CCAC training module on: genetically-engineered farm animals

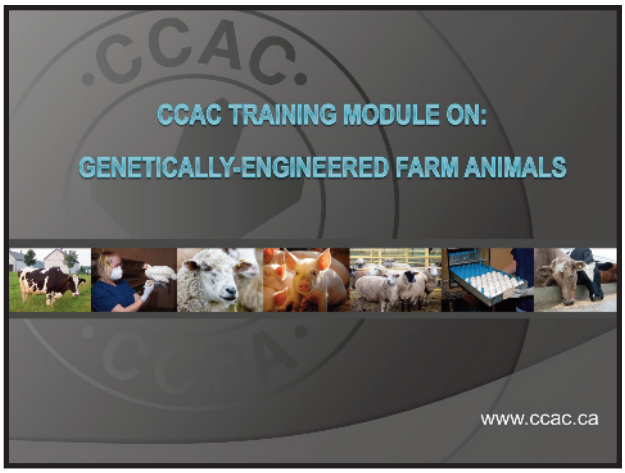
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CCAC training module on: genetically-engineered farm animals

Companion Notes

Slide 1 CCAC training module on: genetically-engineered farm animals



The use of genetic engineering in the production of farm animals is an evolving science in which the impacts on the welfare of the animals are not always known.

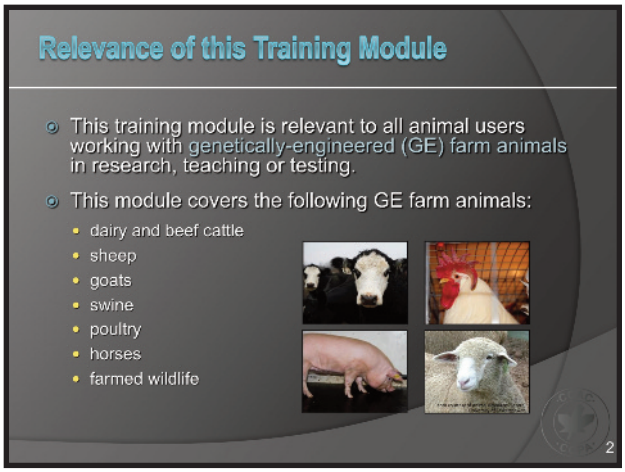
Where animal welfare issues have been identified, investigators must be prepared to address these by altering farm animal care practices accordingly. In the production of new genetically-engineered animals, where the effects of the genetic-engineering on the welfare of the animals is unknown, a basic welfare assessment must be undertaken, and strategies employed to mitigate any welfare concerns.

Investigators must also be aware of relevant federal, provincial and municipal regulations concerning the care, handling and transportation of genetically-engineered farm animals.

This module is based on section 9.8 of the *CCAC guidelines on: the care and use of farm animals in research, teaching and testing* (2009) and the *CCAC guidelines on: genetically-engineered animals* (in prep.). It is meant to be completed in conjunction with the *CCAC training module on: the ethical use and care of farm animals in science* (2010), in which basic principles of farm animal welfare, acquisition, handling, husbandry, specialized procedures and disposition are covered, as well as any other relevant modules. Visit the CCAC website at www.ccac.ca to access and consult these guidelines documents and this training module.

Slide 2 Relevance of this Training Module

The general considerations outlined in this training module are applicable to all genetically-engineered farm animals, including genetically-engineered dairy cattle, beef cattle, swine, poultry, sheep, goats, horses and farmed wildlife.



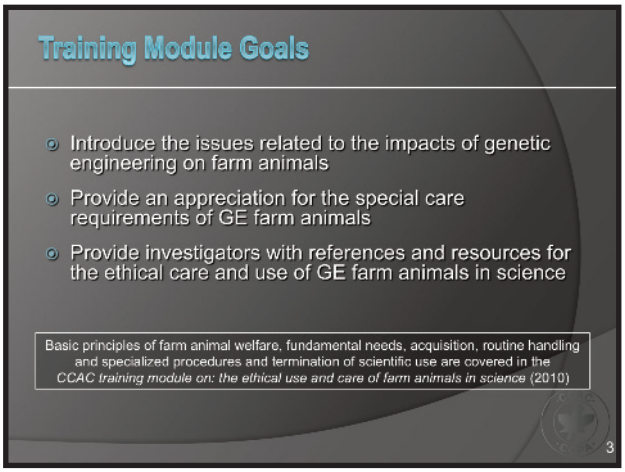
Slide 3 Training Module Goals

This training module aims to achieve three goals:

1. **To present an overview of issues related to the impacts of genetic engineering on farm animals.**

2. **To provide an appreciation for special care that may be required for genetically-engineered farm animals.**

3. **To provide references and resources for issues concerning the ethical use and care of genetically-engineered farm animals used in science.** Where appropriate, hyperlinks have been embedded into the module to provide direct access to the texts and guidelines.

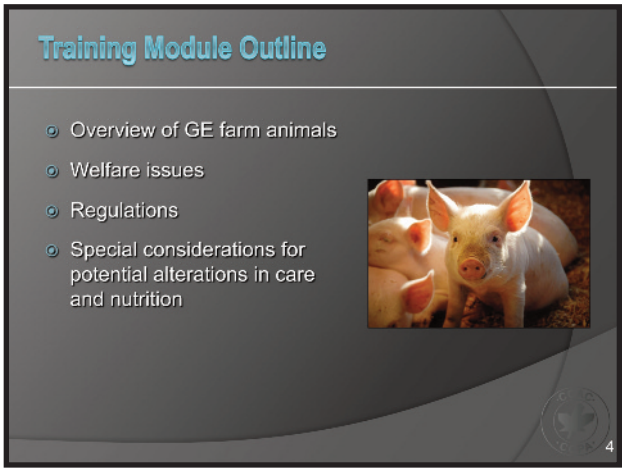


References cited in this module are intended to provide direction to further information; however, investigators should consult relevant experts and scientific literature for the most recent information on the species and techniques under consideration.

Care has been taken to ensure that all web links are up-to-date; however, the dynamic nature of the internet may result in some links becoming out-of-date. Therefore, keyword search suggestions are provided for situations in which links to additional resources may be broken. The keywords can be entered into any standard internet search engine.

Slide 4 Training Module Outline

This training module introduces the topic of genetically-engineered farm animals and outlines the potential for welfare concerns for farm animals as a result of genetic engineering. Additional topics include regulations, and considerations with regard to husbandry and nutrition that must be addressed when using genetically-engineered farm animals in science.

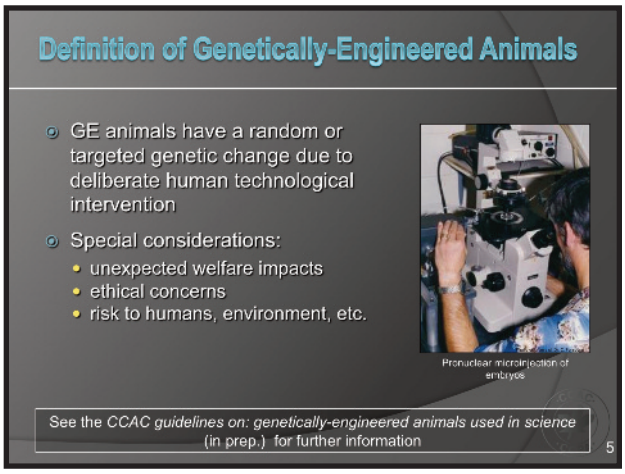


Since expression of genetic modifications is a complex process, it may be difficult to predict all potential changes in the physiology of the animal; this makes it difficult to predict how specific management techniques may need to be altered. Therefore, this training is intentionally broad.

See the *CCAC guidelines on: genetically-engineered animals* (in prep.) for more information on genetically-engineered animals. Visit the CCAC website at www.ccac.ca to access and consult this guidelines document.

Slide 5 Definition of Genetically-Engineered Animals

For the purpose of CCAC guidelines documents and training modules, a **"genetically-engineered animal" is an animal that has had a random or targeted change in its nuclear or mitochondrial DNA (addition, deletion or substitution of some part on the animal's genetic material) achieved through a deliberate human technological intervention.** The key feature of the CCAC definition of a genetically-engineered animal is that the genetic modification must be deliberately achieved through human technological intervention.



All types of animals that fall under this definition are covered by the *CCAC guidelines on: genetically-engineered animals* (in prep.) for the following reasons:

- the possibility of unexpected effects on the phenotypes of these animals that could compromise animal welfare
- the generation, maintenance and use of these types of animals raises ethical issues and public concern (Ormandy et al., 2009)
- these types of animals must be assessed for risk and housed according to federal, provincial and municipal regulations

Examples of animals covered by this guidelines document include animals that have undergone the following procedures and the offspring of those animals (due to the rapid evolution of this field, the following should be seen as examples rather than an inclusive list):

- transfer of DNA via viral vectors or pronuclear microinjection
- embryonic stem cell or germ cell-mediated mutagenesis to produce targeted mutations (knock-out and knock-in), transgenic, or gene-trap alleles in animals
- non-selective induced mutation (such as high through-put mutagenesis projects)
- cloning animals produced through nuclear transfer from diploid cells (such as by somatic cell nuclear transfer or embryonic cell nuclear transfer) or by cell fusion
- xenotransplantation where the source material has been genetically altered by technological intervention

Cloning is a form of genetic engineering that is used to make duplicates of a single organism. One method of cloning is embryo splitting, where the end result is two genetically identical organisms. Another form of cloning, somatic cell nuclear transfer (SCNT), uses a differentiated cell and allows for the production of multiple, nearly identical copies of a donor animal with specific genetic qualities of interest.

Cloning has many applications, including:

- perpetuation or dissemination of genetic information
- preservation of valuable genotypes
- identification of genotype versus environmental impacts on production traits
- making multiple copies of an existing genetically-engineered animals

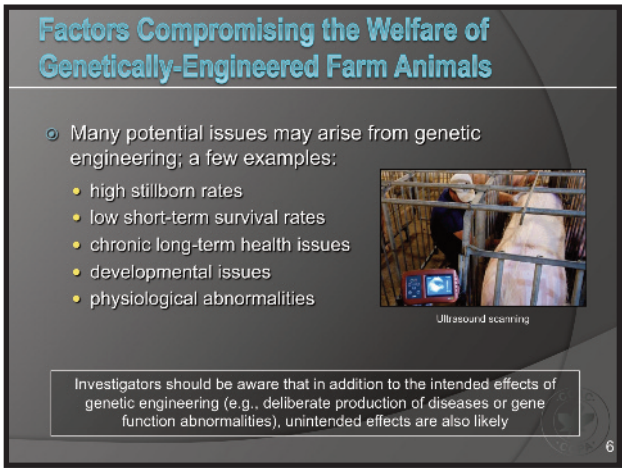
Cloning is a developing science and many uncertainties exist. These unknowns may result in negative animal welfare consequences for the cloned animals, and investigators should be prepared to address such issues.

For more information, see the *CCAC guidelines on: genetically-engineered animals used in science* (in prep.). Visit the CCAC website at www.ccac.ca to access and consult this guidelines document.

Additional References and Resources:

Ormandy E., Schuppli C.A. and Weary D.M. (2009) Worldwide trends in the use of animals in research: The contribution of genetically modified animal models. *Alternatives to Laboratory Animals* 37(1):63–68.

Slide 6 Factors Compromising the Welfare of Genetically-Engineered Farm Animals



As methods of genetic engineering are developed and further refined, the potential impacts on the animals produced with these methods will change as well. **Genetic engineering methods may have both intended (e.g., deliberate production of diseases or gene function abnormalities) and unintended effects on the animals.**

The following welfare concerns are to be considered examples; due to the dynamic nature of genetic engineering research, other concerns may exist. Investigators should be prepared to address other welfare issues caused by the specific methods of genetic engineering being used. Numerous reviews are available covering welfare concerns in more detail and discussing the ethical concerns of genetic engineering and cloning of farm animals (e.g., Van Reenen et al., 2001; Kaiser, 2005; Wells, 2005). **Investigators are strongly encouraged to become familiar with the ethics behind producing and working with genetically-engineered animals.**

In genetically-engineered animals, transgene introduction or deletion (e.g., mutations or loss of function to endogenous genes) may have effects on the welfare of the animals; furthermore, additional effects of transgene expression that were not intended are also possible. Numerous developmental issues have been noted that negatively impact farm animal welfare. For instance, high stillborn and post-natal mortality rates may occur (Loi et al., 2006) or congenital malformations may exist (Wells, 2005). Some offspring have also been noted to be larger than conventional offspring, impacting the welfare of the dams during the birthing process (Kruip and den Dass, 1997).

Welfare problems may also occur in later life stages. Typically, these effects are unintended by-products of the genetic engineering methods employed. Compromised immune function (Renard et al., 1999), as well as other chronic conditions such as musculoskeletal problems (Wells et al., 2004), are examples of potential long-term, unintended effects that could compromise animal welfare. **Methods of genetic engineering may produce unintended and undesired effects, which create ethical and animal welfare concerns. Investigators should be aware of the potential for such welfare issues, and develop mitigation strategies relevant to their specific work.**

It should be noted that many genetically-engineered animals do not have different welfare concerns than conventional animals; however, investigators must aim for timely identification of any welfare concerns that may arise and for the creation of appropriate strategies to address those concerns. **Investigators must balance the potential benefits of research outcomes with the potential animal welfare consequences associated with the intended scientific applications.**

Additional References and Resources:

Kaiser M. (2005) Assessing ethics and animal welfare in animal biotechnology for farm production. *Revue Scientifique et Technique de l'Office International des Epizooties* 24(1):75–87.

Kruip T.A.M. and den Dass J.H.G. (1997) In vitro produced and cloned embryos: effects on pregnancy, parturition and offspring. *Theriogenology* 47(1):43–52.

Loi P., Clinton M., Vackova I., Fulka J. Jr, Feil R., Palmieri C., Della Salda L. and Ptak G. (2006) Placental abnormalities associated with post-natal mortality in sheep somatic cell clones. *Theriogenology* 65(6):1110–1121.

Renard J.P., Chastant S., Chesne P., Richard C., Marchal J., Cordonnier N., Chavatte P. and Vignon X. (1999) Lymphoid hypoplasia and somatic cloning. *Lancet* 353(9163):1489–1491.

Van Reenen C.G., Meuwissen T.H., Hopster H., Oldenbroek K., Kruip T.H. and Blokhuis H.J. (2001) Transgenesis may affect farm animal welfare: A case for systematic risk assessment. *Journal of Animal Science* 79(7):1763–1779.

Wells D.N. (2005) Animal cloning: problems and prospects. *Revue Scientifique et Technique de l'Office International des Epizooties* 24(1):251–264.

Wells D.N., Forsyth J.T., McMillan V. and Oback B. (2004) The health of somatic cell cloned cattle and their offspring. *Cloning and Stem Cells* 6(2):101–110.

Slide 7 Regulations



The same federal health and safety regulations that apply to conventional use of farm animals in science apply to genetically-engineered animals. These regulations are detailed in the *CCAC training module on: the ethical use and care of farm animals in science* (2010). Visit the CCAC website at www.ccac.ca to access and consult this training module.

However, there are additional regulations of which investigators also need to be aware:

Canadian Environmental Protection Act (CEPA)

The responsibility for regulating the environmental release and indirect human health impacts of genetically-engineered animals is shared between Environment Canada (EC) and Health Canada (HC), under the *Canadian Environmental Protection Act* (CEPA,1999).

All animals manipulated through science and engineering are considered to be biotechnology-derived animals. The term biotechnology is defined as "the application of science and engineering to the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms" (CEPA 1999).

The classification of a product as "new" is given to substances that do not appear on the *Domestic substances list* maintained by the CEPA registry. All "new" substances, including living organisms, are governed by CEPA (1999).

Where required, EC and HC must be notified prior to the manufacture or import of a new substance according to timelines prescribed in the *New Substances Notification Regulations (Organisms) (NSNR(O))*; "new" animals reported to these authorities are then evaluated for any risk to the environment and indirect human health. All genetically-engineered animals must be kept in secure facilities as defined under CEPA (1999).

Note: At the time of publication of this module, the *New Substance Notification Regulations (Organisms) (NSNR(O))* were under revision.

Health Canada

2003 Interim Policy: Products and by-products derived from SCNT farm animal clones and progeny are considered "novel food" and are regulated under Division 28, Part B, of the *Food and Drug Regulations*:

- Novel foods are not allowed to enter the food chain unless they have gone through a pre-market safety assessment
- http://www.healthcanada.gc.ca/novelfoods (Note: if link broken, search: Health Canada - Genetically Modified (GM) Foods and Other Novel Foods)

Canadian Food Inspection Agency

The Animal Feed Division of the Canadian Food Inspection Agency is responsible for administering the Feeds Act and Regulations as well as for approving feeds. "Novel feeds" (e.g., comprised of an organism or organisms, or parts or products thereof, that have a novel trait, or if that have not been previously used in Canada) must be approved for use.

Before any "novel" products are allowed to enter the food chain, a safety assessment must occur. The assessment process considers the safety of the feed in relation to:

- livestock;
- humans via worker/bystander exposure;
- humans by consumption of farm animal products; and
- the environment.
- http://www.inspection.gc.ca/english/anima/feebet/bio/bfeebete.shtml (Note: if link broken, search: CFIA – Novel Feeds)

Slide 8 Identification & Tracking



Genetically-engineered farm animals should be given at least two separate forms of identification. Identification redundancy is necessary in case one form of identification is lost or fails. One form should be unique and permanent (e.g., tattoo or microchip), while the other form should be visual and easy to read, (e.g., ear tag). For swine, Pig Trace Canada has developed standardized ear tags that are intended to provide quick traceability of individual swine.

Records documenting the nature and method of genetic manipulation for each animal must be kept. For cattle, the Canadian Cattle Identification Agency allows for records to be assigned to its tagging system. **Tracking individual animals is essential for individual health-care and follow-up.**

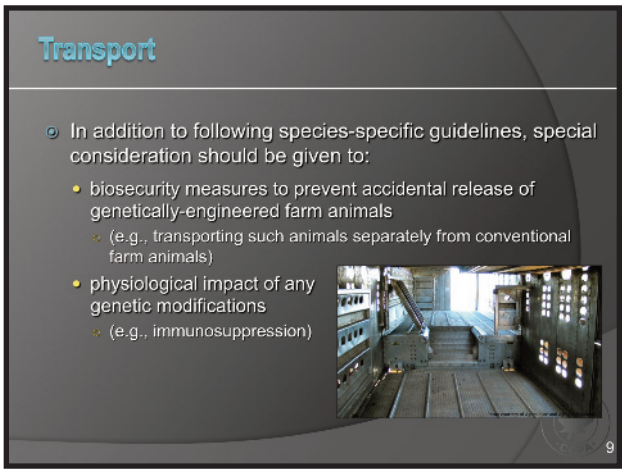
Investigators should be aware of the requirements of their institution and any relevant regulatory agencies regarding the level of identification of the genetically-engineered animals with which they are working. Some breed associations now have registries open specifically for genetically-engineered farm animals.

Research continues in regards to linking DNA markers with genetic modifications, with the end goal being the development of an identification tool for genetically-engineeredfarm animals.

Additional References and Resources:

- Canadian Cattle Identification Agency: http://www.canadaid.com/ (Note: if link is broken, please search: Canadian cattle identification agency)
- Pig Trace Canada: http://www.pigtrace.ca (Note: if link is broken, please search: pig trace Canada)

Slide 9 Transport



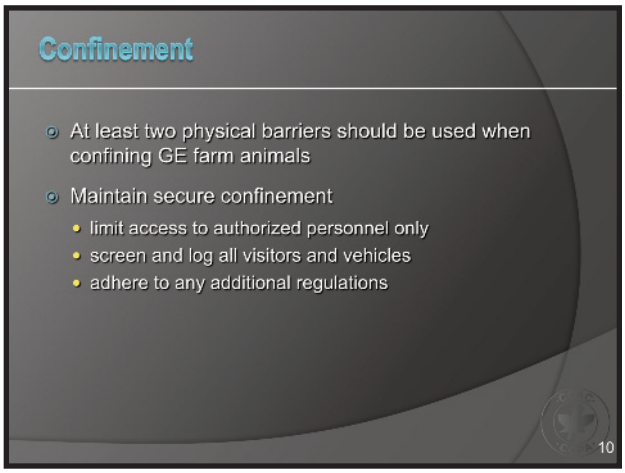
Biosecure transit must be in place to prevent accidental release of genetically-engineered farm animals. **Regulations relating to the transport of genetically-engineered farm animals must be followed.** For instance, EC recommends that drivers and transport companies have experience in handling accidentally released animals and that a contingency plan be prepared for such releases.

To minimize stress related to transport, the following standards should be consulted whenever transporting any farm animals:

- Species-specific codes of practice listed on the National Farm Animal Care Council website: http://www.nfacc.ca/code.aspx (Note: if link is broken, please search: NFACC codes)
- *Recommended Code of Practice for the Care and Handling of Farm Animals – Transportation*, 2001: http://www.nfacc.ca/pdf/english/Transportation2001.pdf (Note: if link is broken, please search: NFACC codes and select "Transportation (2001)")

When transporting genetically-engineered animals, it should be considered that genetic modifications may have impacts on farm animal physiology and consequently alterations to transportation methods may be required (e.g., ensuring transport vehicles are well sanitized when hauling farm animals with compromised immune function). Each group of animals should be evaluated for such special requirements. Furthermore, to prevent mixing, it is recommended that genetically-engineered farm animals be transported separately from conventional farm animals.

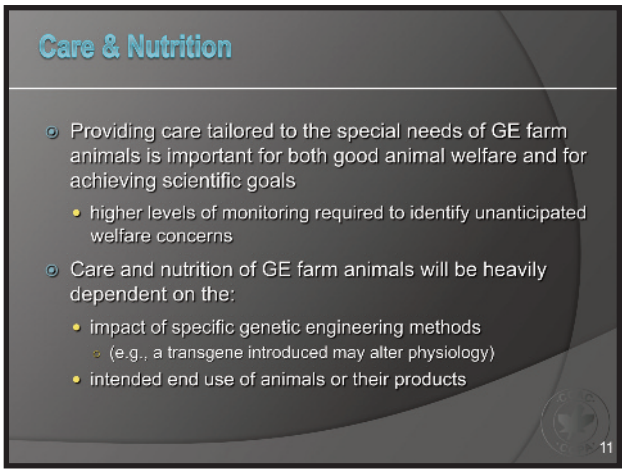
Slide 10 Confinement



Genetically-engineered farm animals should be confined within at least two physical barriers at all times. For instance, animals may be in a pen, which is within a facility. However, since animals may at times be out of the stalls/pens, it is recommended that there be a perimeter fence around the facility as well, ensuring that animals are behind at least two barriers at all times. Accidental release of genetically-engineeredanimals could pose problems if these animals mix in with conventionally bred, neighbouring livestock.

Standard operating procedures (SOPs) should be in place to ensure that only authorized personnel have access to facilities confining genetically-engineered animals. Detailed entry and exit logs must be kept of all visitors and vehicles. The SOPs must address any municipal by-laws, as well as provincial or federal regulations regarding security of facilities housing genetically-engineered farm animals.

Slide 11 Care & Nutrition



The housing and husbandry requirements of genetically-engineered farm animals depend on the effects of the genetic modification.

Consideration must be given to meeting any additional housing and husbandry requirements of genetically-engineered animals; the welfare of the animals and the quality of the research outcomes are based on maintaining care practices which address the consequences of the genetic engineering methods employed.

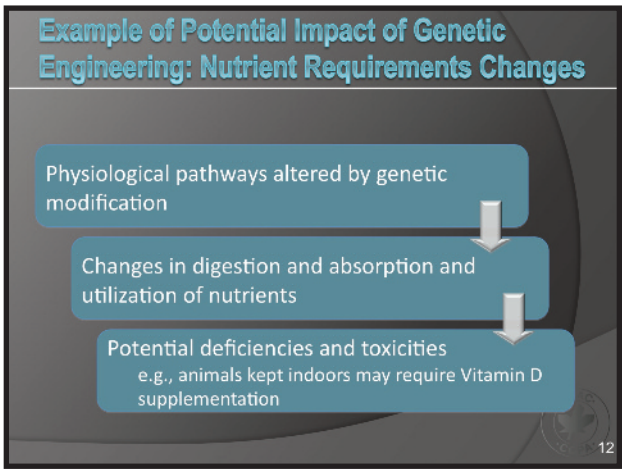
The needs of genetically-engineered farm animals depend on the impact of the specific methods of genetic engineering. For instance, a genetically-engineered animal's physiology may be altered by either the introduction of a transgene itself, or by interruption of a functional gene; in such cases, the animal may require special care to compensate for the resulting change. Some genetically-engineered animals have been noted to have deficiencies such as a decreased or completely absent sucking reflex and require extra care to ensure they receive adequate nutrition. Furthermore, the intended end use of the animals or their products will also impact requirements for animal care and management (see slide 13, "Example of Potential Impact of End Use: Feeding Regimes").

For species-specific nutrition guidelines, see the applicable species section of the *CCAC guidelines on: the care and use of farm animals in research, teaching and testing* (2009). Visit the CCAC website at www.ccac.ca to access and consult this guidelines document.

Slide 12 Example of Potential Impact of Genetic Engineering: Nutrient Requirements Changes

It is important to note that some genetically-engineered animals may have substantially altered physiological pathways. In such cases, conventional feeding regimes will need to be amended to accommodate changes in the animal's ability to digest and absorb nutrients, to prevent the animals from experiencing nutrient deficiencies and/or toxicities.

Housing and husbandry techniques may also require additional nutritional considerations. For instance, farm animals kept entirely indoors may need vitamin D supplementation due to lack of sunlight exposure. **Investigators should be aware of how management techniques specific to their research protocols may impact the animals' nutritional needs.**



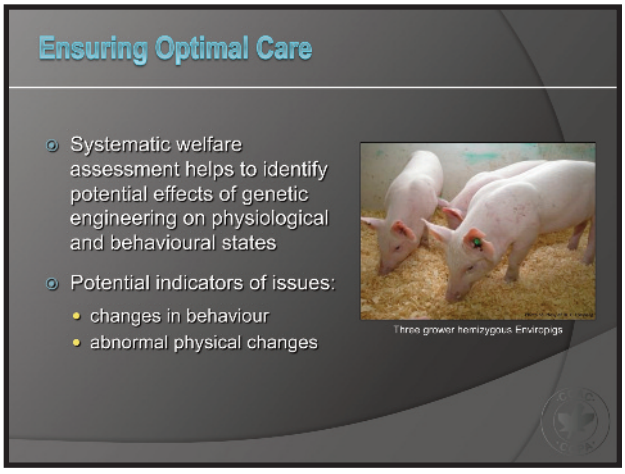
Slide 13 Example of Potential Impact of End Use: Feeding Regimes

The end use of genetically-engineered farm animals may dictate changes in standard feeding regimes. For instance:

- animal by-products may need to be eliminated from feed in order to prevent animal exposure to Transmissible Spongiform Encephalopathies;
- animals genetically-engineered to produce pharmaceuticals in their milk may need to be fed feeds free of pesticides, herbicides and fungicides; and
- the offspring of animals producing specialty products in their milk will need a feeding program. Often such feeding regimes are already established for dairy animals; however, if the offspring are also genetically-engineered, the standard milk replacement products may need to be altered to address particular nutritional requirements of those animals.



Slide 14 Ensuring Optimal Care



Systematic welfare assessment of genetically-engineered farm animals is necessary to identify potential effects of genetic engineering on the physiological and behavioural state of the animals. Additional care may be required depending on the effects of the particular genetic modification (see slide 6 "Factors Comprising the Welfare of Genetically-Engineered Farm Animals"). Information gathered during the welfare assessment is important for determining optimal care and nutrition practices. This information should accompany the animals if transported elsewhere.

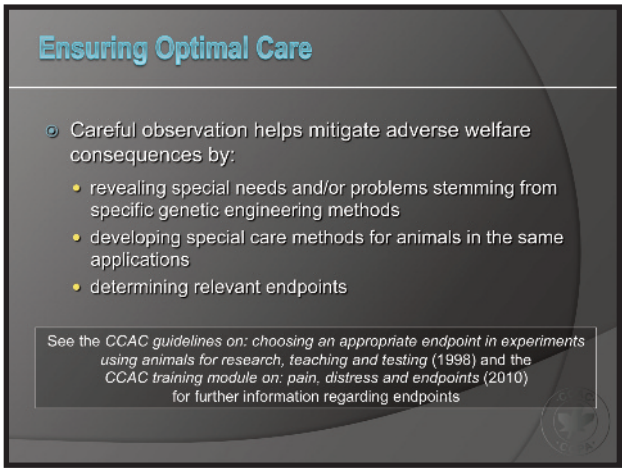
The effects of the specific method of genetic engineering on the animal's physiology should be characterized and recorded. Naturally occurring behaviours for the target species should be compared to the behaviours displayed in the genetically-engineered animal. Some genetic modifications may affect the animal's physiological (e.g., mobility issues), behavioural (e.g., anxiety) and motivational states (e.g., lack of appetite). Some examples of potential indicators of underlying issues include:

- behavioural changes: feeding abnormalities, decreased/absent sucking reflex, vocalizations, activity rate
- physical changes: posture, coat quality, body mass, abnormal growths, body temperature regulation issues

Additional References and Resources:

Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research (2003) *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Washington DC: National Research Council of the National Academies.

Slide 15 Ensuring Optimal Care



Timely identification of specific welfare effects allows for efficient development of mitigation strategies. If carefully monitored and recorded, these strategies can be used to guide the care required for future generations of farm animals derived from similar methods of genetic engineering. Mitigation strategies can also help determine endpoints.

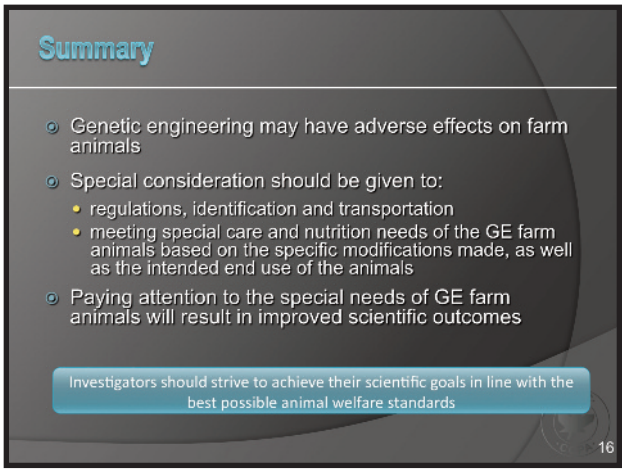
For more information regarding endpoint determination, see the *CCAC training module on pain, distress and endpoints* (2010) and the *CCAC guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing* (1998). Visit the CCAC website at www.ccac.ca to access and consult this training module and guidelines document.

Additional References and Resources:

Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research (2003) *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Washington DC: National Research Council of the National Academies.

Expert Panel on Husbandry of Animals Derived from Biotechnology (2001) *A Working Tool for the Assessment of Animal Wellness*. Second Report. Interdepartmental Committee on Livestock and Fish Derived from Biotechnology. Government of Canada.

Slide 16 Summary



This training module provided a broad overview of considerations for the ethical use and care of genetically-engineered farm animals in science. It covered the potential for welfare impacts on the animals (both anticipated and unanticipated) and the need for timely development of mitigation strategies. The module also covered regulatory, identification, and transportation requirements when working with genetically-engineered animals.

In addition to following the guidelines and standards outlined, **investigators should be aware that welfare issues will be strongly dependent on the specific methods of genetic engineering employed and how these impact the individual animals used**; therefore, appropriate care and management protocols should be developed in consultation with experts in the field, the most up-to-date research and other relevant sources.

The best scientific outcomes will be achieved when special care requirements are understood and addressed by investigators.