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COMPARING DIFFERENT STRATEGIES IN REDUCING THE ECONOMIC IMPACT OF RECESSIVE GENETIC DISORDERS AFFECTING REPRODUCTIVE EFFICIENCY IN DAIRY CATTLE: A SIMULATION STUDY

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ABSTRACT

The objective of this study was to describe changing pattern in frequency of carriers of lethal haplotypes over time under different scenarios and to estimate of economic loss resulting from carrier by carrier matings in dairy cattle population. Three scenarios were developed.In the first scenario, the mating of a pair of two carriers of the same lethal haplotype was avoided. In the second scenario, there was no interference for matings between carrier animals. In the third scenario, all carrier bulls were eliminated from the population. In first scenario, frequency of carriers reduced slowly from 0.67 in year 1 to 0.56 in year 25. In the second scenario, frequency remained almost constant and showed insignificant decrease. In the third scenario, frequency of carriers reduced from 0.68 in year 1 to 0.14 in year 25. Less genetic progress was achieved for scenario 3 compared with other two scenarios. A significant difference was observed between animals in scenario 2 and those in scenario 1 ($P<0.002$); and between animals in scenario 2 and those in scenario 3 ($P<0.002$) for days open. Total economic losses resulting from mating between carriers ranged from $45248 to $59045, on average for 2074 matings per year.

Key words: lethal recessive, haplotype, dairy cattle, pregnancy losses.

INTRODUCTION

One of the challenges that affect profitability of the dairy cattle industry is decline in reproduction efficiency of dairy cows. Pregnancy losses are undoubtedly one of the major reasons of decline in reproductive performance and economic losses. The economic losses caused by pregnancy losses are mainly due to extended calving interval and culling due to reproductive failure. Numerous researches have indicated extra days in which cows aren't pregnant after voluntary waiting period (VWP) are costly for the herd. Based on LeBlanc (2007) estimation, the average cost of a day open between 70 and 300 DIM was $2. Different values were reported for the cost of pregnancy loss that has ranged from $90 to $2333 based on different studies. These differences are caused by the stage of gestation in which the abortion occurs and by the differences in the factors suchas predicted cow performance, breeding and replacement decisions, feed and milk price and the stage of lactation (Peter, 2000; Weersink *et al* . 2002; Eicker and Fetrow, 2003; De Vries, 2006; Lee and Kim, 2007;Hovingh, 2009).In during the past few years many studies have attempted to investigate pattern, extent, causes and mechanisms of embryonic mortality. One of the factors contributing to pregnancy losses is recessive defects. The intensive use of artificial insemination and international trading of a limited number of elite bulls has facilitated spread of recessive defects. So far, several autosomal recessive defects have been identified in dairy cattle and reported for dairy cattle breeders such asFactor XI (Kociba *et al* . 1969),Citrullinemia (Harper *et al* . 1989), DUMPs (Shanks and Robinson, 1989), BLAD (Shuster *et al*. 1992), CVM (Agerholm *et al*. 2001),Brachyspina (Agerholm *et al*. 2006). For management of such disorders we require identifying carrier animals. Previously, the process of detection of carrier genotypes responsible for genetic defects in dairy cattle was expensive and time consuming. In recent years, advancements in the field of genomics have created a new opportunity in which identifying genes with specific effects are easier and less costly. DNA sequencing is a new powerful tool for identifying mutations underlying recessive disorders (Drögemüller *et al* . 2010), and DNA sequencing costs has decreased dramatically in recent years, dropping from $500 per Mb in January 2007 to $0.05 per Mb in January 2014 (Wetterstrand, 2014).At present, using genotyping technology researchers are able to genotype thousands of SNPs to cover whole genome. Without genomic data lethal recessive genes that cause embryo losses are difficult to detect, even with very large sets of phenotypic and pedigree data (VanRaden and Miller, 2006). Through genomic data, lethal recessives may be discovered from haplotypes that are common in the population but are never found in a homozygous state in live animals. This approach requires genotypes only

from phenotypically normal individuals and not from affected embryo that die. Using this approach VanRaden *et al* . (2011) identified five recessive lethal haplotypes in three cattle breeds. These haplotypes affect fertility by early death of homozygous embryo. Two years later in 2013, Fritz *et al*. and Sahana *et al*. following this approach, found new haplotypes with undesirable effects on fertility.In literature two strategies are recommended for managing of genetic defects in cattle.One proposed strategy to eliminate recessive defects from the population is early identification of carrier influential sires and selecting against them. This approach has been used to eliminate carriers of defects as BLAD and CVM (Sattler, 2002; Thallman *et al*. 2009). The criticism to this strategy is that excellent genetic materials existing in carrier animals are discarded from population. The second strategy is to identify the carriers and preventing of mating between them (VanRaden *et al*. 2011).

The objective of this study was to describe changing pattern in frequency of carriers of lethal haplotypes over time under three different scenarios. Besides, we wanted to study the impact of lethal haplotypes on fertility and to estimate of approximate economic loss resulting from carrier by carrier matings.

MATERIALS AND METHODS

The model: A dynamic stochastic model that describes the biological, reproduction and genetic characteristics was used for simulation of a dairy cattle population. All events such as: allelic frequency, heat detection, conception, sex and viability of the calf, abortion, involuntary culling were generated stochastically, using random numbers sampled from a uniform distribution. The model was written under the visual basic 6.0 programming language. F-test was used for Statistical analyses and comparison of means was done by Duncan method and using of SAS version 9.1 (SAS Institute,2003).

Genome: For each replicate, a genome was simulated including a chromosome with 100 cM long. Fifteen hundred bi-allelic markers were distributed across the genome. The alleles were coded as 0 and 1 with primary frequency of 0.7 and 0.3, respectively. The haplotypes were defined as a combination of marker alleles for three adjacent loci which resultedin eight possible haplotypes for each locus (0 0 0, 0 0 1, 0 1 0, 0 1 1,1 0 0, 1 0 1, 1 1 0, 11 1). One of the haplotypes was considered as lethal haplotype (1 1 1). In total 200 lethal haplotypes were distributed across the genome. The position of lethal haplotypes on chromosome was assigned randomly on the condition that the position of each lethal haplotype was unique and none of the lethal haplotypes were overlapping. The positions of lethal haplotypes on chromosome were kept constant in different runs of the simulatedprogram.

Population structure: A population with 100 individuals was simulated in which half of the individuals were male and the other half were female. This structure was continued for 50 generations by random mating. Generating of progenies in each generation was done by randomly sampling of parents from the previous generation. The probability of recombination was determined based on Haldane's Mapping Function (Haldane, 1919). The r^2 statistic was used to measure linkage disequilibrium (LD) (Hill and Robertson, 1968). After 50 generations, efficient LD was achieved between adjacent marker pairs. It was assumed that no mutation occurred. In mating between two carriers there is a 0.25 probability that the embryo inherits two copies of the same lethal haplotype and will not survive. In order to maintain population size constant (100 animals per each generation), in mating between carriers if parental gametes combination led to an affected progeny, this animal was discarded and parental gametes were re-sampled otherwise the calf was considered normal. After achieving the intended LD, size of population were extended to 2500 animals (2000 female and 500 male) that established initial population. It was assumed that initial herd consists of males and females that are eligible for breeding. Age at first mating was considered 450 days for heifers and 360 days for males. Males and females who reached the maturity age could participate in mating. For the purpose of recording of events, all animals were monitored based on daily time steps. The status of each animal in the herd was assessed daily from the perspectives of aging, insemination, pregnancy status, abortion, calving, replacement, culling and beginning new lactation. For non-pregnant cows there was a probability of pregnancy, replacing, culling and for pregnant cows there was probability of abortion or to calve at the end of gestation. Calving was occurred in 280 d. Cow after calving was proceeded to the next parity and VWP was begun. After the end of VWP (45 d), cows were eligible for insemination. Heat detection rate for all cows and conception rate for heifers and lactating cows was set at 50, 65 and 40%, respectively. Cows that failed to conceive were remained in open status and after 21 days (next heat cycle) re-inseminated, if found in heat. The cows were culled if the number of services per conception within lactation exceeded 10. The cows stayed in the herd for a maximum of nine lactations. In addition, cows had a probability of involuntary culling through their productive life. The average probabilities of involuntary culling by parity and month after calving were taken from results reported by De Vries (2004). Abortion risk by month of pregnancy (2 to 8) was set to 3.58, 3.36, 3.27, 2.49, 1.66, 1.67, and 1.67%, respectively (Rafati, 2008). The cows that aborted, stayed in the same lactation and after 45 days were inseminated, if found in heat. Male and female calves were produced with equal probability. Every year, about 70% of female offspring

born, stayed in the herd as replacements and the rest were removed and only 5% of the top male calves were selected based on simulated true breeding value to be used as sires of the next generation. Sires were allowed to remain in the herd until eight years of age.

Simulating breeding values: An infinitesimal model was used to simulate the breeding value for milk yield. Under this model, the trait is determined by an infinite number of unlinked loci, each with an infinitesimal effect (Fisher, 1918).

Using the following equations and parameters true breeding value for milk yield trait was simulated (Jahanbakhshi *et al*. 2011; Clark *et al*. 2011).

The default values of input parameters that were used in the model were taken from literature and personal knowledge.

$$\sigma_p^2 = 1690000, h^2 = 0.27 \text{ and mean} = 6500 \text{ kg}$$

$$BV_{InitialPop.} = Z * \sigma_A$$

$$BV_{Offspring} = \frac{1}{2}(BV_{Sire} + BV_{Dam}) + MS$$

$$MS = \sqrt{\frac{2 - INB_{Sire} - INB_{Dam}}{4}} * \sigma_A$$

Where σ_p^2, h^2 and mean are phenotypic variance, heritability and mean of milk yield, respectively. $BV_{InitialPop.}$ and $BV_{Offspring}$ are true breeding value for milk yield in initial population and next generations, respectively. BV_{Sire} and BV_{Dam} are true breeding value of sire and dam, respectively. Z is a number with standard normal distribution. σ_A is standard deviation of breeding value. MS is Mendelian sampling term. INB_{Sire} and INB_{Dam} are inbreeding coefficient of sire and dam, respectively.

Scenarios: With respect to mating decisions, three scenarios were developed. It was assumed that in the first scenario and the third scenario all bulls and cows used in matings have been genotyped. Thus, result of mating of a bull and cow was predictable. In the first scenario, the mating of a pair of two carriers of the same lethal haplotype was avoided but if animals had different lethal haplotypes could mate together. In the second scenario, matings was done randomly and there was no interference for matings between carrier animals so in this scenario, there was no need for genotyping of the animals. The second scenario wasn't a management strategy for control of genetic defects. Indeed the aim of planning of the second scenario was to study the impact of lethal haplotypes on fertility and to estimate of approximate economic loss resulting from carrier by carrier matings. In this scenario it was probable that the cows experience abortion in different stages of pregnancy due to having a fetus homozygous for a lethal haplotype. Three stages were considered for pregnancy losses: Embryonic losses (pregnancy losses before 42 days), fetal losses (pregnancy losses between 42-260 days) and stillbirth (calf mortality in 260 days). Frequency was considered 25% (76% of lethal haplotypes), 3% (9% of lethal haplotypes) and 5% (15% of lethal haplotypes) for embryonic losses, fetal losses and stillbirth, respectively (Forar *et al* . 1995; Meyer *et al* . 2001; Kirk, 2003; Hansen *et al* . 2004; Hovingh, 2009). Lethality stage was determined by haplotype number; in such a way that, lethal haplotypes 1 to 152 were responsible for embryonic losses, 153 to 170 for fetal losses and 171 to 200 for Stillbirth. More lethal haplotypes were considered for embryonic losses, because more pregnancy losses occur during this stage. In the third scenario all carrier bulls in initial population and next generations were eliminated therefore no carrier bull was present in the population.

Fertility performance: Calving to conception (days open) as a fertility trait was used to examine reproductive performance between the three scenarios. It is expected that the average days open for second scenario to be greater than two other scenarios. The average days open was calculated for each scenario in each year and the difference of animals for this trait between scenarios was assessed using the F- test.

Economic aspects: Economic loss resulting from mating between carriers (the second scenario) of two aspects was considered: the cost of extra days open and the cost of pregnancy losses.

The cost of extra days open: The losses resulting from the increase of days open was calculated as follows:

The first scenario was considered as the base. Extra days open for second scenario in each year were calculated by subtracting days open in scenario 1 from days open in scenario 2. It is assumed that the cost of one extra day open is $2, based on LeBlanc (2007) estimation. The costs of extra days open per year for the second scenario were calculated as follows:

$$CEDO_i = EDO_i * NMY_i * \$2$$

Where $CEDO_i$, EDO_i and NMY_i are the cost of extra days open, extra days open and the number of matings for i^{th}year, respectively.

The cost of pregnancy losses: The cost of pregnancy losses depends on the stage of gestation that abortion occurs. In this study, the average cost of an abortion was considered $555, following De Vries (2006). The cost of pregnancy losses per year was obtained from the following equation:

$$CPL_i - NL_i * \$555$$

Where CPL_i and NL_i are the cost of pregnancy losses and the number of losses for i^{th}year, respectively. Total

economic losses resulting from mating between carriers in each year (TEL_i) was the sum of $CEDO_i$ and CPL_i.

The scenarios were planned for 25-year time horizon and the results were recorded when the herd reached a steady state. Each simulated scenario was repeated 10 timesand presented results are the average of 10 replicates.

RESULTS AND DISCUSSION

Figure 1 shows changes in frequency of undesirable haplotypes carriers from base population to extended population for lethal loci. With eight possible haplotypes (alleles) per locus there were totally 64 types of mating for each haplotype. 49/64 offspring produced would be non-carrier, 14/64 carrier and 1/64 recessive homozygous (affected). Considering all loci simultaneously, the frequency of carriers in the base population was equal to one (100%) and this trend continues until the 7th generation. At first glance it may seem critical. But in fact, an animal isn't carrier for all of lethal haplotypes. Each animal carries only a few lethal haplotypes and animals are carrier in different loci. Currently, approximately 450 traits and disorders are known in cattle species in which the causative mutation of almost 90 disorder have been characterized at DNA level (OMIA, 2014) and new conditions are frequentlyidentified (VanRaden *et al* . 2011; Charlier *et al* . 2012; Fritz *et al*. 2013; Sahana *et al*. 2013; Sonstegard *et al*. 2013; kadri *et al*. 2014). Therefore, we can expect that every animal would be likely to carry several genes with undesirable effects. After seven generations, frequency of carriers with little fluctuation starts to decrease. This trend continues until the 50th generation. In generation 50, frequency of carriers for 200 lethal loci reaches to 0.74. Fifty generations of random mating was simulated to reach sufficient LD and allow for elimination of recessive lethal genes similar to the way of natural selection. This situation is similar to the condition that natural selection acts against a recessive lethal gene and elimination of recessive homozygous is complete with no heterozygous advantage or disadvantage (Falconer and Mackay, 1996).

Changes in frequency of carriers over 25 years for each scenario are presented in Figure 2. When carriers of the same undesirable haplotype were prevented from mating (scenario 1), frequency of carriers reduced slowly from 0.67 in year 1 to 0.56 in year 25. In this scenario, chance of carriers for mating relative to normal homozygous was less or in other words carriers had a less fitness than normal homozygous. These results are in line with results reported by Thompson *et al*. (2006), when there was a small selective disadvantage of heterozygote over the normal homozygous. First scenario only requires a reliable test for the detection of carriers. Cows have rarely been genotyped but almost all bulls that are used for artificial insemination are genotyped. It is easy to identify cows that are likely carrier through testing their sires or their maternal grandsires. Therefore, it is possible to predict almost all potential matings among service sires that are carriers of an undesirable haplotype to cows whose sires or maternal grandsires are carriers of the same haplotype. In this study, we assumed that cows have been also genotyped. With regard to high frequency of carriers in population it may seem difficult to avoid mating between carriers. But in fact animals carry undesirable haplotypes in deferent loci. For example, if a bull is carrier for 10 undesirable haplotypes and a cow is carrier for 5 other lethal haplotype, both of them are carrier but not in the same lethal loci, thus mating between them will be safe.

In the second scenario, frequency remained almost constant and showed insignificant decrease. This scenario may be somehow comparable with study of Thompson *et al* . (2006) when fitness of carriers (heterozygotes) and normal homozygotes were equal; lethal recessive allele frequency was reduced very slowly in the population.

The second scenario is similar to situation that the carriers of genetic defects in the population have not yet been identified and can mate without any restriction. For instance, defects identified by VanRaden *et al* . (2011), indeed have been in population for several generations so that birth year of earliest carrier was prior to 1980 and carriers of these defects have been largely used in matings. Different patterns were observed for frequency of carriers of each of lethal haplotypes across time for genotyped animals in the study of VanRaden *et al*. (2011). Trend of changes in frequency of carriers in current study was different from observed changes across time for some lethal haplotypes in the study of VanRaden *et al*. (2011). Of course, their results have been obtained with real data that naturally been affected by a series of factors that are not considered in this study.

In the third scenario, lethal haplotypes vanished rapidly in the sires and frequency of carriers in the whole population began to decrease steadily so that frequency of carriers reduced from 0.68 in year 1 to 0.14 in year 25. Through this strategy, defects frequency as BLAD and CVM that in the past were at high frequency has been diminished so that frequency of BLAD carriers from 5% in 1992 reached to 1.28% in 2007 (Van Doormaal and Kistemaker, 2008). When we increased the number of lethal loci (-> 200), almost all individuals in the initial population were carriers, so that accomplishment of scenario 3 wasn't feasible.

In the current study, scenarios assigned patterns of changes in frequency of carriers of lethal haplotypes across time. But in natural situation other factors may also affect changes in frequency of carriers. Under some conditions selection for/or against the gene that is linked

closely with lethal haplotype or pleiotropic effects of a gene or lethal haplotype itself may affect frequency of carriers. Furthermore, if lethal defects present in a small number of popular bulls and haven't been detected, the lethal gene frequency can increase rapidly in population. VanRaden *et al*. (2011) reported the frequency of carriers for five identified harmful haplotypes in three breeds of Jersey, Brown Swiss and Holstein from 2 to 21 percent. For each of identified defects, 2.7 to 20.7% of elite animals were carriers.

Genetic trend: Genetic trend of milk yield was computed as regression of true breeding values on year for three scenarios. Similar pattern was observed for the first two scenarios and there was no difference between the scenarios 1 and 2 – At least with the number of replicates used in this simulation (Figure 3).In scenario 3, although the lethal haplotypes frequency have been reduced dramatically in the population, the question has been remained is that what is the cost of eliminating of the carrier bulls from the breeding program? As it is shown in Figure 3, elimination of the carrier bulls in scenario 3 led to less genetic progress compared with two other scenarios. In this scenario elite bulls may be eliminated from matings**.**

Effect of undesirable haplotypes on fertility performance: A significant difference was observed between animals in scenario 2 and those in scenario 1 ($P<0.002$); and between animals in scenario 2 and those in scenario 3 ($P<0.002$) for days open(Table 1). Effect of undesirable haplotypes on increasing of days open ranged from 1.74 to 4.91 days (Table 1). Based on study by Sahana *et al*. (2013), effect of 17 harmful recessive haplotypes on the increase of calving interval was estimated between 2.4 - 47.2 days. Estimated effects on conception rate for harmful recessive haplotypes identified by VanRaden *et al*. (2011) ranged from -3.0 to -3.7%. Total costs due to extended days open in the current studyranged from $6953 to $19640, on average for 2074 matings per year(Table 1).

The estimated costs caused by pregnancy losses: The number of pregnancy losses was different over 25 years (Table 1). These differences were due to difference in the number of matings per year (NMY) and difference in frequency of matings that both males and females were carrier of the same lethal haplotypes.The estimated costs caused by pregnancy losses, ranged from $35520 to $42735, on average for 2074 matings per year (Table 1). Rafati *et al*. (2010) estimated the annual cost of pregnancy losses around US$40 millionfor Iranian dairy industry. It has been estimated that economic loss of abortion per animal in the Tehran region is 82-1302 US$ (Samia-Kalantari *et al*. 2008). In these studies several factors have affected the pregnancy losses. In the present study, we considered only the effect of lethal haplotypes on pregnancy losses. Total economic losses resulting from mating between carriers ranged from $45248to $59045, on average for 2074 matings per year(Table 1).

Because the frequency of each lethal gene varies from one population to another, and the degree of lethality is different for each of them, therefore it is not possible to present a cost which is consistent among all circumstances and populations. The idea we wanted to provide in the second scenario was that if these 200 lethal haplotypes are not controlled, to what degree they can affect the population's reproductive performance and economic losses due to this fact.

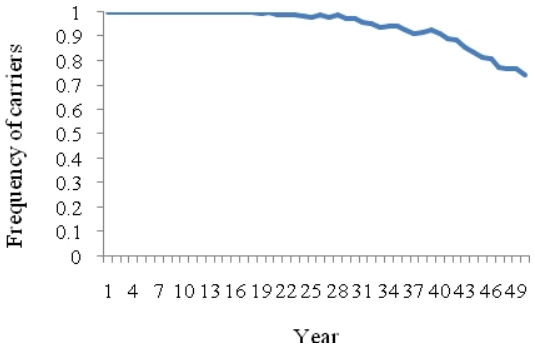

Figure 1.Change in frequency of lethal haplotypes carriers from base population to extended population over 50 generations

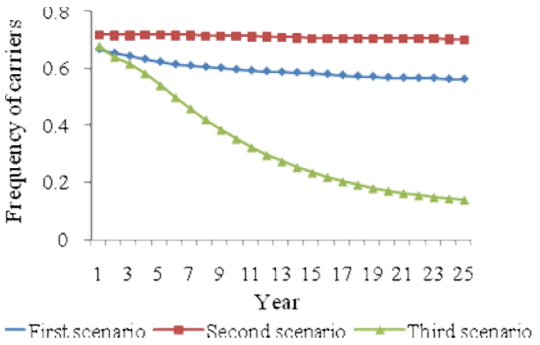

Figure 2.Change in frequency of lethal haplotypes carriers over 25 years for three scenarios. In the first scenario, the mating of a pair of two carriers of the same lethal haplotype was avoided. In the second scenario, matings was done randomly. In the third scenario all carrier bulls were eliminated and no carrier bull was present in the population.

In this study, two strategies were compared for the management of genetic defects (scenario 1 and scenario 3). No significant difference was found between two scenarios for days open. Neither of these two scenarios had pregnancy losses resulting from lethal

haplotypes. Scenario 3 resulted in a greater reduction in frequency of lethal haplotypes carriers compared with scenario 1 over years. But less genetic progress was achieved for scenario 3 compared with scenario 1. This is one of the weaknesses of this scenario. Scenario 3 is possible when the number of animals identified as carrier in the population is low. List of detected defects is continually expanding therefore; in the near future the strategy of eradicating of all carrier animals would not be feasible and desirable. With respect to the results, scenario 1 as an appropriate strategy for the management of genetic defects is proposed.The second scenario wasn't introduced as a management tool for controlling genetic defects but describes a situation that is inevitable and naturally occurs in the populations. Despite substantial progresses made in identifying of the genetic defects, there are carrier animals in population who have not yet been identified. With respect to obvious genetic progress for many of the traits in the past, in spite of mating among carriers, it is expected that identifying such defects and controlling them by planned matings can make even a greater progress in the future.

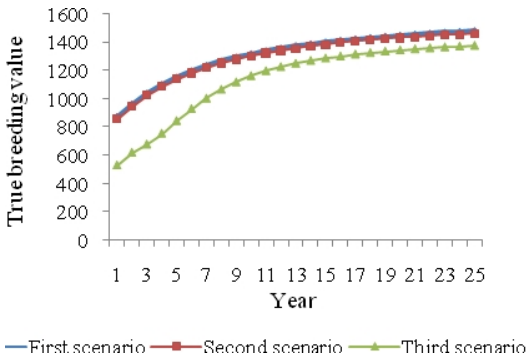

Figure 3.Aerage genetic trend for milk yeild trait for three scenarios over 25 years. In the first scenario, the mating of a pair of two carriers of the same lethal haplotype was avoided. In the second scenario, matings was done randomly. In the third scenario all carrier bulls were eliminated and no carrier bull was present in the population.

Table1. Days open for three scenarios and annual cost due to excessive days open and pregnancy losses from mating carriers (the second scenario) and total annual economic loss from mating of carriers (the second scenario).

Year	Days open			EDO	NMY	CEDO	NL	CPL	TEL
	First scenario	Second scenario	Third scenario						
1	116.59	119.09	118.02	2.5	1948	9740	65	36075	45815
2	116.13	119.17	116.02	3.04	1969	11971.52	68	37740	49711.52
3	115.76	119.03	116.99	3.27	1970	12883.8	67	37185	50068.8
4	115.55	119.18	115.83	3.63	1973	14323.98	64	35520	49843.98
5	117.05	118.79	115.56	1.74	1998	6953.04	69	38295	45248.04
6	115.62	120.53	117.94	4.91	2000	19640	71	39405	59045
7	116.33	120.04	115.73	3.71	2017	14966.14	69	38295	53261.14
8	116.07	118.51	116.51	2.44	2034	9925.92	73	40515	50440.92
9	116.01	118.91	116.71	2.9	2032	11785.6	71	39405	51190.6
10	116.46	119.33	116.01	2.87	2041	11715.34	72	39960	51675.34
11	117.58	120.10	114.53	2.52	2055	10357.2	71	39405	49762.2
12	116.55	119.91	115.17	3.36	2050	13776	69	38295	52071
13	115.82	118.39	115.26	2.57	2056	10567.84	70	38850	49417.84
14	116.32	120.22	115.11	3.9	2082	16239.6	74	41070	57309.6
15	116.07	120.41	116.25	4.34	2097	18201.96	70	38850	57051.96
16	116.30	120.15	117.19	3.85	2095	16131.5	71	39405	55536.5
17	115.81	119.29	115.20	3.48	2134	14852.64	74	41070	55922.64
18	115.62	118.71	115.89	3.09	2132	13175.76	74	41070	54245.76
19	115.30	117.82	114.50	2.52	2122	10694.88	73	40515	51209.88
20	116.72	119.07	115.16	2.35	2153	10119.1	72	39960	50079.1
21	116.33	119.68	115.19	3.35	2150	14405	77	42735	57140
22	117.54	120.39	115.75	2.85	2163	12329.1	75	41625	53954.1
23	116.01	119.63	116.03	3.62	2182	15797.68	73	40515	56312.68
24	116.49	118.88	116.14	2.39	2194	10487.32	75	41625	52112.32
25	116.43	118.96	116.21	2.53	2213	11197.78	75	41625	52822.78

EDO= Extra days open, NMY= Number of matings per year, CEDO= Cost of extra days open ($), NL= Number of pregnancy losses, CPL= Cost of pregnancy losses ($), TEL= Total economic losses ($).

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