

reference paper

Charles River Laboratories

Volume 11 #1 1999

Charles River Laboratories' International Genetic Standard (IGS®)

Introduction

The intent of this paper is to expand on the International Genetic Standard (IGS®) and give you a better definition of its meaning.

The term IGS refers not just to research models, but an entire **system** of managing the health and genetics of laboratory animals. This system embraces the standardization of four basic elements -- health, genetics, quality assurance, and operations, and was adapted by CRL with help from experts in the field of genetics.

Over the years, we have used several terms when discussing what is now called the International Genetic Standard ... the International Standard, the Gold Standard, the Foundation Colony. We have adopted the term International Genetic Standard to denote those stocks and strains that are managed and standardized under the four basic elements - health, genetics, quality assurance, and operations. The term "Gold Standard" is used synonymously with "Foundation Colony".

The International Genetic Standard system ensures our customers that, whether they buy CRL animals in Europe, the United Kingdom, Japan, the U.S., or any other Charles River location, the animal will be bred with uniformity. This new generation of animals provides similarity and reliability from plant to plant and country to country.

What is the IGS Animal?

The International Genetic Standard laboratory animal is not a new animal. No foreign genetic material in the form of breeders from other stocks or inbred strains is used to create an IGS model and no selection for specific traits is done. Instead, steps are taken to stabilize the genetic diversity that already exists in production colonies while putting in place a system to standardize this diversity between production colonies worldwide.

Researchers who have used non-IGS models in the past should not expect to see results that differ from their established control values with the new IGS models. In fact, the range of variation researchers may have experienced in animals ordered from different production colonies should be reduced. In studies conducted on Crj:CD®(SD)IGS rats in Japan, several observations were made.

- There were no significant differences in general observations among CD®(SD)IGS and CD®(SD) rats.
- The body weight of CD®(SD)IGS was found smaller than the CD®(SD) for both males and females during the study period. At 31 weeks old, male CD®(SD)IGS animals weighed 14.3% less than those of the CD®(SD) animals, and female CD®(SD)IGS animals weighed 16.8% less than those of the CD®(SD) animals.

Contributing
to the **search**
for **healthier**
lives.



- Feed consumption of the CD[®](SD)IGS animals was also found to be lower than the CD[®](SD) animals.
- No significant hematological differences were found among the CD[®](SD)IGS rat and the CD[®](SD).
- For blood chemistry values, only the total cholesterol and neutral fat values of the IGS[®] rats were found lower than the CD[®](SD) rats in both males and females. All other values were found similar among IGS and traditional CD's.

This study concluded that there were no significant differences between the Crj:CD[®](SD)IGS rat and the traditional Crj:CD[®](SD) rat and they should be considered similar animals suitable for reproductive developmental toxicology evaluation.¹

The History of IGS

The motivation for implementing the IGS program began with observations by researchers that two-year survival rates for CD[®] and Sprague-Dawley rats appeared to be decreasing. This caused concern that two-year product registration studies might be affected by this decrease in longevity. While health status, genetics, and nutrition have all been suggested as contributing factors, only genetics would appear to fit the epidemiologic circumstances associated with the development of this phenomenon.

Less commonly reported but also of significant concern, were alterations in the CD[®] rats' reproductive performance. These reports prompted Charles River Laboratories to institute a male proven breeder program whereby all male animals destined to become breeders undergo an initial timed mating with a known fertile female. Only those males that sire a litter within the appropriate time span are admitted to the breeding program.

After meeting with concerned members of the biomedical research community and participating in a number of study groups in the United

States and Europe, Charles River re-examined its animal breeding practices. As a result, we undertook a program to modify outbred models in such a way as to reduce selection pressures which may be linked to the reported problems in longevity and reproductive performance.

Genetics

Genetic drift over time and genetic divergence among colonies are the inevitable results of sampling error and mutation. Over many generations, random genetic drift can be expected to cause at least moderate genetic divergence among outbred colonies.

The challenge in breeding outbred animals is to maintain this individual diversity by preventing inbreeding, yet somehow standardize multiple production colonies of these animals that are geographically separated, such that each colony has the same range of genetic variation.

Up until the development of the International Genetic Standard CD[®] rat, commercial breeders, including Charles River, started new colonies of outbred animals by cesarean rederivation, colony transfer, or other methods. The new colony, in turn, used a random mating system to hopefully ensure that genetic diversity was maintained.

When developing the IGS CD[®] rat, a Foundation Colony, originally referred to as the Gold Standard Colony, was established at corporate headquarters in Wilmington, Massachusetts in 1992. This colony was established using 100 pair of breeders from Charles River colonies located throughout the world. Four of these colonies had been separated for at least 10 years, and four had been separated at least 22 years, with no infusions from outside colonies. This "fixed" the genetic diversity and gave us the makings for diverse populations. One pup from

Visit us:
www.criver.com
or E-mail us:
comments@criver.com

each of 200 litters obtained by cesarean rederivation was used to set up three family lines.

Instead of a random mating system within the barrier production room, IGS[®] rats were produced using a purposeful outbreeding system in order to minimize the chance of inbreeding. Maximal outbreeding was assured by computerized tracking of each family tree back 20-30 generations. The computer then shows the animals least related. It also keeps track of each single animal, which makes inbreeding even less likely. Every three years, animals from the Foundation Colony are sent back out into production colonies to replace some of the breeders. After five years, we bring a small number of animals back into the Foundation Colony. This causes the Foundation Colony to change a bit to reflect all colonies produced.

This trading of genetic materials by forward and backward migration links all of the colonies and assures that none diverge too far from the others. In other words, migration acts as a "genetic glue" that holds colonies together and sets a limit on the amount of genetic divergence that can occur. In effect, all of the colonies are genetically merged into one large colony that resides in multiple geographic locations.

Approximately 1500 embryos are cryopreserved every three years. Approximately 1,000 serve as a bank for Charles River in case of a disaster while the other 500 are reserved for customers who have a need to have the exact animals that were in the colony at the time they were frozen. A similar program was set up to develop the IGS Wistar Han model and will be used for future models.

Health

Charles River also instituted a new health monitoring reporting system in conjunction with the International Genetic Standard. The goal of this system is to provide ready access to any and all health monitoring information our customers may require.

The first tier of our health monitoring report reviews the status of agents for which CRL would

immediately terminate a colony and recycle a room. There is also a remarks section containing information about frequency of screening and CRL's policies with regard to the specific agents listed. Another section lists testing profiles and dates on which specific tests were conducted for each area. The "Complete HM" profile refers to bacteriology, parasitology, and pathology testing procedures.

The second tier of the report is an additional profile report that provides information on serology, bacteriology, and parasitology for those agents not considered part of the VAF definition but whose presence or absence may be important to certain customers with specific research requirements. Additional information regarding such agents can be obtained by calling Charles River's Technical Assistance Department at 1-800-338-9680.

The standard profile and the additional profile reports are routinely generated once a quarter and mailed to any customer who requests them, as well as to our professional contacts list. Information, updated weekly, is also available on our homepage at <http://www.criver.com>.

Operations

One of the first steps Charles River undertook in conjunction with the International Genetic Standard was to institute a program to recycle and upgrade all barrier production rooms. These modernized rooms are then populated with rederived stock. Many other improvements have been made, for instance:

- Face masks, caps, and gloves are now changed every two hours.
- Footwear is sanitized weekly.
- Strict procedures for the detection and control of insects and feral and wild rodents have been implemented.
- Updated room surface and equipment decontamination and sterilization procedures have been put into place.



REFERENCE PAPER

publication of
Charles River
Laboratories
251 Ballardvale St.
Wilmington, MA 01887
(508) 658-6000

comments:
comments@criver.com

Inquires may be
addressed to
Peggy Bramanti,
Editor

- Additional testing of rederived animals is done PRIOR to stocking.
- Sophisticated system for controlling airborne contaminants was developed and implemented.

Our efforts to standardize methods for breeding animals at all locations may vary from country to country but variations are compatible with our standards. For instance, feed in the U.S. is normally corn-based, whereas in Japan it is rice-based and in Europe it is wheat-based. The International Genetic Standard allows for this difference, but ensures that the nutritional content of the feed is the same.

Quality Assurance

A team is continually studying and monitoring all processes that effect the quality of our animals. Improvements are constantly being made whenever and wherever the need arises. Standard Operating Procedures have been developed for every aspect of our barrier room production. Comprehensive training and awareness educational sessions are conducted for employees. Significant changes were made to our rederivation process to ensure the microbiological status of the animals. All of these procedures are audited on a regular basis to ensure compliance and effectiveness.

In Conclusion ...

Charles River IGS® models are NOT new models, SIMPLY BETTER ONES! The system and procedures put into place ensure that our colonies are standardized while at the same time maintaining genetic diversity. For more information on IGS, please contact our Technical Assistance Department at 1-800-338-9680.

¹ This study group has published the first in a series of books on the CD®(SD)IGS model. This book entitled "*Biological Reference Data on CD(SD)IGS Rats - 1998*" can be ordered by contacting:
Sumiko Bilson, Charles River Laboratories,
251 Ballardvale Street, Wilmington, MA 01887,
(978) 658-6000.