Quality management systems and GLP in Laboratory Animal Facility and Research

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11th International Course, Care & Use of Laboratory Animals
April 15, 2025 | Heraklion, Crete, Greece

Quality system in research

is a set of rules defined by a collection of policies, processes, documented procedures and records aiming to improve the quality of the research

Why?

to ensure the accuracy, the reliability of all aspects of the operations, safety and efficacy of the discoveries and the reported test results

Poor quality management can result in redundant treatment or treatment complications, failure to provide correct treatment, delayed diagnosis and unnecessary follow-up experimental design

Quality management systems

Three internationally available quality systems for animal units:

- ISO 9000:2000
  (International Organization for Standardization) –
  focuses on customers (to whom the animals and their products and services are provided)

- GLP Guidelines
  (Good Laboratory Practice Guidelines) –
  addresses the reliability and reproducibility of experimental data

- AAALAC International
  (Association for Assessment and Accreditation of Laboratory Animal Care International) –
  principally addresses the quality of the broad environment within which animal care and use takes place

Quality management systems in animal research

ISO 9000 family: specifications to ensure that materials, products, processes and services are fit for their purpose (check you do what you say you do)

Animal welfare (legal, self-imposed requirements)

GLP: addresses the reliability and reproducibility of experimental data generated by the use of animals (check you do what you say you do, extra level of paperwork)

Animal welfare (legal, self-imposed requirements)

Authority of Study Director for the conduction of protocols in the study

AAALAC: peer-reviewed system which evaluates the organization and practices in a laboratory animal facility for humane care and use of animals (check if what you do is good for animals)

Focus on animal welfare (3Rs)

Reviewers are specialists

Similarities - Differences

- institutional interest, management support (all)
- confidentiality (all)
- level of focus on animal welfare (AAALAC > ISO, GLP)
- resources needed, quality assurance unit (GLP > ISO > AAALAC)
- international recognition (depends on the field)
- specialization of inspectors/site visitors (AAALAC > ISO, GLP)

- GLP is mandatory, whereas AAALAC and ISO are voluntary

but they can be combined!

Schemes characteristics

Table 1 Comparisons of the strengths and weaknesses of the various quality systems for animal units

	AAALAC	GLP	ISO 9000:2000
Subject	Strengths		
Principal focus	The animal care and use programme	The consistency of studies	The customer
Applicability	An animal facility alone can be accredited. Peer review of animal units	Details of studies for which GLP compliance is claimed are documented	Customer focused—i.e. business friendly. ISO standards are available for a wide range of businesses so the philosophy is transferable
Animal welfare and law	Heightens awareness of laboratory animal welfare globally. Where there is no existing law, the ILAR Guide is the minimum standard	GLP requires compliance with National law—animal welfare is assured to this extent	Meets regulatory requirements concerning animal welfare
External consideration	Well respected in institutions conducting experiments on live animals, including US agencies	Assures sponsors and regulatory bodies that work is rigorously carried out and documented	Gives customer confidence that quality is provided
Internal quality assurance	A facility manager can introduce it without seeking specialist assistance	Quality assurance unit is obligatory and leads to better consistency	Obliges internal review of the management system

	AAALAC	GLP	ISO 9000:2000
Subject	Strengths		
Working processes	Support processes are reviewed	All steps in the process are described in SOPs and legal documents	Principally a management tool to ensure processes are coordinated and effective
Inspection	Site inspections are carried out by external visitors	External independent (government-appointed) inspectors	External inspectors
Direct costs	No costs except for the annual fee	Inspections are free of charge	Cost of certification is relatively low
Ongoing costs	Annual report, annual fee. Ongoing quality assurance reports and SOPs are not obligatory, so relatively inexpensive	Costs are associated with the QA unit and setting-up and maintaining SOPs; there is a continuing need for documentation (expensive)	No major expenditure required. Maintenance of an established accreditation is relatively cheap
Flexibility (1)	Flexibility towards local situation—if local legislation is more stringent than the ILAR-Guide, then that becomes the standard	Mandatory government requirement for certain studies. SOPs are prepared by the establishment and so can reflect its needs	Facility specifies its own procedures providing these raise overall performance
Flexibility (2)	Working standards can be changed whenever you wish, providing they meet the minimum defined standard	High-quality working standards may positively influence other, 'non-GLP' studies in the same unit	The need to retain and adhere to policy documents assures consistency of management. Facilities are encouraged to continually innovate and improve

Systems drawbacks

Subject	AAALAC	GLP	ISO 9000:2000
	Weaknesses		
Bureaucracy	It is necessary to describe and adhere to a detailed, programme description	Slowness of procedures due to the bureaucratic nature of the process. Needs for paperwork and confidentiality may make procedures appear rigid	There may be a large amount of paperwork at the beginning of the process, depending on the 'starting position'
Resources	High initial demands on time and resources, even if a different QA system is already in place. Less to maintain the system	High ongoing costs in terms of personnel and time. Animal care staff, analytical staff and directors are subordinated to the QA process	Once the system is in place, ongoing maintenance needs are minimal and principally address improvements
Standards and applicability	In some respects ILAR Guide standards differ from EU standards. Standards also differ between European countries. In all cases, the requirements of national legislation have to be met, although if the AAALAC standards exceed other requirements, the highest standard is applicable	A study-based system, not primarily directed at the animal facility. Animal facility can only be accredited as part of a larger establishment conducting regulatory work (e.g. pre-clinical safety studies) or as a CRO for in-life parts of studies	The customer and final product count, rather than the way the process works. The management frame-work is less rigidly defined, so operational standards are less critical than production settings
Subjectivity	Subjectivity may be introduced by individual site visitors; review by 32-Member Council minimizes inconsistencies	Each facility determines its own working practices but needs to ensure that these are audited. Approval is by the inspectors; policies may vary between countries	Provides no detailed guidelines for implementation. Variability between business types, certifying bodies and auditors, means that subjective differences may lead to inconsistencies in quality

Good Laboratory Practice (GLP)

a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental studies are planned, performed, monitored, recorded, archived and reported

The history of GLP

- The formal regulatory concept of GLP originated in the US in the 1970 by the FDA (Food and Drug Administration)
- The inspection of studies and test facilities revealed fraudulent activities and cases of poor laboratory practice
- FDA's publication of Proposed Regulations on GLP in 1976, with establishment of the Final Rule in June 1979 (21 CFR 58)
- In 1981 the Organization for Economic Co-operation and Development (OECD) formulated GLP principles on the international level

Purpose of the GLP Principles

- promote the development of quality test data
- basis for the mutual acceptance of data
- avoid duplication of data
- avoid technical barriers to trade
- provide a tool to ensure a proper approach to the management of laboratory studies

The GLP Principles

1. Test facility organization and personnel
2. Quality Assurance program
3. Facilities
4. Apparatus, materials and reagents
5. Test systems
6. Test and reference items
7. Standard Operating Procedures (SOPs)
8. Performance of the study
9. Reporting of study results
10. Storage and retention of records and materials

1. Test facility organization and personnel

- test facility management’s responsibilities
- study director’s responsibilities
- principal investigator’s responsibilities
- study personnel’s responsibilities

2. Quality Assurance (QA) program

to assure that studies performed are in line with these GLP Principles

Responsibilities of the QA personnel:

- designated individuals directly responsible to the management, but not involved in the conduct of the study being assured
- access to up-to-date study plans
- prepare documented verification of the compliance of the study plan to the GLP principles
- conduction of inspections to determine compliance of the study with GLP principles – study-based, facility-based or process-based inspections

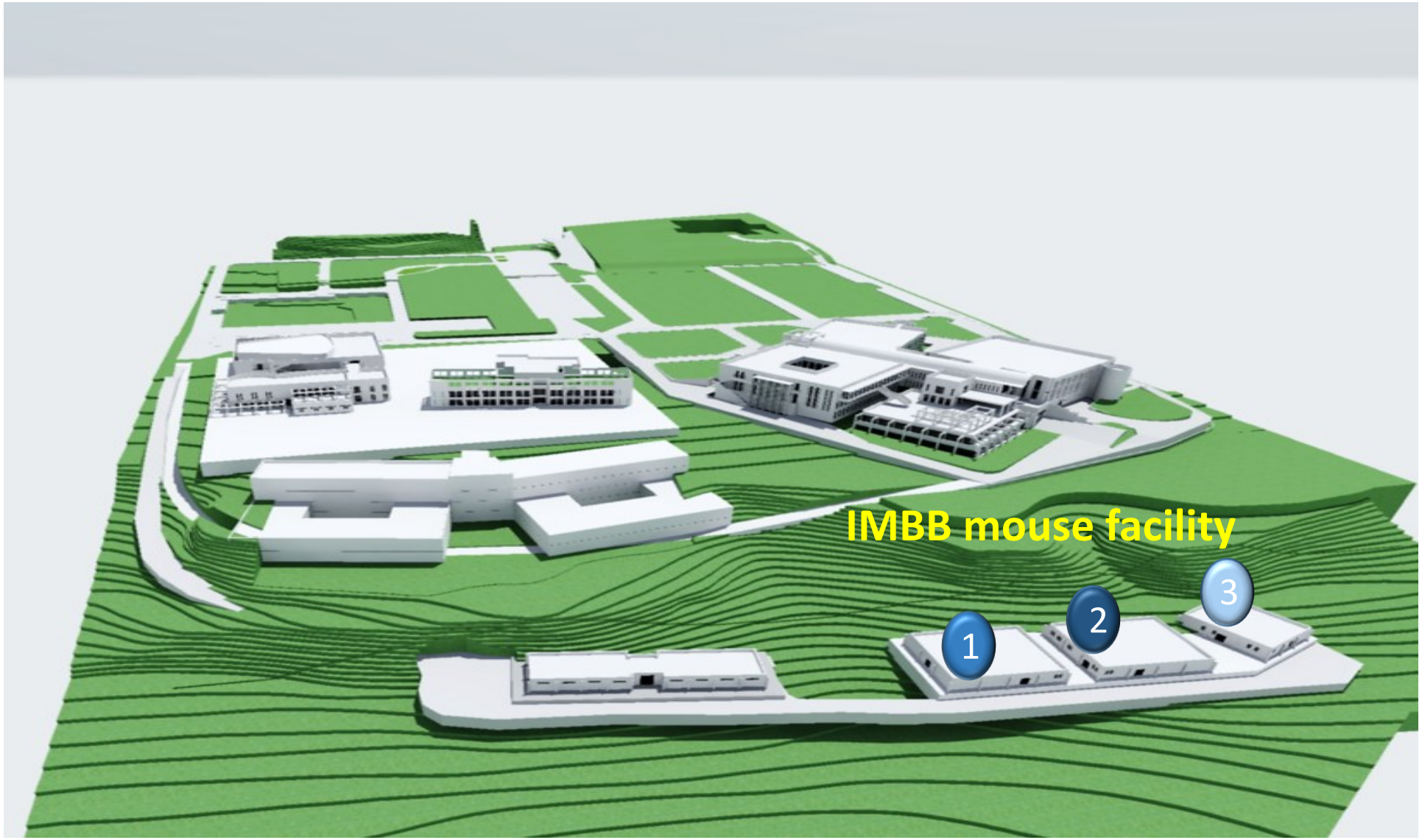
3. Facilities

- suitable size, construction and location to meet the requirements of the study
- adequate degree of separation of the different activities
- isolation of test systems and individual projects to protect from biological hazards
- suitable rooms or areas for the diagnosis, treatment and control of diseases
- storage rooms for suppliers and equipment

Animal research facility

- designed and operated to control selected parameters (temperature, humidity, ventilation, airflow, light-12 hour light and dark cycles)
- organized to prevent animals to contact with disease
- restricted entry only to staff using personal protective equipment (coat, gloves, face mask, cap, foot wares)
- the building should provide enough space for animals and studies to be separated and allow the operators to work efficiently

IMBB Animal Facility



1 : BSL2

2 : SPF

3 : Quarantine

A well designed animal house should provide areas for:

- different species
- quarantine
- changing rooms
- experimentation
- receipt and storage of materials (bedding, diet, cages)
- cage washing area with autoclave facility
- necropsy
- waste disposal

Work safety in animal house – Basic rules

- have a look around (emergency exits, telephone, emergency phone numbers etc)
- wear protective clothing
- plan ahead: organize and prepare everything before starting the experiment
  - keep workbench clean and tidy
  - have a second empty cage near
  - do not leave the mice unattended when cages are open
- learn safe animal handling
- do not eat, drink or smoke in animal facility
- do not contaminate surrounding surfaces (door handles, phones)
- proper waste management (needles, syringes, biological materials)
- clean up after
- remove protective clothing when leaving animal house

4. Apparatus, materials and reagents

- apparatus and validated computerized systems of appropriate design and adequate capacity
- documented inspection, cleaning, maintenance and calibration of apparatus
- reagents and materials should be properly labelled

5. Biological test systems

- proper conditions for storage, housing, handling and care
- isolation of newly received animal/plant test systems until health status is evaluated
- humanely destruction of inappropriate test systems
- records of source, arrival date and conditions
- proper identification of test systems in their housing
- cleaning and sanitization of housing

6. Test & reference items

- records for dates of receipt, expiry date, quantities received and used in the study
- appropriate identification of each test or reference item

7. Standard Operating Procedures

- approved SOPs to ensure the quality and integrity of the laboratory data
- each facility unit should have immediately available current SOPs relevant to the activities being performed
- deviations from SOPs should be acknowledged by the study director and/or the PI
- SOPs for: test and reference items, apparatus, computerized systems, materials and reagents, test system etc.

8. Performance of the study

- approved written plan, verified for GLP compliance, approved by the study director and by the test facility management
- justification for amendments and approval by dated signatures
- description and explanation of deviations
- content of the study plan (e.g. description, purpose, methods, justification of test system, experimental design)

9. Reporting of study results

- final report for each study
- signed by scientists
- approval by the study director
- corrections, additions, amendments signed and dated by the study director

10. Storage and retention of records and materials

retain archives (e.g. study plan, raw data, samples, final report, index of materials, validation documentation)

Quality management - Examples

1. Animal bedding

2. Laboratory animal diets

1. Animal bedding

Production according to:

- Good Manufacturing Practices (GMP)
- Energy Management System (reducing energy consumption and CO_2 emissions)

CERTIFICATE

This is to certify that

J. Rettenmaier & Söhne GmbH + Co KG

Holzmühle 1
73494 Rosenberg
Germany

has implemented and maintains an **Energy Management System**.

Scope:
Development, production, processing and sales of organic fibre materials based on wood, cellulose, annual plants, cereals and fruit components as well as processing of external customer products. Production of electricity by waterpower and biomass

Through an audit, documented in a report, it was verified that the management system fulfills the requirements of the following standard:

ISO 50001 : 2011

Certificate registration no.	274559 EMSt
Excerpt from certificate registration no.	274559 EMSt
Date of revision	2016-06-07
Valid from	2015-05-28
Valid until	2018-05-27
Date of certification	2016-06-07

DAkkS Deutsche Akkreditierungsstelle D-ZM-18402-01-00

DQS CFS GmbH
German Association for Sustainability

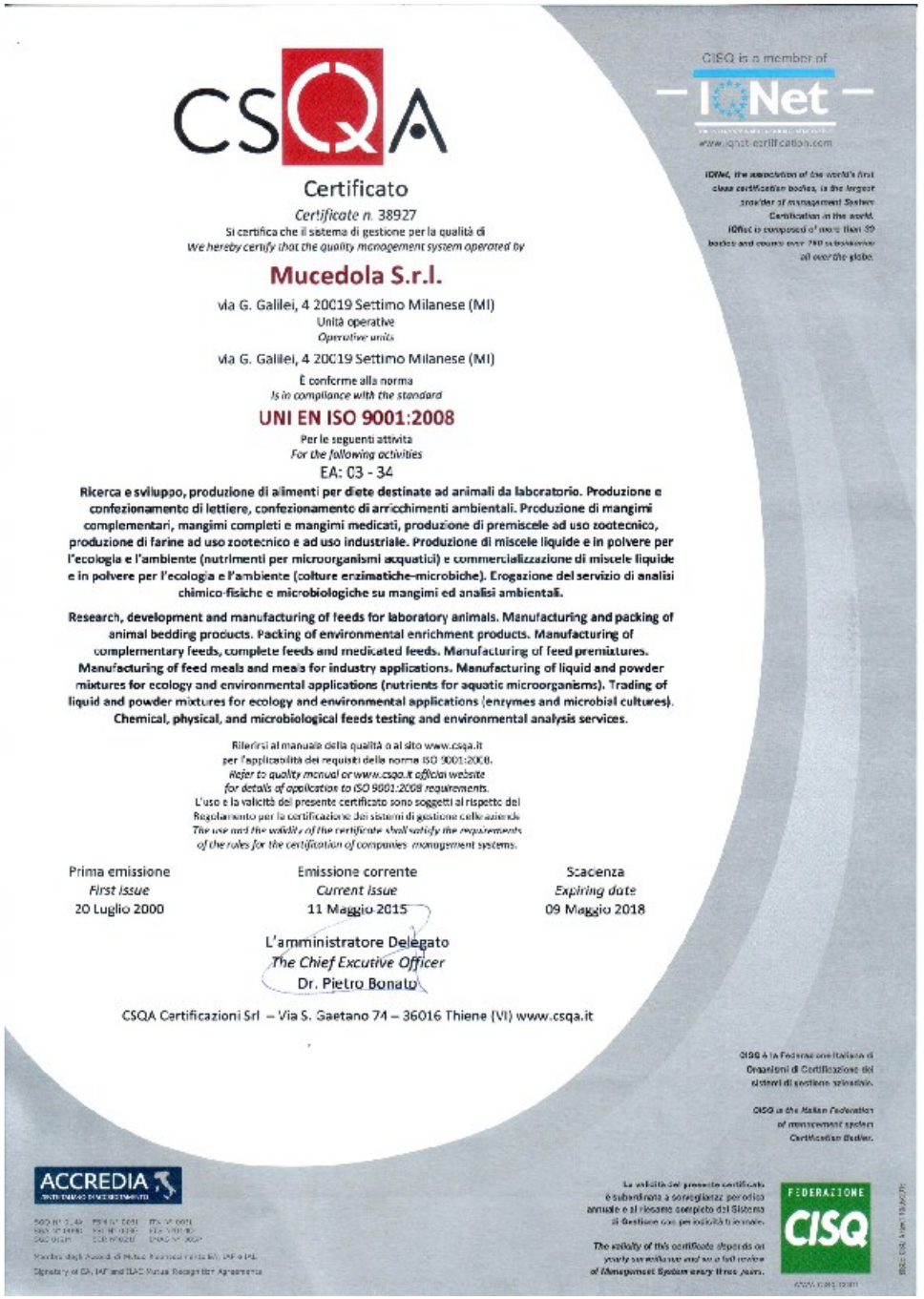
Dr. Sied Sadek
Managing Director

Accredited Body: DQS CFS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany

2. Laboratory animal diets

Laboratory animal diet manufacturers is important to have quality certification (ISO 9001):

- Research, development and manufacturing of diets for lab animals
- Manufacturing and packaging
- Environmental analysis services



CSQA

CISQ is a member of IQNet

Certificato

Certificate n. 38927

Si certifica che il sistema di gestione per la qualità di
We hereby certify that the quality management system operated by

Mucedola S.r.l.

via G. Galilei, 4 20019 Settimo Milanese (MI)
Unità operative
Operative units
via G. Galilei, 4 20019 Settimo Milanese (MI)

È conforme alla norma
Is in compliance with the standard

UNI EN ISO 9001:2008

Per le seguenti attività
For the following activities

EA: 03 - 34

Ricerca e sviluppo, produzione di alimenti per diete destinate ad animali da laboratorio. Produzione e confezionamento di lettiere, confezionamento di arricchimenti ambientali. Produzione di mangimi complementari, mangimi completi e mangimi medicati, produzione di premiscele ad uso zootecnico, produzione di farine ad uso zootecnico e ad uso industriale. Produzione di miscele liquide e in polvere per l'ecologia e l'ambiente (nutrimenti per microorganismi acquatici) e commercializzazione di miscele liquide e in polvere per l'ecologia e l'ambiente (colture enzimatiche-microbiche). Erogazione del servizio di analisi chimico-fisiche e microbiologiche su mangimi ed analisi ambientali.

Research, development and manufacturing of feeds for laboratory animals. Manufacturing and packing of animal bedding products. Packing of environmental enrichment products. Manufacturing of complementary feeds, complete feeds and medicated feeds. Manufacturing of feed premixtures. Manufacturing of feed meals and meals for industry applications. Manufacturing of liquid and powder mixtures for ecology and environmental applications (nutrients for aquatic microorganisms). Trading of liquid and powder mixtures for ecology and environmental applications (enzymes and microbial cultures). Chemical, physical, and microbiological feeds testing and environmental analysis services.

Riferirsi al manuale della qualità o al sito www.csqa.it
per l'applicabilità dei requisiti della norma ISO 9001:2008.
Refer to quality manual or www.csqa.it official website
for details of application to ISO 9001:2008 requirements.
L'uso e la validità del presente certificato sono soggetti al rispetto del Regolamento per la certificazione dei sistemi di gestione delle aziende
The use and the validity of the certificate shall satisfy the requirements of the rules for the certification of companies' management systems.

Prima emissione	Emissione corrente	Scadenza
First issue	*Current issue*	*Expiring date*
20 Luglio 2000	11 Maggio 2015	09 Maggio 2018

L'amministratore Delegato
The Chief Excutive Officer
Dr. Pietro Bonato

CSQA Certificazioni Srl – Via S. Gaetano 74 – 36016 Thiene (VI) www.csqa.it

CISQ è la Federazione Italiana di Organismi di Certificazione dei sistemi di gestione aziendale.
CISQ is the Italian Federation of management system Certification Bodies.

ACCREDIA

La validità del presente certificato è subordinata a sorveglianza periodica annuale e al riesame completo del Sistema di Gestione con periodicità triennale.
The validity of this certificate depends on yearly surveillance and on a full review of Management System every three years.

FEDERAZIONE CISQ

Hazard Analysis and Critical Control Points (HACCP)

- The HACCP system is a preventive approach to food safety from biological, chemical or physical hazards in production processes designed to identify, balance and mitigate key threats to animal wellness

- The HACCP system is used at all stages of a food chain, from food production and preparation processes including packaging and distribution

BUREAU VERITAS
Certification

Certificate

awarded to

J. RETTENMAIER & SÖHNE GMBH + CO KG

JRS

Fibers designed by Nature

Holzmühle 1
73494 Rosenberg, Germany

Bureau Veritas Certification herewith that the **HACCP-System** of the above mentioned company has been assessed and fulfils the following requirements.

Standards

Codex Alimentarius Food Hygiene, Basis Text, Fourth Edition
Food and Agricultural Organization
of United Nations - World Health Organization, Rome

Scope of supply

Development, production and distribution of
ARBOCEL, LIGNOCEL and RÄUCHERGOLD
Smoking Agents and Premium Hygienic Animal Bedding

Certification cycle start date: **23. November 2016**

Subject to the continual satisfactory operation of the organisation´s Management System, this certificate expires on: **22. November 2017**

Certificate n°: **DE003123-5_HACCP** Date: **18. November.2016**

Certification Manager

Certification body address: Bureau Veritas Certification Germany GmbH, Veritaskai 1, 21079 Hamburg

To check this certificate validity you may contact Bureau Veritas Certification, Further clarifications regarding the scope of this certificate and the applicability of the Management Systems requirements may be obtained by consulting the organisation

Certificate of batch analysis : Diet and Bedding

mucedola

Certificate of Analysis n° 63 of February 21, 2018 Update -

Standard Diet 4RF25 *certificate*

Complete feed for MICE and RATS
Reproduction, Weaning and Growth

Shape: pellet 8x16 mm vacuum packed - irradiated
SHELF-LIFE: Best Before 24 months from DOM (Date of Manufacture)

BROMATHOLOGICAL ANALYSIS	Method of analysis	Control Batch 3343 Value %	Batch 334301 DOM 16/01/2018 Value %
Moisture	MUC.UM	9.48	11.09
Crude protein	MUC.PR	22.73	21.97
Crude fat	MUC.GR	3.88	-
Crude fibre	MUC.CF	4.24	-
Ash	MUC.CN	7.08	6.90

IT COMPLIES TO THE ORIGINAL

PESTICIDES ANALYSIS	Value [µg/kg]	Method of analysis	D.L.
Organochlorine			
Hexachlorobenzene	ND	EPA - 8081 A	5 µg/kg
α-BHC, β-BHC	ND	EPA - 8081 A	5 µg/kg
γ-BHC (Lindane)	ND	EPA - 8081 A	5 µg/kg
Keltane	ND	EPA - 8081 A	5 µg/kg
Eptaclor	ND	EPA - 8081 A	5 µg/kg
Eptacloroepossido	ND	EPA - 8081 A	5 µg/kg
DDE, DDD, DDT	ND	EPA - 8081 A	5 µg/kg
Dieldrin	ND	EPA - 8081 A	5 µg/kg
Endrin	ND	EPA - 8081 A	5 µg/kg
Thiodan	ND	EPA - 8081 A	5 µg/kg
Organophosphorus			
Phosdrin	ND	EPA - 8141 A	10 µg/kg
Diazinon	ND	EPA - 8141 A	10 µg/kg
Disulfoton	ND	EPA - 8141 A	10 µg/kg
Phyrimiphosmethyl	ND	EPA - 8141 A	10 µg/kg
Ronnel	ND	EPA - 8141 A	10 µg/kg
Dimethoate	ND	EPA - 8141 A	10 µg/kg
Fenthion	ND	EPA - 8141 A	10 µg/kg
Methylparathion	ND	EPA - 8141 A	10 µg/kg
Malathion	ND	EPA - 8141 A	10 µg/kg
Fenitrothion	ND	EPA - 8141 A	10 µg/kg
Parathion	ND	EPA - 8141 A	10 µg/kg
Phosphamidon	ND	EPA - 8141 A	10 µg/kg
Methydathion	ND	EPA - 8141 A	10 µg/kg
Phenthoate	ND	EPA - 8141 A	10 µg/kg
Ethion	ND	EPA - 8141 A	10 µg/kg
Dichlorvos	ND	EPA - 8141 A	10 µg/kg
Chlorpyriphos-methyl	ND	EPA - 8141 A	10 µg/kg
PCB	ND	EPA - 8082	25 µg/kg

ND = not detectable
D.L. = detection limit

MICROBIOLOGICAL ANALYSIS	Value CFU/g	Method of analysis
Total Viable Organism	< 10	MUC.CBT
Total Coliforms	< 10	MUC.COI
Enterobacter sakazakii	< 10	MUC.ENTSAK
Yeasts	< 10	MUC.ML
Molds	< 10	MUC.MF
Fecal indicators		
Enterococcus faecium	< 10	MUC.ENT
Enterococcus faecalis	< 10	MUC.ENT
E.coli	< 10	MUC.E.coli
Pathogens		
Staphylococcus aureus	< 10	MUC.STAPH
Clostridium perfrigens	< 10	MUC.PERF
Salmonella	absent in 25 g	MUC.SAL

	Value		Method of analysis	D.L.
INHIBITING SUBSTANCES	absent		MUC.INIB	-
MYCOTOXINES				
Total Aflatoxines (B1,B2 - G1,G2)	ND	µg/kg	MUC.AFLA2	5 µg/kg
HEAVY METALS AND MINERALS				
Lead (Pb)	0.61	mg/kg	EPA - 7420	0.25 mg/kg
Cadmium (Cd)	0.059	mg/kg	EPA - 7130	0.05 mg/kg
Selenium (Se)	ND	mg/kg	EPA - 7740	0.05 mg/kg
Arsenic (As)	ND	mg/kg	EPA - 7060 A	0.05 mg/kg
Mercury (Hg)	ND	mg/kg	EPA - 7471	0.06 mg/kg
OTHERS				
Nitrite ($NaNO_2$)	5.02	mg/kg	Colorimetric method	0.5 mg/kg
Nitrate ($NaNO_3$)	41.51	mg/kg	Ionic chromatography	5 mg/kg
Fluoride (F)	4.46	mg/kg	Potenziometry	0.25 mg/kg
Nitrosodimethylamine	ND	µg/kg	GC-MS	1 µg/kg
Nitrosodimethylamine	ND	µg/kg	GC-MS	1 µg/kg

Comply with PF1609
The Quality Control
Dr Federica CARACCIOLO

Approved
The Technical Manager
Dr Elisabetta MUCEDOLA

The original certificate of analysis and the samples are kept in our archives

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mucedola

Certificate of Analysis n° 137 of May 8, 2018 Update -

SCOBIS UNO

Certified wooden dust-free bedding

IT COMPLIES TO THE ORIGINAL

Batch: FR - 18 - 02 B

ANALYSIS OF CONTAMINANTS

PESTICIDE RESIDUES

Phosphoric acid esters		analysis	spec max
Bromophos ethyl	mg/kg	< 0.01	0.05
Bromophos methyl	mg/kg	< 0.01	0.05
Chlorfenvinphos	mg/kg	< 0.01	0.05
Chlorpyriphos ethyl	mg/kg	< 0.01	0.05
Chlorpyriphos methyl	mg/kg	< 0.01	0.05
Diazinon	mg/kg	< 0.01	0.05
Dichlorvos	mg/kg	< 0.01	0.05
Diethion (Ethion)	mg/kg	< 0.01	0.05
Dimethoate	mg/kg	< 0.01	0.05
Fenitrothion	mg/kg	< 0.01	0.05
Fenthion	mg/kg	< 0.01	0.05
Malathion	mg/kg	< 0.01	0.05
Mecarbam	mg/kg	< 0.01	0.05
Methidathion	mg/kg	< 0.01	0.05
Parathion ethyl	mg/kg	< 0.01	0.05
Parathion methyl	mg/kg	< 0.01	0.05
Profenofos	mg/kg	< 0.01	0.05
Pyrimiphos ethy	mg/kg	< 0.01	0.05
Sulfotep	mg/kg	< 0.01	0.05

Chlorinated hidrocarbons			
Lindane	mg/kg	< 0.002	0.02
α HCH	mg/kg	< 0.002	0.02
β-HCH	mg/kg	< 0.004	0.01
δ-HCH	mg/kg	< 0.002	0.05
HCB	mg/kg	< 0.002	0.01
Aldrin	mg/kg	< 0.002	0.01
Dieldrin	mg/kg	< 0.002	0.01
Heptachlor	mg/kg	< 0.002	0.01
Heptachlor epoxide	mg/kg	< 0.004	0.01
Quintozene	mg/kg	< 0.002	0.02
Endrin	mg/kg	< 0.003	0.01
o,p' DDD	mg/kg	< 0.002	0.05 (o,p' DDD to p,p' DDT)
p,p' DDD	mg/kg	< 0.002	
o,p' DDE	mg/kg	< 0.002	
p,p' DDE	mg/kg	< 0.002	
o,p' DDT	mg/kg	< 0.002	
p,p' DDT	mg/kg	< 0.002	
α-endosulfan	mg/kg	< 0.002	0.1 (α-endosulfan to Endosulfansulfate)
β-endosulfan	mg/kg	< 0.002	
Endosulfansulfate	mg/kg	< 0.004	

MICROBIOLOGICAL ANALYSIS

		analysis	spec max
Aerobic count	UFC/g <	1000	$1x10^6$
Coliforms	UFC/g <	100	100
Fecal coliforms	UFC/g <	10	10
Coag.positive staphylococci	UFC/g <	100	100
Anaerobic sulfite-reducing bact.	UFC/g <	10	10
Salmonella	none/25 g		none/25 g
Yeasts	UFC/g <	10	1000
Moulds	UFC/g <	10	1000

MYCOTOXINS

Aflatoxin B1	µg/kg <	0.1	5 (Aflatoxin B1 to G2)
Aflatoxin B2	µg/kg <	0.1	
Aflatoxin G1	µg/kg <	0.1	
Aflatoxin G2	µg/kg <	0.1	

HEAVY METALS and MINERALS

Lead	mg/kg	0.27	1.5
Cadmium	mg/kg	0.06	0.16
Arsenic	mg/kg <	0.1	1
Mercury	mg/kg <	0.005	0.1
Selenium	mg/kg <	0.2	0.5
PCB-NDL	mg/kg <	0.04	0.04

Comply with PF 3907
The Quality Control
Dr Federica CARACCIOLO

Approved
The Technical Manager
Dr Elisabetta MUCEDOLA

The original certificates of analysis and the samples are kept in our archives

Case study: Quality control

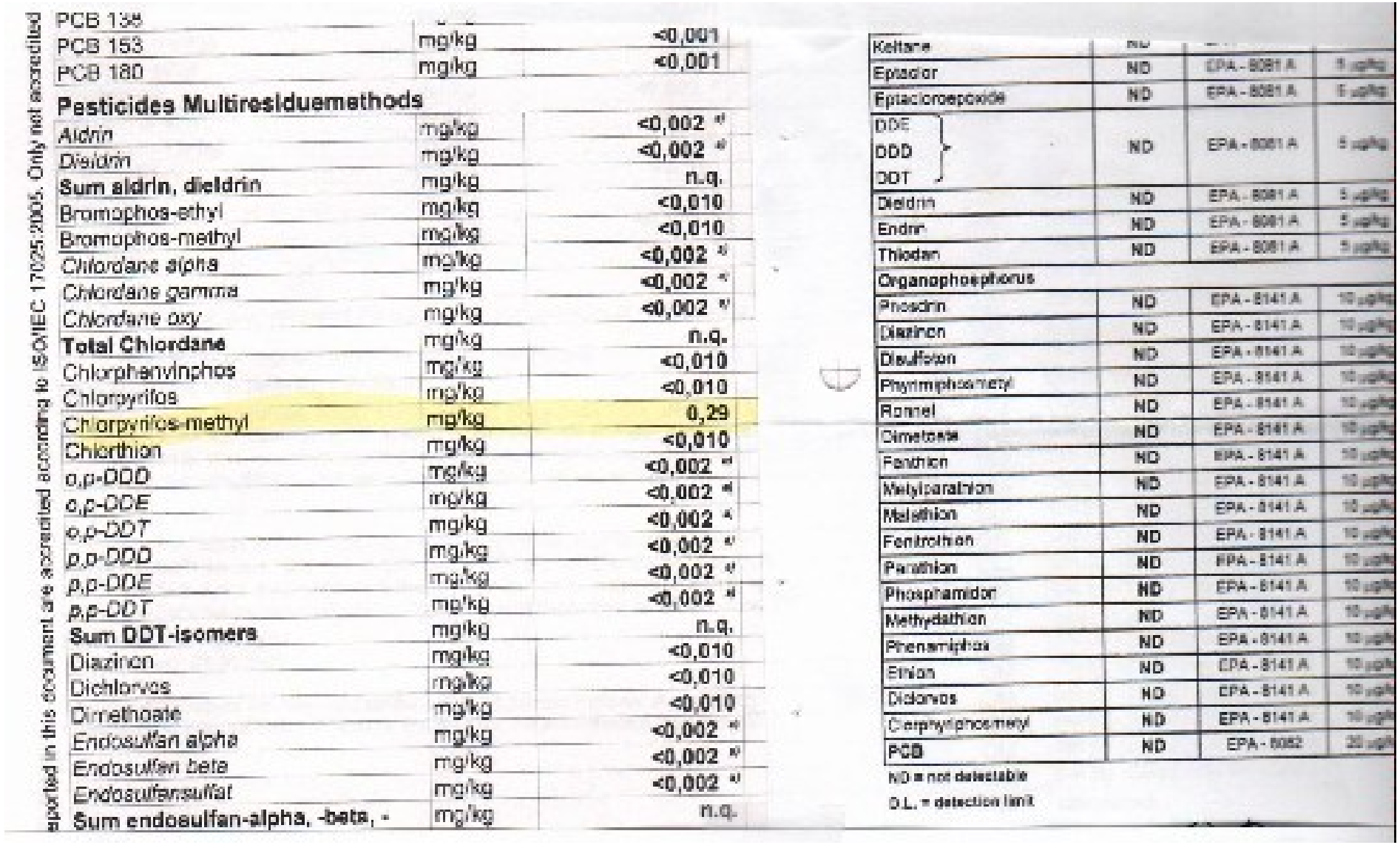
Procurement for the purchase of animal diet 8,000 kg

Vacuum packed
Gamma irradiated
Protein: 18% - 22%, Crude Fat: 3% - 6%, Crude Fiber: 4% - 6%

Two offers: Difference of 4.800 euros

Examine certificate of analysis

Certificates of analysis



PCB 138		
PCB 153	mg/kg	<0,001
PCB 180	mg/kg	<0,001
Pesticides Multiresiduemethods		
Aldrin	mg/kg	<0,002
Dieldrin	mg/kg	<0,002
Sum aldrin, dieldrin	mg/kg	n.q.
Bromophos-ethyl	mg/kg	<0,010
Bromophos-methyl	mg/kg	<0,010
Chlordane alpha	mg/kg	<0,002
Chlordane gamma	mg/kg	<0,002
Chlordane oxy	mg/kg	<0,002
Total Chlordane	mg/kg	n.q.
Chlorphenvinphos	mg/kg	<0,010
Chlorpyrifos	mg/kg	<0,010
Chlorpyrifos-methyl	mg/kg	0,29
Chlorthion	mg/kg	<0,010
o,p-DDD	mg/kg	<0,002
o,p-DDE	mg/kg	<0,002
o,p-DDT	mg/kg	<0,002
p,p-DDD	mg/kg	<0,002
p,p-DDE	mg/kg	<0,002
p,p-DDT	mg/kg	<0,002
Sum DDT-isomers	mg/kg	n.q.
Diazinon	mg/kg	<0,010
Dichlorvos	mg/kg	<0,010
Dimethoate	mg/kg	<0,010
Endosulfan alpha	mg/kg	<0,002
Endosulfan beta	mg/kg	<0,002
Endosulfansulfat	mg/kg	<0,002
Sum endosulfan-alpha, -beta, -	mg/kg	n.q.

Kelthane	ND	EPA - 8081 A	5 µg/kg
Eptadur	ND	EPA - 8081 A	5 µg/kg
Eptaclorepoxide	ND	EPA - 8081 A	5 µg/kg
DDE, DDD, DDT	ND	EPA - 8081 A	5 µg/kg
Dieldrin	ND	EPA - 8081 A	5 µg/kg
Endrin	ND	EPA - 8081 A	5 µg/kg
Thiodan	ND	EPA - 8081 A	5 µg/kg
Organophosphorus			
Prosdrin	ND	EPA - 8141 A	10 µg/kg
Diazinon	ND	EPA - 8141 A	10 µg/kg
Disulfoton	ND	EPA - 8141 A	10 µg/kg
Phynmphos-metyl	ND	EPA - 8141 A	10 µg/kg
Ronnel	ND	EPA - 8141 A	10 µg/kg
Dimetoate	ND	EPA - 8141 A	10 µg/kg
Fenthion	ND	EPA - 8141 A	10 µg/kg
Metylparathion	ND	EPA - 8141 A	10 µg/kg
Malathion	ND	EPA - 8141 A	10 µg/kg
Fentrothion	ND	EPA - 8141 A	10 µg/kg
Parathion	ND	EPA - 8141 A	10 µg/kg
Phosphamidon	ND	EPA - 8141 A	10 µg/kg
Methydathion	ND	EPA - 8141 A	10 µg/kg
Phenamiphos	ND	EPA - 8141 A	10 µg/kg
Etrion	ND	EPA - 8141 A	10 µg/kg
Didanos	ND	EPA - 8141 A	10 µg/kg
Clorpyriphos-metyl	ND	EPA - 8141 A	10 µg/kg
PCB	ND	EPA - 8082	20 µg/kg

ND = not detectable

D.L. = detection limit

Levels of the pesticide e.g. Chlorpyrifos-methyl is 0,29 mg/kg

Would you purchase this diet?

- EU-guidelines allow a maximum residue levels of 0,01 mg/kg Chlorpyrifos-methyl in the diet
- High levels of Chlorpyrifos-methyl may induce hepatotoxicity, nephrotoxicity and neurodevelopmental problems
- In the EU, the use of Chlorpyrifos-methyl is NOT authorized in: DE, DK, FI, LT, LU, LV, MT, NL and SE

A final rule issued in August 2021, effectively stopped the use of the pesticide chlorpyrifos on all food and animal feed

Case study: Colony management and planning

- Every year the Animal Facility Manager or the Veterinarian in charge is responsible for sending a yearly EU report on the species and the number of animals used and the field of research

- Last year, the manager noted that one lab's colony size is overbreeding by 40% and that the mice not used were culled as surplus

Which measures or recommendations would you take to resolve this problem?

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BREEDING COLONY SIZE PLANNING WORK SHEET

Determine your Research Needs

Line 1....How many mice do you need? .....

Line 2....What age range is acceptable for your experiments?
If they all must be born in the same week, enter 1
If age range is 2 weeks, (e.g., 5-6 weeks of age), enter 2
If age range is 4 weeks (e.g., 5–8 weeks of age), enter 4.....

Line 3....How often do you need the mice?
If needed weekly, enter 1
If needed every other week, enter 2
If needed once a month, enter 4.....

Line 4 ... Divide Line 1 by the smaller of Line 2 or Line 3
(round *up* to the nearest whole number).....

Line 5....What gender do you need?
If only one gender is needed (i.e. either male or female), enter 2
If both genders can be used, enter 1.....

Line 6....What breeding scheme are you using to maintain the colony?
If homozygote x homozygote, enter 1
If heterozygote x homozygote, (or the reciprocal) enter 2
If heterozygote x heterozygote, enter 4.....

Line 7....Can you do your experiment with fewer mice?
If yes, enter 1
If no, enter a "fudge factor" to ensure sufficient production of the mice you will need (e.g., if you need 10% over, enter 1.1).....

Calculate the Number of Mice you Need to Produce Weekly

Line 8.....Multiply the following: Line 4 x Line 5 x Line 6 x Line 7
(round *up* to the nearest whole number).....

Determine your Breeding Colony Productivity

Line 9.....What is the average number of pups weaned per litter? .....

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Line 10....How many litters are produced by each breeding female? (hint: a female will *usually* produce a litter ~every 2 months, if left with her mate continuously).....

Line 11....What is the breeding lifespan of your matings (in weeks)? .....

Calculate the Number of Weaned Pups per Female Each Week

Line 12....Divide Line 10 by Line 11, multiply by Line 9 (round to nearest hundredth).....

Calculate the Number of Breeding Females Needed

Line 13....Divide Line 8 by Line 12 (round *up* to the nearest whole number).....

Refining your Breeding Colony Size:

To ensure a consistent inventory of weaned mice, remove non-productive breeders (i.e. no pregnancy and no weaned pups by 60-90 days after mating or successfully weaning a litter) and/or breeders at the end of their breeding cycle:

- Replace equal numbers of mice weekly or monthly
- Raise enough mice to produce breeders as well as meet your experimental needs

Calculate Number of Breeding Females Needed to Maintain Colony

Line 14.....To determine the number of replacement female breeders needed weekly, divide Line 13 by Line 11 (round *up* to the nearest half).....

Line 15.....To determine number of additional females needed as breeder replacements, multiply line 14 by 2 then divide by line 12
(round *up* to the nearest whole number).....

Line 16.....**Final Number of Breeding Females** needed to maintain colony *and* provide sufficient mice for experiments, add Line 13 and Line 15.....

Note: There are situations in which this worksheet is less accurate, such as colonies maintaining sub-lethal genes or stocks with gene penetrance issues.

- In managing a mouse colony, your received a request for 200 C57Bl/6 females per month, aged 6-8 weeks

  From the mouse database, we know that this colony has an average litter size of 5.7 pups

- How many mating trios do you need to supply this number of mice requested?
- In how many weeks would you be able to start supplying these mice?

Reproductive characteristics:

- Mating age: 6-8 weeks of age
- Gestation: ~19-21 days
- Wean age: ~21 days; up to 28 days if preferred
- Litter size: 2-12 pups; highly strain-dependent
- Replace breeders: ~7-8 months of age (several mutant strains have considerably shorter windows of optimal breeding performance)
- Select appropriate breeding schemes

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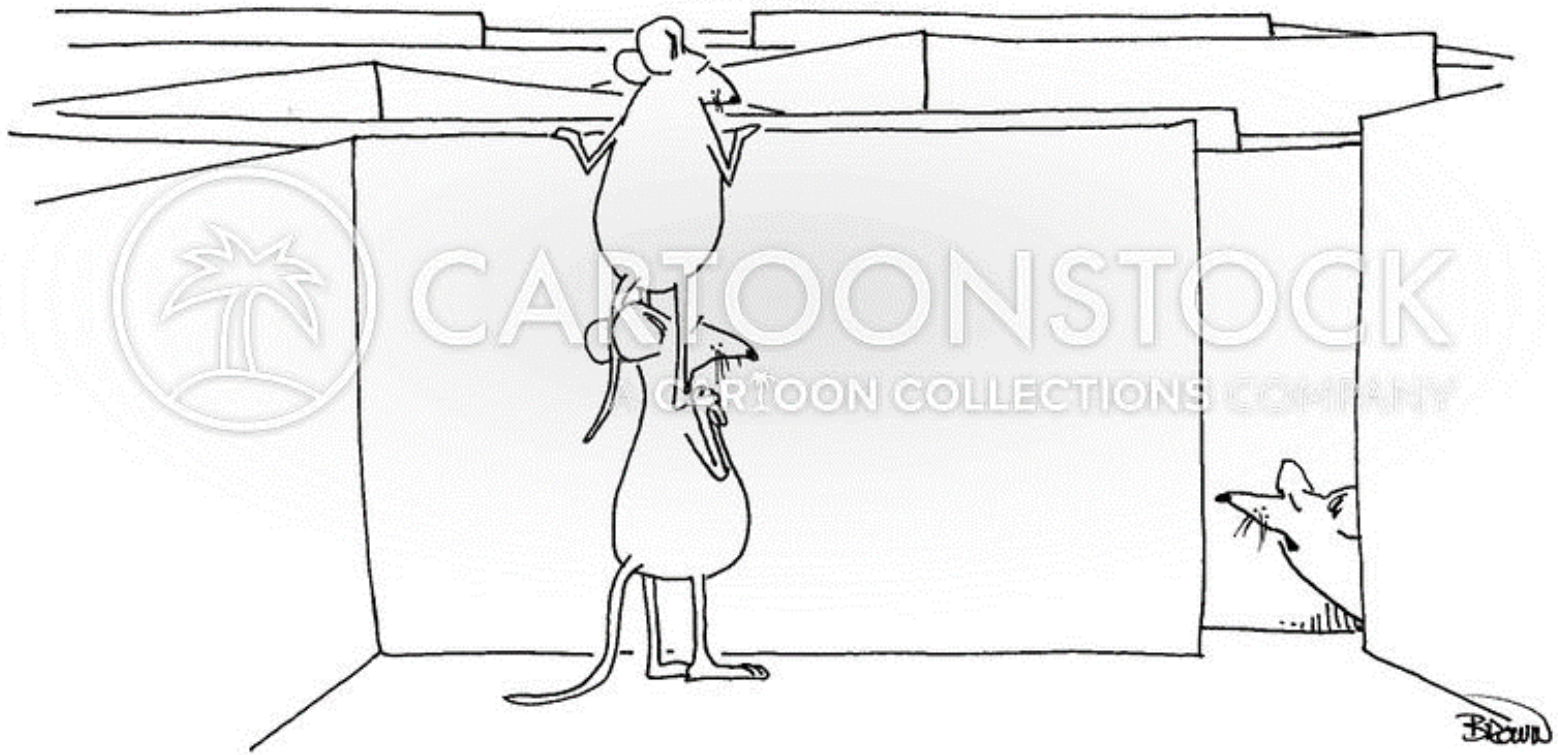

"Well, I'm not setting any records. How about you?"