

**Generation of Biosafety Level (BL) 1  
Transgenic Rodents under the *NIH*  
*Guidelines:*  
A Proposed Exemption**

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# Agenda

- **Current *NIH Guidelines* requirements for the generation of transgenic rodents that may be housed at Biosafety Level (BL) 1**
- **Original Language Discussed at the March 2010 RAC Meeting**
- **Revised Proposed Exemption Language**

# **Current *NIH Guidelines***

## **Section III-E**

- **Section III-E of the *NIH Guidelines* covers experiments that are of low biosafety risk, i.e. may be conducted at BL1, and may be initiated upon registration with the Institutional Biosafety Committee**
  - IBC review and approval is still required.

# Current *NIH Guidelines*

## Section III-E-3 Experiments Involving Transgenic Rodents

- Experiments that involve the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived there from, into the germ-line (transgenic rodents) may be initiated upon registration with the IBC provided the transgenic rodent can be housed at BL1 containment
- “Generation” of a transgenic rodent includes mating between two different transgenic rodents or mating of a transgenic rodent and a non-transgenic rodent
  - Breeding within a strain of transgenic rodents to maintain a line is not subject to this section of the *NIH Guidelines*

# **Impetus for Considering an Exemption for Mating of Certain Transgenic Rodents**

- **The overwhelming majority of matings of transgenic rodents that require BL1 containment will result in a rodent that can also be housed at BL1 and would therefore not pose an appreciable risk to human health**
- **While each registration is not a significant burden, the total number of registrations required leads to an administrative burden on the IBC and researchers that does not appear to be commensurate with the biosafety risk**

# Proposed Exemption: Mating of Transgenic Rodents

## March 2010

- The mating of two different transgenic rodents or the mating of a transgenic rodent with a non-transgenic rodent with the intent of creating another transgenic rodent that can be housed at BL1 containment, will be exempt from the *NIH Guidelines* if:
  - Both parental rodents can be housed under BL1 containment,

AND

# Proposed Exemption: March 2010

–Each parental transgenic rodent does not contain any one of the following genetic modifications:

- a) A transgene that codes for amyloid or a prion; or
- b) More than 50% of the genome of an exogenous virus from a single family; or
- c) Expression of the transgene is under the control of a retroviral long terminal repeat;

AND

–It is anticipated that the transgenic rodent that results from this mating will not:

- a) Contain more than 50% of an exogenous viral genome from a single family; or
- b) Contain a transgene that codes for amyloid or a prion.

# **Does a Transgene for a Protein that can be Converted to an Amyloid or a Prion Increase the Risk of Breeding?**

- **Amyloids are not known to be infectious in any natural or practical sense**
- **Transgenic rodents may:**
  - **Contain a wild type PrP gene from a different species and may be more susceptible to infection upon inoculation with a prion from that species**
  - **contain a gene that expresses mutated PrP that might, in very rare instances, convert spontaneously to prions**

# Transgenic Animals that Contain Amyloid or Prions, cont. . . .

- **Transgenic rodents containing a wild type PrP gene do not generate prions spontaneously, and:**
  - Are able to be housed under BL1 conditions
  - Mating of such animals does not increase risk
  - The introduction of the prion to generate infection in that animal is a separate experiment
- **Work with Bovine Spongiform Encephalopathy prion is regulated as a Select Agent by HHS/CDC**

# Transgenic Animals that Contain Amyloid or Prions, cont. . . .

- **Transgenic rodents containing mutated PrP genes**
  - Are currently able to be housed under BL1 conditions
  - Rarely produce prions and risk of infection limited by:
    - Species/transmission barriers to prion disease
    - Extremely inefficient transmission by peripheral routes of exposure
    - The fact that infection would require injection of substantial amount of material- a bite or needle stick is insufficient to result in infection
  - Mating of such animals does not increase risk

# Proposed Exemption: Mating of Transgenic Rodents

## March 2010

–Each parental transgenic rodent does not contain any one of the following genetic modifications:

- ~~a) A transgene that codes for amyloid or a prion; or~~
- b) More than 50% of the genome of an exogenous virus from a single family; or
- c) Expression of the transgene is under the control of a retroviral long terminal repeat;

AND

–It is anticipated that the transgenic rodent that results from this mating will not:

- a) Contain more than 50% of an exogenous viral genome from a single family; or
- ~~b) Contain a transgene that codes for amyloid or a prion.~~

# Transgenes under Control of Retroviral LTRs

- Mating of a rodent could potentially lead to recombination with an endogenous mouse retrovirus and result in mobilization of transgene in replication competent mouse retrovirus
  - While risk is low may be prudent to continue IBC review and approval
  - Risk of recombination and possible transmission to humans more likely with gamma RV LTRs (e.g. MLV, XMRV, FeII)
    - Excludes other RV LTR (e.g. HIV, RSV, MMTV)

# Proposed Exemption: Mating of Transgenic Rodents

## March 2010

–Each parental transgenic rodent does not contain any one of the following genetic modifications:

- ~~a) A transgene that codes for amyloid or a prion; or~~
- b) More than 50% of the genome of an exogenous virus from a single family; or
- c) Expression of the transgene is under the control of a **gamma** retroviral long terminal repeat;

AND

–It is anticipated that the transgenic rodent that results from this mating will not:

- a) Contain more than 50% of an exogenous viral genome from a single family; or
- ~~b) Contain a transgene that codes for amyloid or a prion.~~

# Proposed Exemption: Mating of Transgenic Rodents

## June 2010

- The mating of two different transgenic rodents or the mating of a transgenic rodent with a non-transgenic rodent with the intent of creating another transgenic rodent that can be housed at BL1 containment, will be exempt from the NIH Guidelines if:
  - Both parental rodents can be housed under BL1 containment,

AND

# **Proposed Exemption: Mating of Transgenic Rodents June 2010**

**–Each parental transgenic rodent does not contain any one of the following genetic modifications:**

- a) More than 50% of the genome of an exogenous virus from a single family; or**
- b) Expression of the transgene is under the control of a gamma retroviral long terminal repeat;**

**AND**

**–It is anticipated that the transgenic rodent that results from this mating will not:**

- a) Contain more than 50% of an exogenous viral genome from a single family**