3.1.1. Transgenerational epigenetic inheritance

Limited data are available on whether epigenetic dysregulations occurring during the reprogramming of nuclear activities in clones can be transmitted to their sexually reproduced offspring. Several reports in the mouse indicate that, after cloning, epigenetic abnormalities such as those resulting in an obese phenotype are corrected in the germ cells of clones such that the offspring of clone × clone crosses do not exhibit the obese phenotype (Tamashiro *et al.*, 2000). Many genes with epi-alleles may exist in the genome but their detection requires a visible effect on the phenotype in both the clone and its progeny (Peaston and Whitelaw, 2006). Recent data indicated that 19 female and 11 male offspring generated by the same bull clone, lost all the abnormalities observed at birth and postnatally in the genitor (Ortegon *et al.*, 2007).

Transgenerational epigenetic inheritance in response to various conditions has been documented in many eukaryotes and may play an important role in mammals. In particular, environmental influences may induce a number of epigenetic modifications leading to the silencing or activation of specific genes, especially when pregnant females are maintained in conditions resulting in stress in the dam and foetus. The epigenetic modifications observed in the offspring of those pregnancies may then be transmitted to their progeny. These phenomena, which are considered as mechanisms of adaptation, have been found to be reversible after three generations (Gluckman *et al.*, 2007a; Gluckman *et al.*, 2007b). Epigenetic inheritance has also been shown to occur occasionally in mouse embryos under *in vitro* experimental conditions (Roemer *et al.*, 1997). Different mouse models are now available to investigate how epigenetic marks, such as DNA methylation, existing in specific non-imprinted alleles are transmitted as epi-alleles through the paternal and/or maternal germ cell line (Wolff *et al.*, 1998; Cooney *et al.*, 2002). There is now evidence suggesting that RNA can be a determinant of inherited phenotype. In the mouse *Agouti* phenotype, the white tail tip trait is not transmitted in a Mendelian fashion but by RNAs packaged in sperm and down regulating *Kit* gene expression by an RNA interfering mechanism (Rassoulzadegan *et al.*, 2006). No similar studies or outcomes have been identified in the livestock species that are the subject of this scientific opinion. The relevance of these observations to clones and their progeny is not entirely clear. It is also expected that the epigenetic modifications of clones will disappear in future generations as it is the case for those that are naturally induced.

3.1.2. Epigenetic telomere modifications

One epigenetic mechanism that has been linked to the ability of donor somatic nuclei to drive the development of SCNT embryos is the length of telomeres of clones. Telomeres are short, highly repetitive DNA sequences located at the ends of chromosomes that prevent those ends from inappropriate fusions and heal them when they are degraded. Telomeres shorten at each round of cell division due to problems associated with DNA replication. Thereby, telomeres have a function in the control of the ageing process. An enzyme, telomerase, present in various renewal tissues including germ cells and embryonic cells has the ability to extend, or to hold constant, the length of the telomere over multiple cell divisions. Telomeres of the first mammalian clone, ("Dolly") were found to be shorter than those of the age-matched, naturally bred counterparts (Shiels *et al.*, 1999). For this reason, clones were first considered to show premature ageing. Subsequently however, the vast majority of studies have reported that telomere length in cattle, pig and goat clones are comparable with or even longer than age-matched naturally bred controls, even when senescent donor cells were used for cloning (Lanza *et al.*, 2000; Jiang *et al.*, 2004; Betts *et al.*, 2005; Jeon *et al.*, 2005; Schaetzlein and Rudolph, 2005). Current data indicate that telomere length restoration is normal in clones derived from fibroblast donor cells (which are the cells predominantly used). The telomere lengths of 30

offspring from the same bull clone were not different from age-matched controls (Ortegon *et al.*, 2007).

3.1.3. Epigenetic dysregulation in perspective

Epigenetic dysregulation is not a phenomenon unique to cloning and has been observed in all other forms of reproduction, but particularly in ARTs that have a considerable *in vitro* component. This has been observed in cattle when *in vitro* fertilized embryos and embryos derived via SCNT were compared with *in vivo* produced embryos (Camargo *et al.*, 2005), as well as in other species (Gardner and Lane, 2005; Wrenzycki *et al.*, 2005). It is not known whether these abnormalities are due to the stresses of SCNT *per se*, or are the result of the *in vitro* environment, that the early embryos are exposed to, prior to transfer to the surrogate dam. Furthermore, it should be remembered that the epigenetic status of any embryo is in part a response to its environment, as is the epigenetic status of any life stage of any organism.

3.2. Genetic aspects

It can be considered that the well-conserved mechanisms that prevent an altered genome from affect the complex process of development have the same efficiency with SCNT as with meiotically-derived embryonic genomes. Chromosomal disorders after SCNT are routinely observed at a high frequency during the preimplantation stages but mainly in morphologically abnormal embryos (Booth *et al.*, 2003). The chromosomes of 30 healthy offspring from the same bull clone showed no abnormalities (Ortegon *et al.*, 2007).

Chromosome stability may differ in the mouse between embryonic cells derived *in vitro* from cloned or fertilised embryos but this is probably because of epigenetic rather than genetic causes (Balbach *et al.*, 2007).

3.2.1. Mitochondrial DNA modifications

Genetic differences between clones might derive from mitochondrial DNA. Mitochondria serve mainly as a source of energy for the cell but have other important roles in cellular physiology, notably in steroid synthesis and in programmed cell death, both of which are required for embryonic development. In sexual reproduction, male mitochondria are recognized as foreign and are eliminated in the oocyte cytoplasm in a species-specific manner. Thus the mitochondria show a strict maternal inheritance. After SCNT, embryos can possess mitochondrial DNA from the oocyte cytoplasm only (homoplasmy) or from both the donor cell and the recipient cytoplasm (heteroplasmy) (Steinborn *et al.*, 2000). Adult somatic cells typically contain from a few hundred to several thousand mitochondria. This number is even lower during the specification of the germ line but increases dramatically during oocyte growth and may become as high as 100,000 in the mouse oocyte at the time of fertilisation (Shoubridge and Wai, 2007). It is perhaps not surprising that the vast majority of clones analysed so far have shown little evidence of heteroplasmy but the number of studies is small (Hiendleder *et al.*, 2005). It has been speculated that changes in mitochondrial copy number and function, or the transmission of mitochondrial dysfunction from the recipient oocyte could be risk factors for adult metabolic diseases with a developmental origin (McConnell, 2006).

3.2.2. Silent mutations

The extent to which SCNT induces silent mutations in the nuclear DNA of clones that could be transmitted to later generations (through sexual reproduction) remains largely undetermined.

Such mutations occur spontaneously although at a low frequency in animals born from sexual reproduction and the same is probably true after nuclear transfer. These mutations can lead to aberrant phenotypes at the next generation, depending on the allelic combination of individual offspring, and can be screened for and eliminated in conventional breeding programs.

There are examples in normal breeding showing that mutations occurring spontaneously in the DNA can interfere with the expression but not with the epigenetic status of imprinted genes resulting in a modification of their contribution to the phenotype of offspring. This is the case in the sheep with the "callipyge phenotype", an inherited muscular hypertrophy that affects only heterozygous individuals receiving a mutation from their male parent (Charlier *et al.*, 2001). A related situation has also been observed in the pig (Van Laere *et al.*, 2003). There is now evidence to suggest that RNA and not only DNA can be a determinant of inherited phenotype (Rassoulzadegan *et al.*, 2007).

Since nuclear reprogramming requires a marked reorganisation of the somatic cell nucleus chromatin, SCNT could increase the occurrence of silent mutations in the donor genome which could further affect the outcome of the breeding schemes used today for genetic selection in livestock.

3.3. Other aspects

The cloning process includes several modifications of the oocyte cytoplasm. Part of the oocyte cytoplasm is removed during the nucleus aspiration and the remaining cytoplasm may become disorganized. This may result in a lack of fully functional cytoplasm required for embryo development. Some protocols, aiming at restoring oocyte cytoplasm, involve the addition of exogenous oocyte cytoplasm or the fusion of several enucleated oocytes. Cytoplasmic modification may also result from the fusion of the enucleated oocyte with the donor cell. This introduces donor cell cytoplasm, including functional mitochondria, into the oocyte. These cytoplasm disturbances may result in the malfunctioning of the cytoplasm and its organelles which could have an impact on the development of the embryo clone.

3.4. Conclusions of epigenetic and genetic aspects of SCNT

- Epigenetic dysregulation is the main source of potential adverse effects that may affect clones and result in developmental abnormalities.
- Clinically healthy clones show that epigenetic reprogramming is functioning satisfactorily.
- The DNA sequence of a clone is a copy of the donor animal, but other differences may exist (e.g. the methylation status of genomic DNA).
- Currently, based on the available limited data, there is no evidence that epigenetic dysregulation induced by SCNT is transmitted to the cattle and pig progeny (F1).

4. Animal health and welfare implications of SCNT

Animal health includes physical fitness, freedom from infectious and non-infectious diseases and the ability to carry out essential life-maintaining tasks. Animal welfare includes the absence of pain, distress and suffering. The evidence for poor health and welfare, or improved health and welfare, is reviewed in the context of the various phases in the life of an animal with reference to clones and to data derived by comparing clones with animals that are not clones.

It is important, in regard to the risks associated with the cloning technology, to distinguish clearly between the risks directly related to the technology of cloning itself, and those related to

the stage of development of the technology and the degree of the control of the processes which are used.

As the literature on cloning is based on reports of work carried out in highly monitored populations and environments, the effects observed and recorded may not reflect the conditions of husbandry that exist in everyday production systems. Clones are derived from animals with characteristics deemed valuable often consisting of production traits that may place them outside of the normal distribution of a population for that particular trait. Therefore, care must be exercised in making comparisons between clone and normal population parameters as well as with animals produced with ARTs.

4.1. Animal health

Animal health is considered in relation to the animals originating the somatic cells and oocytes used in cloning, the surrogate dams, the clones themselves and their progeny.

4.1.1. Health of source animals for somatic cells and oocytes

Cells used as nucleus donors in the SCNT process are usually obtained either from existing cell cultures or from minimally invasive procedures such as ear punches of live animals with desirable phenotypes. The oocyte donor could be any animal of the same species whose oocytes are available after slaughter or it could be a highly valued and/or monitored animal whose oocytes are collected by ovum pick up *in vivo*. As such, these techniques do not pose significant health risks to the source animals. In the remainder of this section, the role of the health of the source animals and the implications of their health for the health of subsequent clones are discussed.

The disease status of the source animals can have an impact on the infection risk for the clone. Some disease causing agents, such as intracellular mycoplasma and viral nucleotide sequences integrated in the genome, can be directly associated with the somatic cell nucleus and oocyte cells (Philpott, 1993).

At present, voluntary guidelines published by organisations involved with embryo transfer, are aimed at reducing the risk of infection in relation to trade. The OIE (World Organisation for Animal Health, www.oie.int) has developed guidelines for embryo transfer in close cooperation with IETS (International Embryo Transfer Society, www.iets.org). Detailed protocols for the biosecure management of source animals and surrogate dam have been developed for animals involved in embryo transfer procedures (*in vivo* derived gametes and embryos) but not all protocols applied to embryos produced *in vivo* are applicable to *in vitro* derived embryos, cloned and transgenic embryos (Stringfellow *et al.*, 2004).

4.1.1.1. The somatic cell nucleus source

The source of the somatic cell nucleus is often an animal with the desirable trait that the cloning procedure is designed to propagate, and as such would be subject to health monitoring and surveillance during its lifetime. Selection of the disease status (susceptibility or resistance) of the source animal is important as the clone may be affected by such disease traits. The likelihood of disease transmission may vary with the type of tissue from which the nucleus is collected, since pathogens may vary in their affinity for certain tissues (Sharp, 1971; Lilja *et al.*, 1997; Dinglasan and Jacobs-Lorena, 2005; Erne *et al.*, 2007).

With SCNT there is the possibility of bringing intracytoplasmic pathogens within the somatic cell into the recipient oocyte. However, this hazard also exists if and when pathogens adhere to sperm or to instruments during *in vitro* fertilization and intracytoplasmic sperm injection (ICSI). This risk is reduced by sanitary management of source animals ((World Organisation for Animal Health and OIE, 2007).

4.1.1.2. The oocyte source

Health risks related to the procedures for oocyte recovery from live animals or from abattoir material and their handling *in vitro* are of equal importance to those encountered in the *in vitro* collection of embryos for transfer. The collection of oocytes from animals at slaughter (as opposed to surgical interventions) increases the risk of contamination with bacteria and viruses which may be retained by the clones and may affect their viability *in utero* or after birth. These risks have already been carefully identified (Bielanski, 1997) and procedures for their prevention have been proposed by the IETS as licensing guidelines and have been adopted by the OIE. While there are steps in the SCNT technique which differ from the *in vitro* fertilisation procedure, no specific health risks related to oocyte enucleation, the fusion of oocyte with a somatic cell nucleus or the injection of the somatic cell nucleus directly into the cytoplasm of the enucleated oocyte have been reported.

It is not known to what extent the disease resistance of the oocyte source animal will affect the clone as it does not contribute to the genetics of the clone in the same way as the somatic cell nucleus. The source animal of the enucleated oocyte may, however, contribute through mitochondria-associated inheritance stemming from the oocyte cytoplasm.

4.1.2. Health of surrogate dams

Initial pregnancy rates (at Day 50 of gestation after transfer) in cattle serving as surrogate dams were found to be similar between those carrying clones (65 %) and those produced through the use of other artificial methods such as embryo transfer (58 %) and artificial insemination (67 %) (Heyman *et al.*, 2002; Lee *et al.*, 2004). However, there is a continued pregnancy loss throughout the entire gestation period in those surrogate dams carrying clones which is not observed in other ARTs, and embryo survival is only one-third of that following *in vitro* embryo production (Lee *et al.*, 2004; Wells, 2005).

Losses of pregnancy in surrogate dams in the second and third trimester are associated with placental abnormalities, hydrops, enlarged umbilical cords with dilated vessels, and abnormally enlarged and fewer placental cotyledons (Wells *et al.*, 1999; Hill *et al.*, 2000; Chavatte-Palmer *et al.*, 2002; Batchelder *et al.*, 2005).

The high rate of pregnancy failure in the surrogate dam has been linked to the finding of abnormal and/or poorly developed placental formation. Such placental defects have been associated with early embryonic loss, abortions, stillbirths, dystocia and pre- and post-natal deaths (Wakayama and Yanagimachi, 1999; Hill *et al.*, 2001; Tanaka *et al.*, 2001; De Sousa *et al.*, 2002; Hashizume *et al.*, 2002; Humpherys *et al.*, 2002; Suemizu *et al.*, 2003). A detailed histological study of the placenta found that pregnancies of seven cattle clones were associated with abnormalities (Lee *et al.*, 2004; Batchelder *et al.*, 2005; Constant *et al.*, 2006). Abnormal placental development expressed as a reduction in placentome number and consequences on maternal, foetal exchange is seen as one of the main limiting factors in ruminant SCNT pregnancies (Arnold *et al.*, 2006). This abnormal placental development is present from the early stages after implantation but does not necessarily prevent the development and birth of

686 live clones (Hill *et al.*, 2000; Hoffert *et al.*, 2005; Chavatte-Palmer *et al.*, 2006). An early
687 detection of placental abnormalities offers the possibility to terminate pregnancy without
688 threatening the health of the surrogate dam (Hill and Chavatte-Palmer, 2002).

689 It is interesting to note that, in some ruminants, it is the foetus that helps determining the time
690 of birth through the release of adrenocorticotropic hormone (ACTH) and foetal cortisol
691 (Liggins *et al.*, 1967) and that gestation is prolonged when the foetal pituitary gland is
692 destroyed. The clone may therefore affect the incidence of dystocias through some pituitary
693 malfunction.

694 The incidence of birth by Caesarean section is higher in surrogate dams carrying cattle or pig
695 clone foetuses although there is some difficulty in determining causation since elected
696 Caesarean sections were often carried out. In a cattle study an initial elective Caesarean rate of
697 100 % in 2000 dropped to 54 % in 2005 (Panarace *et al.*, 2007).

698 The future fertility of the surrogate dams is not recorded in the literature on cloning. After
699 normal breeding, the fertility of cows requiring an elective Caesarean section to assist the
700 delivery of their calf is not altered whereas the fertility is significantly reduced if the Caesarean
701 section is needed because of severe dystocia (Tenhagen *et al.*, 2007), principally due to
702 infection resulting in endometriosis (Gschwind *et al.*, 2003).

703 **4.1.3. Health of clones (F0)**

704 Four different conditions can be identified concerning the health of clones: (i) clones which
705 present serious abnormalities and where the pregnancy needs to be terminated; (ii) clones
706 which present disorders and die during the postnatal period; (iii) clones which present
707 reversible disorders but which survive after birth; and (iv) clones with no detectable defects.

708 The most critical time for the health and development of cattle clones occurs during the peri-
709 natal period (Chavatte-Palmer *et al.*, 2004; Wells *et al.*, 2004; Panarace *et al.*, 2007). This can
710 be explained by the fact that most of the observed pathologies are associated with, and
711 secondary to, placental dysfunctions (Constant *et al.*, 2006).

712 Possible reactivation of bovine endogenous retroviruses (BERV) was analysed and compared
713 between sexually reproduced cattle and cattle clones (Heyman *et al.*, 2007a). BERV sequences
714 were not transcribed and no RNA was detected in the blood of clones, donor animals or
715 controls.

716 Further data are required to evaluate whether SCNT has an impact on immune functions and
717 susceptibility of clones to infectious agents. Moreover, it should be noted that, although not
718 specifically related to SCNT, depending on the infectious status of the surrogate dam,
719 transplacental infection from the dam to the clone may occur with some specific viruses (e.g.
720 pestiviruses, herpesviruses). This is not specifically related to SCNT and would also be
721 encountered with other ARTs in which an embryo is introduced into a surrogate dam.

722 *4.1.3.1. Health of clones during gestation and the perinatal period*

723 Large Offspring Syndrome (LOS) has been observed in clones from cattle and sheep together
724 with changes observed in late gestation that give rise to an increase in perinatal deaths, excess
725 foetal size, abnormal placental development (including an increased incidence of hydrops),
726 enlarged internal organs, increased susceptibility to disease, sudden death, reluctance to suckle
727 and difficulty in breathing and standing (Kato *et al.*, 1998; Galli *et al.*, 1999; Wells *et al.*, 1999;

Young and Fairburn, 2000). In a study by Heyman *et al.* the incidence of LOS at birth was 13.3 % for somatic cloning, compared with 8.6 % for embryonic cloning and 9.5 % for a group of IVF calves (Heyman *et al.*, 2002). For somatic cloning the incidence of LOS could be related to the tissue origin of the somatic cells used and an LOS rate of up to 47 % has been observed when calf clones were derived from skin, ear or liver cells (Kato *et al.*, 2000).

In a study where not all the clones were derived by SCNT, the overall incidence of hydroallantois was 6 % of all pregnancies but 17 % for pregnancies with cloned foetuses where pregnancies lasted more than 60 days (Pace *et al.*, 2002). Out of 2170 cattle receiving embryo clones, 106 live births occurred and 82 survived for more than 2 days.

Foetuses, placentas and calves resulting from both *in vitro* production and SCNT can differ significantly in morphology, physiology and developmental competence compared with embryos produced *in vivo* (Farin *et al.*, 2006). Mechanisms proposed to explain how *in vitro* conditions may influence subsequent embryo development focus on the modification of epigenetic patterns associated with the DNA, which can affect gene expression without altering the primary DNA sequence.

There are similar findings in sheep where peri- and post-natal lamb losses were considered to be due to placental abnormalities (Loi *et al.*, 2006). Initially the implanted blastocyst was comparable with that of *in vitro* derived fertilised (IVF) embryos but losses after that time were marked with only 12 out of 93 clones reaching full-term development, compared with 51 out of 123 lambs born from the IVF control embryos.

In contrast to the LOS syndrome observed in cattle and sheep clones, some pigs produced by SCNT have an increased incidence of intrauterine growth retardation. A comparison of 23 SCNT litters (143 individuals) with 112 artificial insemination (AI) litters (1300 individuals) showed a significant increase (1.8 ± 0.3 for SCNT versus 0.7 ± 0.1 for AI) in the number of intrauterine growth retardations per litter (Estrada *et al.*, 2007).

4.1.3.2. Health of clones after birth up to sexual maturation

A study of calf clones delivered by Caesarean section, reported that in the first 48 hours of life the red and white cell counts were reduced in comparison with control calves and their plasma electrolytes were more variable, suggesting that calf clones take longer to reach normal calf levels than the controls (Batchelder *et al.*, 2007a). Calf clones were also reported to have higher total bilirubin levels and fibrinogen levels than normal calves (Batchelder *et al.*, 2007b). However an increase in the level of bilirubin and fibrinogen is not necessarily abnormal since these increases remained within the normal range.

One study in cattle reported that a mean of 30 % of the calf clones died before reaching 6 months of age with a wide range of pathological causes, including respiratory failure, abnormal kidney development, and liver steatosis (fatty livers) (Chavatte-Palmer *et al.*, 2004). Heart and liver weights were increased relative to body weight. However after 1 to 2 months the surviving calf clones became indistinguishable from calves born from artificial insemination. Once past the first few months after birth most calf clones develop normally to adulthood (Chavatte-Palmer *et al.*, 2004; Wells *et al.*, 2004; Heyman *et al.*, 2007a).

From 988 bovine embryo clones transferred into recipient cows, 133 calves were born and 89 (67 %) of those survived to weaning at 3 months of age (Wells *et al.*, 2003; Wells *et al.*, 2004). Similar findings were reported by Panarace *et al.* who summarised 5 years of commercial experience of cloning cattle in 3 countries (Panarace *et al.*, 2007). On average 42 % of cattle

772 clones died between delivery and 150 days of life and the most common abnormalities were
773 enlarged umbilical cords (37 %), respiratory problems (19 %), depressed or weak calves
774 displayed by prolonged recumbency (20 %) and contracted flexor tendons (21 %).

775 The Viagen data set provided to EFSA and used in the US FDA draft risk assessment provides
776 data on porcine clones and their progeny (FDA, 2006). Pig clones were delivered by Caesarean
777 section whilst comparator controls were delivered vaginally. Birth weights were considered
778 comparable. A controlled study in a research environment indicates that litter weight and
779 average birth weight, when adjusted for litter size, are significantly ($p<0.05$) higher in AI
780 derived litters compared with SCNT derived litters. Additionally, there was a trend towards
781 higher stillbirths and higher postnatal mortality in the SCNT population (Estrada *et al.*, 2007).

782 After the perinatal period, no significant differences were detected between clones and controls
783 for a number of parameters in cattle and pigs. Cattle clones at about 6 months of age showed no
784 significant differences from age-matched controls with regard to numerous biochemical blood
785 and urine parameters, immune status, body condition score, growth measures and reproductive
786 parameters. Similarly a large number of physiological parameters (blood profile) showed no
787 differences between clones and age-matched controls (Laible *et al.*, 2007; Panarace *et al.*,
788 2007; Walker *et al.*, 2007; Yamaguchi *et al.*, 2007; Heyman *et al.*, 2007a; Watanabe and Nagai,
789 2008). Studies on swine clones at 14 and 27 weeks of age showed that they were
790 indistinguishable from their comparators in terms of growth, health, clinical chemistry and
791 immune function (Archer *et al.*, 2003a; Mir *et al.*, 2005).

792 Placental overgrowth has been recently sh n to induce an increase in the fructose provided to
793 the foetus during the neonatal period resulting in hypoglycaemia and hyperfructosaemia
794 affecting muscle functions including cardiac muscle (Batchelder *et al.*, 2007b). These data
795 provide the first insight to explaining why calves clones experience greater difficulty adjusting
796 to life *ex utero*.

797 *4.1.3.3. Health of clones after sexual maturation*

798 In a matched study of heifer clones and controls reared under the same conditions, the heifer
799 clones reached puberty later than the controls. However, there was no significant variation
800 regarding gestation length, and calf survival after birth (Heyman *et al.*, 2007b). Subsequent
801 305-day lactation curves, as a health parameter, were also comparable for yield, fat and mean
802 cell counts. The mean protein content in milk was significantly higher but this could be
803 accounted for by the fact that three of the heifer clones were from the same source mother,
804 which had a lower milk production but higher protein content, and by the small sample size (12
805 clones and 12 controls). There were no effects on health and subsequent reproductive data
806 showed no significant differences.

807 The same study found other significant differences between clones and control cattle although
808 there were no outward signs of health effects. Variations have also been observed in
809 haematological and biochemical parameters, muscle metabolism, fatty acid composition and
810 higher oxidative activity in the muscle biopsies of the semitendinosus muscle at the 8 to 12
811 month stage (Tian *et al.*, 2005; Yonai *et al.*, 2005).

812 The growth rates of 11 Friesian heifer clones at 15 months of age was comparable with that
813 seen in non-clones reared in New Zealand (Wells *et al.*, 2004). The same workers report that in
814 52 cattle clones there had been no sign of obesity. Reproductive ability in cattle clones showed
815 no significant variation from that found within a population derived by normal sexual