animals,2009; 43: 165-173 : Pinworm infection rate: 0.25%, category C) Treatment: Can be dewormed with ivermectin



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Pinworm eggs are infective for several years in the outside world, so they are troublesome.

Aspiculuris tetraptera

- (Murine colonic pinworm; category C)
- Parasitic on colon of mouse, male 3.4mm, female around 4.4mm Asymptomatic infection, decreased activity, intestinal thickening in the colon, lymphocyte hyperproliferation Severe disease in immunodeficient mice

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Why You Should Avoid Keeping Rodents At Home

Microbial monitoring of 28 mice from 5 pet shops in Tokyo and Kanagawa prefecture was carried out.

Mouse norovirus(60.7 %), Murine encephalomyelitis virus (46.4 %) Mouse hepatitis virus (42.8 %), Mouse pasteurella (35.7 %) Trichomonas intestinalis (67.8%), Pinworm(28.5 %), Small tapeworms (25.0 %)



If an animal with possible infectious disease is found outside of microbiological monitoring

1. Preservation of records and reporting/consultation to relevant parties

- 2. Consider isolating the breeding room where the abnormality occurred and prohibiting the movement of animals
- 3. Definitive diagnosis of infectious disease
- 4. Discuss response

It often takes time to make a definitive diagnosis for infectious diseases other than microbial monitoring test items.

Special attention should be paid to immunodeficient mice.

Infectious diseases in laboratory animals

1. Raising animals and conducting animal experiments that do not cause infectious diseases

2. Rapid surveillance by microbial monitoring



