Research into premature death of pet rats and ferrets

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Abstract

A retro-spective research is set up to investigate the causes of death of young pet rats and ferrets which were submitted for postmortem examination to the Pathobiology Department of the Veterinary Faculty in the years ’93 – ’09. The pet rats that died between the age of 4 and 12 months, and pet ferrets that died between the age of 6 and 36 months old were selected from the archive. Discussed was whether indentified causes of death may be related to welfare issues (improper care, nutrition and housing).
To compare the results to literature, a literature research regarding common causes of premature death of pet rats and ferrets was set up. Based on the literature and retro-spective research, recommendations were done to prevent or reduce the prevalence of diseases and to improve the welfare of pet rats and ferrets.
The most common cause of death of pet rats appeared to be respiratory disease in both researches. There were many factors found in the literature that predisposed rats to respiratory disease. With welfare adjustments like optimum housing conditions include good ventilation, no leaking bottles of water, optimal nutrition, dust and toxin free beddings and frequent cage cleaning, rats appeared to be less predisposed to respiratory problems.
Gastrointestinal tract problems were represented the most in ferrets of the retro-spective research. The gastro-intestinal problems of the ferrets were a collection of different diseases, including enteritis, gastritis and obstruction due to foreign bodies. Adjustments in nutrition, prohibit stress and eating foreign bodies attributed to a lower prevalence of gastrointestinal tract problems.

1 Introduction

Small mammals (rabbits, guinea pigs, rats and ferrets) are increasingly kept as pet and as result increasingly offered as patient to the veterinarian. Most of the health problems in these animals arise from welfare issues like improper care, nutrition and housing. The knowledge of owners is often too little to provide good care of the animals. The lack of knowledge may be the result of the attitude of the owner (impulse buying) and insufficient information provision of the trader (1).
Research of Caneel *et al*. has shown that there is an abnormal distribution in the age of these animals in the Netherlands. There are relatively many young animals and remarkably few older animals. It appears that the average age at death is significantly lower than the life expectancy (2). These animals are rarely offered for post-mortem examination because the relative value of the animal is probably less than the cost of the post-mortem examination for the owner. This makes it difficult to understand the causes of premature death of these animals (3).

In October 2009, a three year project; the *Welfare research small mammals* (rabbits, guinea pigs, rats and ferrets), performed by the Veterinary Pathology Diagnostic Center (VPDC) of the Veterinary Medicine Faculty at Utrecht University is launched. The VPDC has been commissioned by the Dutch Ministry of Economics, Agriculture and Innovation to map the causes of death using pathological examination, and ultimately provide welfare advice for animal owners. Veterinarians and owners can send these small mammals, which died prematurely, for free of charge to the VPDC for pathological examination. The necropsy reports of pet rats and ferrets will be analyzed and compared with the results of the literature and retro-spective research. A historical overview about the background of the *Welfare research small mammals* can be found in annex 1.

The retro-spective research in combination with the literature research will provide a good basis for the *Welfare research small mammals*. In this way it can be seen if trends in welfare aspects already have been changed or still need extra attention.

2 Materials and method

This research exists of three parts:

- Literature research
- Retro-spective research in the archive of the Veterinary Medicine Faculty at the University of Utrecht, Department Pathobiology, ’93 – ‘09
- Assisting in the *Welfare research small mammals* (rabbits, guinea pigs, rats and ferrets) of the Veterinary Medicine Faculty at the University of Utrecht, Department Pathobiology, October ’09 – October ‘12

2.1 The literature research

Per animal (rat and ferret), a literature research was performed to determine the most common causes of premature death, subdivided into infectious and non-infectious causes of death. Literature is collected from books and online databases: Science Direct (4), PubMed (5) and the search function of the literature depot application RefWorks (6). The used literature can be found in the reference list. These references are also online saved in the application RefWorks.

2.2 The retrospective research

The retro-spective research covers the years 1993 to 2009. All necropsy reports of the pet rats and ferrets that were submitted for post mortal examination to the Department Pathobiology of the Veterinary Medicine Faculty at the University of Utrecht, were stored and extracted from database Micros. In October 2008, this database was replaced by Glims.
Complete necropsy reports of rats between 4 and 12 months and ferrets between 6 and 36 months old were evaluated. Laboratory animals were excluded because the welfare research concentrates upon pet animals. The archive of the rats contained 679 reports, 24 reports complied with the selection criteria of this research, the archive of the ferrets contained 1110 reports, 70 reports were selected for this research.

Each necropsy report contains clinical data, an anamnesis, macroscopical and microscopical findings, cytology of the lungs, liver, spleen and hindgut. In the definitive conclusion, an indication is given for the cause of death. There is made a distinction between infectious, suspicious infectious, non-infectious and unknown causes of death.
All the data from the selected necropsy reports was copied from Micros to Microsoft Word. Two new databases were created and made available by Baijens (7) with the application Filemaker Pro. One database contains information about the rats, the other about the ferrets. See annex 2 for an overview of the data saved in these databases. The data from Microsoft Word was processed manually into these welfare research databases. From these databases, the data were exported to Microsoft Excel, were it was further analyzed.

2.3 The *Welfare research small mammals*

Included are rabbits, guinea pigs and ferrets from 6-36 months old, and rats between 4 and 12 months old. Starting October 2010, age limits were extended to respectively 2-36 months and 2-12 months. Animals were submitted to the Department Pathobiology of the Veterinary Medicine Faculty at the University of Utrecht within 24 hours of death. The anamnesis is extensive (see annex 3). A complete necropsy (see annex 4) including cytological evaluation of liver, spleen, lung and hindgut, macropsy and microscopy is performed, when necessary with additional bacteriological culture. Standard procedure included formalin fixed histology of many organs and preservation of frozen samples at minus 20 C of fewer organs (see annex 5). All data are filed in a special dataset in Filemaker Pro, created by Baijens (7).

The author of this thesis assisted in the post-mortem examinations of the animals which were sent in for the *Welfare research small mammals*. Recent data of the necropsy reports were filed in the welfare research database. In time, this data will be analyzed by other students using Microsoft Excel.

3 Results

3.1 The literature research

There are several common diseases of rats and ferrets. These disease are not necessarily associated with mortality and thus with premature death of these animals. In the literature research, only diseases leading to premature death of pet rats and ferrets are being described. Because data about the prevalence and the mean age of onset of diseases are limited available, it's difficult to predict which diseases are the most common causes of premature death. In the literature research, also common diseases with a mean onset in middle-aged rats and ferrets are being described because the age of onset is often variable and may thus affect also younger animals.

3.1.1 Literature research into premature death of pet rats

The life expectancy of a rat is according to Tully 2 to 3 years and according to Bihun 26 to 40 months (8, 9). The life expectancy may not represent the mean of range for certain strains of rats, that's why the values should be interpretated as approximations.
A research from Caneel *et al* shows that 70% of pet rats die before they reach their approximated life expectancy (2). In their research, they have shown a number of factors that play an important role in the premature death of pet rats. The most important factor is experience of the owners with keeping pet rats and taking good care of them (2).
Pet rats are generally exposed to humidity, temperature and light-cycle changes; a broad range of foods, numerous micro-organisms and various types of handling. Because of this, pet rats exhibit a wider range of physiologic and pathologic responses than do laboratorial rats (10).
Wild rats are also exposed to many different environmental factors. But it's not known or these things are harmful for them, partly because their life expectancy of maximum 12 to 18 months is lower than the life expectancy of the domestic rats. In wild, fewer than 50% of rats survive beyond puberty, and still fewer survive to produce. Deaths are often from lack of resources, fighting injuries, disease and due to predation (11).
Human are the main natural host of Streptococcus pyogenes and Streptococcus pneumoniae. Through physical contact between humans and pet rats, pet rats are being exposed to these micro-organisms (12).

3.1.1.1 Infectious causes leading to premature death of pet rats

The selection exists of the next infectious causes:
1: Respiratory disease
- Chronic respiratory disease
- Bacterial pneumonia

2: Ulcerative dermatitis

3.1.1.1.1 Respiratory disease

The most common health problem of pet rats is respiratory disease caused by infectious agents. The three major respiratory pathogens that cause clinical respiratory disease are: Mycoplasma pulmonis, Streptococcus pneumoniae and Corynebacterium kutscheri. The latter one is uncommon in pet rats but common in laboratory rats.
There are a few minor respiratory pathogens such as Sendai virus (a parainfluenza virus), pneumonia virus of mice (a paramyxovirus), rat respiratory virus (a hantavirus), cilia-associated respiratory (CAR) bacillus and Haemophilis spp who causes by themselves rarely clinical disease (13). They can act as co-pathogens when the rat is infected with a major respiratory pathogen to produce two major clinical respiratory syndromes: chronic respiratory disease and bacterial pneumonia (10).

The chronic respiratory syndrome is a multi-factorial respiratory infection, were Mycoplasma pulmonis is the major component. The expression of the disease is influenced by the environment, host and other micro-organisms. As result, the clinical signs are highly variable. The initial infection develops without any clinical signs. After some time clinical signs like sneezing, nasal discharge, polypneu, weight loss, ruffled coat, head tilt and red tears will develop (13, 14).
Rats have very sensitive lungs and dust, ammonia and cigarette smoke can be very harmful for them. An impairment of alveolar clearance was observed after exposure to a high concentration of insoluble particles in subchronic and chronic inhalation studies in rats (15). When the owner cleans the cages not so often, the intracage ammonia concentration soon will rise. A positive correlation has been shown between the environmental ammonia concentration level (25-250 ppm) and M. pulmonis infection in the lungs (14, 16). A research from Broderson *et al* shows that how higher the ammonia concentration, the worser the lesions in the lungs of the with M. pulmonis infected rats. It is thought that chronic exposure to ammonia could injure the nasal mucosa. Indirectly, this injury makes a porte d'entrée for M. pulmonis (16). Dalhalm has reported that environmental concentrations of ammonia as low as 3ppm were effective in causing ciliostasis in rat trachea (17). Cigarette smoke can also cause ciliostasis but has also an effect on the immune system. It interferes with the normal function of the macrophages which normally eliminate the micro-organisms from the distal airway (18). Cilia are tiny hair-like projections which help to sweep dirt waste products out of the lungs. When the cilia are impaired because of exposure to high ammonia concentrations or cigarette smoke, the cilia cannot perform this cleaning process (19). As result, micro-organisms like M. pulmonis are not eliminated in the lungs and may cause an infection.

The bedding of the cage is also an important factor in predisposition to mycoplasmosis. Various types of wooden shavings who are used in the Netherlands contain toxins like abiëtine and fenols. The fenols give an allergic-like reaction in the respiratory system of the rat.

Because of the reaction and the dust of the wooden shavings, damage to the respiratory epithelium can occur. The toxins can enter the bloodstream and causes liver damage after chronic exposure (20).

Also nutrition can play a big part in the development of mycoplasmosis. Many rat owners think that rodents eat a seed-based diet, but this diet lacks a number of nutritional requirements to maintain health (14). Because of a vitamin A or E deficiency, they are more susceptible to airway problems (10, 13).
Ciliated epithelium, like in the lungs contain concentrations of vitamin A and needs it for its function and development. Vitamin A deficiency affect the function and morphology of the ciliated cells, it will undergo squamous metaplastic changes. It's also associated with an increase in airway hyper reactivity (21, 22). The cells will loose their cilia and due to longer lasting deficiency, the mucus producing cells start to produce keratin instead of mucus as a sign of squamous metaplasia. The mucociliary clearance activity of the respiratory epithelium will be decreased and the rat will be more susceptible for respiratory infections (21). Lungs are the primary target for oxidative injury. This is a normal process, were anti-oxidants like vitamin E repair the damage. A vitamin E deficiency creates an accumulation of peroxidation products and a decrease of other anti-oxidants. The cells of the lungs become damaged and micro-organisms may cause an inflammatory response (23).
Also factors like the virulence of the Mycoplasma strain and the genetic susceptibility of the host influences the host-pathogen relationship (10, 13).
Some rat strains have such a strong cellular immune response against M. pulmonis, that it causes damage to the airways. Despite high titers against M. pulmonis and a high dose of antibiotics, the M. pulmonis infection is usually persistent (10, 24).
The severity of the mycoplasmosis appears to be directly proportional to the immune response. Rats with the most severe lesions have the highest complement-fixing antibody titers (24).

A bacterial pneumonia is nearly always caused by Streptococcus pneumoniae but seldom develops in the absence of M. pulmonis, Sendai virus or cilia-associated respiratory (CAR) bacillus. Pneumonia caused by S. pneumoniae can be sudden of onset. Young rats are more severely affected than older rats. Often the only sign they exhibit is sudden death. The older rats demonstrate signs like dyspneu, snuffling, nasal discharge and abdominal respiration. Rats are obligate nasal breathers so open-mouth breathing is a poor clinical sign (14, 25).

3.1.1.1.2 Ulcerative dermatitis

Ulcerative dermatitis is a common disease in pet rats. Most of the time, the dermatitis is caused by opportunistic bacteria like Staphylococcus aureus, Pasteurella pneumotropica and Streptococcus pyogenes. A porte d'entrée can be created by self-trauma, associated with scratching because of ectoparasites or more commonly, an inflamed salivary gland. Also fighting with other rats can cause a porte d'entrée (10). Malnutrition can also be harmful for rats. In a serie of studies from Galler *et al* , rats with history of many generations of protein malnutrition were found to be at a higher risk for the development of dermatitis with S. aureus infection than rats in the same colony maintained on a diet with adequate protein (26).
There are three possible explanations. First, the high incidence of the dermatitis in the group may be a consequence of reduced ability to produce antibodies (26). Second, the integrity of the skin is a major factor to prevent infection. A low diet protein will influence the integrity due to impaired cross-linking and maturation of collagen.

This results in increased skin friability which predisposes rats to trauma, secondary infections and delayed wound healing (27). Third, rats feed with a low protein diet are likely to decrease their total food intake, so a combined deficiency may result. In a second series of studies, Galler *et al* found that deficiency of protein for several generations increases susceptibility to dermatitis in female and male rats. So malnutrition over several generations has a cumulative effect (26).

3.1.1.2 Non-infectious causes leading to premature death in pet rats

The selection exists of the next non-infectious causes:
1: Teeth problems
2: Neoplasia of the mammary glands

3.1.1.2.1 Teeth problems

The incisors of rats grow about 1 mm a day. Every 40-50 days the incisors are renewed (28, 29). The incisors continue to grow during life and remain the right length because of attrition. The rate of eruption of an incisor is mainly regulated by occlusal stress, but it may be influenced by metabolic events. Rats require material to gnaw to maintain normal occlusion of their incisors. Not all owners provide this kind of materials to their pet rats, because of that the incisors keep growing and malocclusion can occur (9, 28).
Malocclusion can also be the result of congenital, functional and environmental causes. Developmental or acquired anomaly of the jaws, like trauma, leads to malocclusion, just as insufficient intake of vitamins and minerals.
At the incisal edge, the tooth is worn by attrition. When the incisors show malocclusion, upper and lower incisors do not meet, attrition is hampered and eruption is accelerated. The incisors grow too long due to improper wear. Complications like tooth fractures, or when the lower incisors touches the palatum, palatal ulcers may develop (29).
In severe cases, the malocclusion of the incisors affects the rat's ability to eat. But also pain can affect the desire to eat. The anorexia can lead to death when the owner doesn't intervene on time (9, 30).

3.1.1.2.2 Neoplasia of the mammary glands

Neoplasia in rats is a common presentation in practice, especially mammary tumors. Al thought mammary tumors are common in rats older than one year; the author of this thesis still finds this an important disease to highlight, because of the high prevalence of the tumor and the advice that can be given in the chapter welfare recommendation to lower this prevalence. A study of Hotchkiss revealed a prevalence in sexually intact Sprague-Dawley rats of 47% (31). In rats 90% of mammary tumors are benign fibroadenomas, less than 10% are malign adenocarcinomas (14). The distribution of mammary tissue is extensive, and the tumors can occur anywhere from the neck to the inguinal region. The fibroadenomas are usually single and firm, and unattached to deep structures. They do not metastasize, but their size can be a problem if not treated early. The mammary tumors can affect both males and females. Recurrence of fibroadenomas is common in involved mammary tissue, and often surgeries are needed (9, 10).

3.1.2 Literature research into premature death of pet ferrets

The ferret has an average lifespan of 5 – 11 years (32). Unfortunately, at some point many ferrets get health problems. As result, many ferrets die before they reach their life expectancy. It's recommended to examine ferrets annually until they are 4 -5 years of age; middle-ages and older animals should be examined twice a year because of the high incidence of metabolic disease and neoplasia (33). Below, there is given an overview of the most common diseases in ferrets that may be related to the premature death of ferrets. Not of every disease is the age of onset described in the literature. The diseases are divided into non-infectious and infectious causes of death.

3.1.2.1 Non-infectious causes of premature death in pet ferrets

The selection exists of the next non-infectious causes:
1: Neoplasms including insulinomas, adrenocortical tumors and lymphomas
2: Gastrointestinal problems due to nutrition
3: Gastrointestinal problems due to foreign bodies
4: Persistent oestrus

3.1.2.1.1 Neoplasms

Neoplasms and the accompanying paraneoplastic syndromes are the most common diseases seen in middle-aged and older ferrets, but also young ferrets are commonly diagnosed with neoplasms. The age when neoplasms arise, varies from a few months to 15 years, the golden age for tumor developing is 4-7 years (34). There are three kinds of neoplasms who are more common than all other neoplasms together, the insulinoma, the adrenocortical neoplasia and malignant lymphoma.

The most common neoplasia in the ferret is the insulinoma (34, 35). This tumor arises in the βeta-cells of the pancreas and secretes insulin, a glucose-regulating hormone. Reported clinical signs are depressions, lethargy, stupor, ptyalism, muscle weakness, ataxia, tremors and seizures (36). The clinical signs are episodic and related to hypoglycemie. Often, the insulinoma is a coincidental finding during surgery for another reason. The treatment of insulinoma can be with medicine or surgery. Medical therapy is only aiming on controlling the clinical signs of hypoglycemia but does not affect or stop the progression of the insulinoma.
The initial drug of choice is a glucocorticoid such as prednisone. Prednisone promotes the hepatic gluconeogenesis and reduces cellular glucose utilization. If prednisone alone doesn't control the signs of hypoglycemia, diazoxide is added to the regimen. This medicine inhibits insulin release, reduces cellular uptake of glucose and promotes glycogenolysis and hepatic gluconeogenesis (37).
Based upon a study of Weiss *et al*, surgery is the treatment of choice. Although hypoglycemia is likely to recur regardless of treatment; surgical treatment significantly increased disease-free intervals and survival times when compared to medical treatment alone (38).

The type of the surgical technique is also an important factor. Ferrets with nodulectomy combined with partial pancreatectomy had increased disease-free intervals and survival times compared to other techniques. Since the recurrence of hypoglycemia is common postoperatively and the potential complication of diabetes mellitus exists if too much pancreas tissue is removed, it is recommended to perform follow-up blood glucose levels one month postoperatively, then every three months for the life of the ferret (34, 38). Metastases are seldom found in ferrets, but multiple signs and recurrent signs are common due to possible development of new tumors. After surgery, the animals remain disease-free for about 10 months after surgery; the average survival time is 1.5 years. After treatment with medications, the average survival time is six months (34, 39).

The second most common neoplasia in the ferret is the adrenocortical tumor. The adrenocortical adenomas are small and slow-growing and the adrenocortical carcinomas are large and grow locally invasive in ferrets. The tumor cells produce estrogenic and other steroid hormones; as a result the ferret will develop hyperadrenocorticism. Common clinical signs like bilateral and symmetric alopecia will develop in both sexes, vulvar swelling and discharge develops in neutered females. Less common signs include pruritus, sexual activity or aggression, stranguria and hind limb weakness. Females may develop a stump pyometra. Because of the high concentrations of estradiol, bone marrow suppression may develop and leading to anemia and thrombocytopenia which may result in death of the ferret (35, 39, 40).

Lymphoma is the most common malignant neoplasm of ferrets and is the third most frequently diagnosed neoplasm of ferrets overall. A neoplastic proliferation of atypical lymfocytes will develop; these can be classified by cell type, affected organ system and age of the ferret (41). The clinical signs are often non-specific and are often chronic. They will develop clinical signs like anorexia, weight loss, lymfadenopathy and problems with the affected organ (39). Juvenile ferrets (under the age of two years) are more likely to develop the lymfoblastic form, with acute onset of clinical signs caused by large mediastinal masses that displace the heart and lungs dorsocaudally. Several potential causes for ferret lymphoma has been suggested, but no definitive etiology has been determined. It is thought that lymphoma in ferrets can be caused by an infectious agent because of cluster outbreaks in juvenile and adult ferrets in multi-ferret households (42).
Only an etiologic agent of gastric lymphoma in ferrets has been demonstrated. Mucosal inflammation and development of both low- and high-grade lymphomas in the gastric mucosa of the ferret can be caused by chronic infection with Helicobacter mustelae. There is found that gastric lymphoma can develop in H. mustelae infected ferrets exposed to other ferrets with lymphoma (41). The long-term prognosis of lymphoma is considered to be poor. Even though ferrets can use chemotherapy, reported overall remission rates were only 10% (34).

3.1.2.1.2 Gastrointestinal problems due to nutrition

Many ferrets appear to have gastrointestinal problems. Stress and poor nutrition can play an important role in gastrointestinal problems (33). Ferrets are strict carnivores that are designed to eat whole, small prey animals. They have a very short gastrointestinal tract with minimal flora and few brush border enzymes, so they cannot use carbohydrates efficiently or digest fiber. A diet with more than 30% carbohydrates and less than 30% protein is associated with poor performance and growth and greater susceptibility to infectious and metabolic diseases (43). Ferrets in nature would only encounter carbohydrates as found in the partially digested stomach contents of their prey. The most common pet ferret food is dry kibble. These diets still contains high level of grain, which is necessary to hold the food in its shape.

So they are not perfect for the ferrets. Unfortunately, ferrets seem to enjoy sweet foods. Commercial pet food companies are producing ferret treats, which exist out of sugar-coated grains. These nutrients can cause serious problems for the ferrets. An excess of carbohydrates can cause pancreas problems and contribute to disease of the beta cells (44).

3.1.2.1.3 Gastrointestinal problems due to foreign bodies

Ferrets like to play and are very curious animals. They like to chew on miscellaneous environmental products, especially rubber and sponge-like products. Rubber foreign bodies are commonly ingested by young ferrets (younger than two years of age); trichobezoars are in contrast to younger ferrets more frequently diagnosed in older ferrets (45). If ferrets receive corticosteroid therapy, pica as side effect may result in ingestion of foreign objects (46). When a foreign body causes an obstruction in the gastrointestinal tract, it may result in serious problems. The problems that are caused vary with the duration that the foreign body is present in the gastrointestinal tract, the location of the foreign body, the degree of the obstruction (partial of complete), and problems associated with the material of the foreign body. Some ingested items, like lead material can cause systemic toxicities. Others may cause regional damage to the gastrointestinal tract due to compression or obstruction. This can even lead to perforation of the gastrointestinal tract and spillage of intestinal contents into the abdomen and causes peritonitis (47).
Common clinical signs include anorexia, ptyalism with facial rubbing, lethargy and diarrhea. Vomiting is possible, but usually not observed by the owners. Most foreign objects do not pass the gastrointestinal tract unassisted. Small objects can pass trough after treatment with dietary lubricants, but most of the time surgery is necessary to remove the foreign object (46).

3.1.2.1.4 Persistent oestrus

The average age for female ferrets (jills) with persistent oestrus is one to two years old (48). Jills are seasonally polyestrous, induced ovulators. To stimulate ovulation, a vigorous, prolonged copulation is needed; it also can be stimulated artifical. Jills who are not bred remain in oestrus for the duration of the breeding season, which normally takes 6 months (49). Ferrets are susceptible for estrogen, and jills that remain in oestrus for a longer period than a month, have a great risk at developing estrogen-induced bone marrow hypoplasia (39, 50). The production of all blood cells will be affected, leading to thrombocytopenia, leucopenia and aplastic anemia. According to Lloyd, up to 50% of jills with a prolonged oestrus will develop aplastic anemia (49).
The signs are similar to the signs of adrenal gland tumors, and include a swollen vulva (eventually with discharge) and bilateral symmetric alopecia. The signs may progress to anorexia, depression, lethargy and general weakness. Because of the aplastic anemia, other signs like pale mucous membranes, petechiation, ecchymosis and systolic murmer may appear (48). Death is often due to hemorrhage, especially when the platelet count falls below 20000 per mm^3 (49).
Treatment exists of ovariohysterectomy. Jills which show signs of anemia must not be operated until the patient is stabilized. Stabilisation is performed by stimulate the ovaries to ovulate. This can be achievd by injecting the jills with human chorionic gonadotropin (50). The prognosis for recovery is dependent on the degree of anemia. Jills with a PVC of <15% have a poor prognosis (48).

3.1.2.2 Infectious causes of premature death in pet ferrets

The selection exists of the next infectious causes:
1: Gastritis due to Helicobacter mustelae
2: Proliferative Bowel Disease
3: Canine Distemper Virus
4: Influenza Virus
5: Aleutian Disease
6: Ferret Systemic Coronavirus

3.1.2.2.1 Gastritis due to Helicobacter mustelae

The gastric mucosa of nearly 100% of adult ferrets is colonized with the bacterium Helicobacter mustelae (51). In a research from Fox *et al*, examination of neonatal, juvenile and adult ferrets have shown that the gastric mucosa in the majority of pre-weaning (age < 6 weeks) ferrets sampled were not colonized with H. mustelae. This implies that young ferrets are infected with H. mustelae during or shortly after weaning (52). Ferrets infected with H. mustelae not often show clinical signs (53). Under conditions of stress caused by a combination of factors like rapid growth, dietary changes and concurrent diseases, illness may develop in ferrets from 12 to 20 weeks of age (54).
When the young ferret is moving to a new owner, it can be a stressful situation for him. The journey itself is stressful. When the ferret arrives in a multi-ferret household, the social order must be determined. This can take a few weeks. The young ferret has to get used to solid food after the weaning period, and perhaps the new owner has a different brand of solid food then the previous owner. All these factors cause a stressful situation for the ferret. As result, his immune system will temporarily not work optimal. In mature ferrets, the disease may become clinically apparent in animals that are stressed because of concurrent disease or surgery for other conditions (54).
Conformation of the disease is very difficult. Because of the high prevalence, PCR and serology are of no use in diagnosis (39). Options for diagnosing an infection with H. mustelae are gastric biopsy, fecal culture and Urea breath test (53).
Ferrets with severe gastritis and ulcers because of H. mustelae may be presented with lethargic, nausea, salivation, vomiting, dehydration, anorexia and melena (39, 54).

3.1.2.2.2 Proliferative Bowel Disease

Proliferative Bowel Disease is a disease of the gastrointestinal tract of ferrets and is caused by the micro-organism Desulfovibrio spp. It affects young ferrets, usually under the age of one year. Rapidly growing juveniles are the most susceptible (54, 48). The organism is often isolated in healthy ferrets and clinical disease develops only in a small percentage of group-housed infected animals (49, 54). Infected animals that are stressed have less resistance to clinical disease. Stress can originate of environmental and nutritional factors.
The decreased incidence of this disease may be the result of improvement in housing, care and nutrition (54). The disease begins with acute colitis, tenesmus, green profuse diarrhea and blood (49). The diarrhea may become chronic. More signs that may develop are anorexia, weight loss, lethargy and rectal prolapse. Because of the diarrhea, the ferret can become very dehydrated and may die if not treated properly. Due may not only ensue because of dehydration, but also perforation of the gastrointestinal tract may lead to a deadly peritonitis (49). The ferret is also more susceptible to other infectious diseases because of the general debility (54). The disease can be confirmed by histopathological tests of biopsies of the colon

or jejunum. Most ferrets treated in the early stage, respond well but still, there are ferrets that do not survive despite aggressive therapy with antibiotics, pain killers and fluid (48).

3.1.2.2.3 Canine Distemper Virus (CDV)

CDV is the most serious infectious disease of ferrets, as the case mortality rate approaches 100%. Because of vaccination of ferrets against CDV, the prevalence of the disease is relative low compared to the time were no safe vaccination was available (55, 56). Unvaccinated ferrets of any age are susceptible to this deathly disease. The first sign of disease is a rash on the chin, with crusts and swelling of the skin. This may expand to the anus and inguinal area (56). Other signs that may be presented are anorexia, depression, photophobia, sneezing, coughing, melena, hyperkeratosis of the footpads and mucopurulent nasal and ocular discharge (39). The respiratory epithelial cells and lymphoid tissue are the primary sites for the virus to replicate. Because the lymphoid tissue is affected in the beginning of the infection, the virus has an immunosuppressive effect on the proliferation of lymphocytes (57). Because of the immunosuppressive effect, secondary bacterial infections have more chance to cause a pneumonia which often leads to death (58, 59). All ferrets with CDV infection will develop neurological manifestations if there not died yet because of respiratory problems (60). Neurological signs like tremors, incoordination, torticollis and nystagmus progress rapidly to seizures or paralysis, and lead to death (61, 62).

3.1.2.2.4 Influenza virus

Several strains of the Influenza virus are capable of infecting ferrets. Human influenza types A and B of the class orthomyxoviridae are pathogenic in ferrets. Ferrets are hosts for influenza A H1N1, H2N2 and H3N2 viruses. Influenza B can also infect ferrets, but illness is less frequent and milder (56). Influenza is considered to be a zoonosis. Smith *et al* demonstrated the transmission of the influenza virus from human to ferrets, when ferrets were inoculated intranasal with throat washings from influenza-infected human. 3 years later they demonstrated that influenza also could be transmitted from ferrets to humans (63).
Swine influenza also affect ferrets, this could be a problem in country areas near pig farms if outbreak of swine influenza occurs (64). Influenza in older animals is usually mild, but can be fatal for young animals (49).
Infection with influenza generally remains in the upper airways but can cause pneumonia in susceptible animals (56). Research from Collie *et al* has demonstrated greater susceptibility of the newborn ferret lung, compared with the adult lung to influenza virus infection. Also has the influenza virus a predilection for growth in ciliated epithelium (65) and newborns have a higher proportion of such epithelial cells in their lungs (66).
Common clinical signs like fever, sneezing and nasal discharge appear 48 hours after infection. They can also become lethargic and anorexic.
Infection of the lower airways is usually due to secondary bacterial infections (58). Newborn ferrets have smaller airways than adult ferrets, they might be expected to suffer even greater difficulties from obstruction caused by inflammation with the possibility of death from asphyxia. Obstruction in the upper respiratory tract can also interfere with feeding, this may result in aspiration of food into the lungs, causing aspiration pneumonia (66).
Vaccination of ferrets against influenza is not recommended. Influenza is relative benign in ferrets, and the wide antigenic variation of the virus strains makes vaccination difficult (58).

3.1.2.2.5 Aleutian Disease Virus (ADV)

Aleutian disease is caused by a parvovirus. This parvovirus is unrelated to the parvovirus causing bloody diarrhea in dogs. Aleutian disease is an immune complex-mediated condition, which ultimately results in multiple organ failure (39). There is a continuous but ineffective response of the immune system to the viral agent. Antibodies are continuous produced, but are incapable of neutralizing the virus. As result, large quantities of circulating antigen-antibody complexes of different sizes circulate in the body. Some of these complexes are being deposit in the walls of small arteries, capillaries or glomerular tufts and induce a inflammatory reaction and cellular proliferation (67).
The severity of the disease depends on the origin of the ADV strain (mink of ferret). In mink, hypergammaglobulinemia is considered to be pathognomonic, but it's not always present in ferrets infected with ADV (68). Mink strains of the ADV virus cause milder lesions and a moderate elevation of gamma globulins. Ferrets infected with ferret ADV strains exhibit hypergammaglobulinemia and periportal lymphocytic infiltrates (69).
The clinical signs are variable. Some ferrets infected with Aleutian disease die without clinical signs in an apparently healthy and good body condition (67).
But usually, they show signs of chronic wasting disease like weight loss, weakness, malaise, melena, ataxia and paresis posterior. Also, neurological signs such as tremors, convulsions and paralysis may occur. After infection, it can take years before the ferrets start showing symptoms. Vaccination against ADV does not exist and is actually contraindicated due to the immune-mediated nature of the disease (56, 70). Vaccination may result in enhancement of lesions because of the increased efficiency of formation of immune complexes (67).
The disease also occurs in mink. In a research of Cho *et al* on mink farms, animals were tested on the Aleutian disease using counterimmunoelectrophoresis. Positive tested animals were eliminated. This method has proved to be effective to lower the prevalence of Aleutian disease on mink farms (71).

3.1.2.2.6 Ferret Systemic Coronavirus (FSCV)

A visceral disease associated with a coronavirus that causes catarrhal enteritis in ferrets has been recognized in ferrets. The clinicopathologic features of this disease closely resemble the features of the dry form of feline corona virus which causes Feline Infectious Peritonitis (FIP) (72). FIP viruses are believed to arise of spontaneous mutations from persisting low pathogenic to non-pathogenic feline enteric coronavirus strains. Because FSCV and FIP are so similar, it's also believed that FSCV arises from the ferret coronavirus which causes ferret epizootic catarrhal enteritis (73). Young and old ferrets are susceptible for FSCV. A sex-predilection in ferrets has not been found.
In a research from Garner *et al*, the average onset of disease was 11 months.
The clinical course of the disease is progressive, doesn't response to therapy and ends almost always in euthanasia or natural death. Signs were similar to those of cats with FIP and included weight loss, lethargy, anorexia, vomiting, diarrhea and intra-abdominal masses (72-74). Also neurological signs may develop and include hind limb paresis or paraparesis, ataxia, tremors and seizures (73). The less common clinical signs include sneezing, coughing, labored breathing, nasal discharge, dehydration, systolic heart murmur, jaundice, erythema of the skin, green urine, reddened rectal mucosa, and rectal prolapse (72). Pyogranulomous inflammations develop on serosal surfaces and within the parenchyma of the thoracic and abdominal organs (74).

3.2 Results of the retro-spective research

3.2.1 Results of the retro-spective research of pet rats

3.2.1.1 Causes of death

In the group of rats, that died prematurely in the period from 1993 to 2009,
were a total of 24 rats between the age of 4 to 12 months old. Based on the conclusion of the necropsy reports, the causes of death were divided into 4 groups: infectious, suspicious infectious, non-infectious and unknown. In the group suspicious infectious, it was known that there was a bacterial, fungal or viral agent, but they couldn't be demonstrated because of the use of antibiotics or other causes.
The division into the four groups resulted in the following numbers:

- Infectious: 25% (N=6)
- Suspicious infectious: 41.66% (N=10)
- Non-infectious: 16.67 % (N=4)
- Unknown: 16.67 % (N=4)

If the infectious and suspicious infectious groups are added together, and it is assumed that the suspicious infectious group really is infectious, then 66.66% (N = 16) of the deaths of pet rats are because of infections.

Figure 1 shows the distribution of the causes of death in a chart.

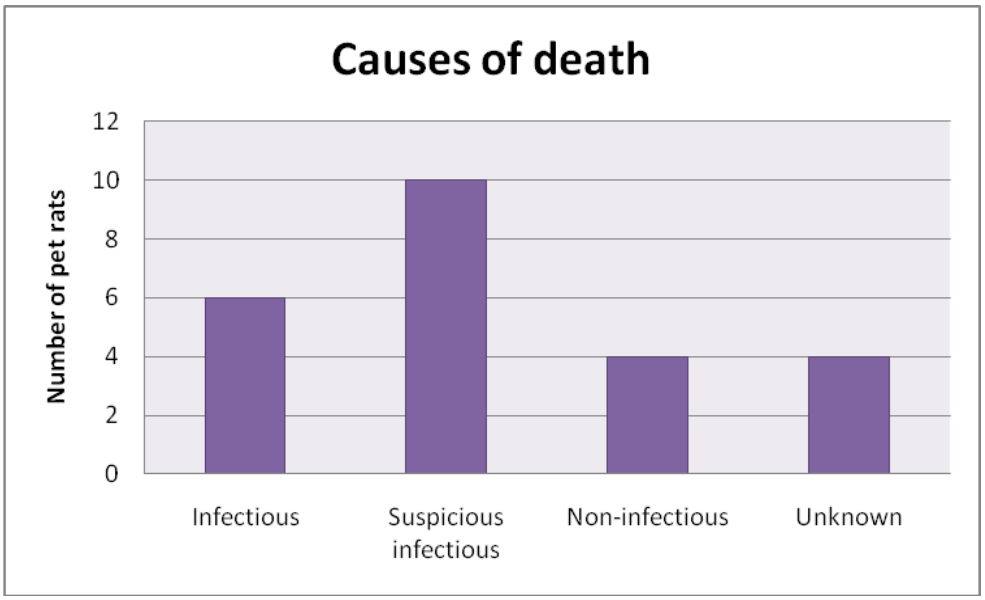

Figure 1

3.2.1.2 Types of death

In a number of cases the pet rats didn't die naturally. The owner and the veterinarian decided to perform euthanasia because of the stadium and severeness of the disease. Not in every necropsy report it is known or the pet rats died naturally of by euthanasia.
The division into the three different groups resulted in the following numbers:

- Euthanized: 21% (N = 5)
- Non-euthanized: 50% (N = 12)
- Unknown: 29% (N = 7)

Figure 2 shows an overview of the types of death.

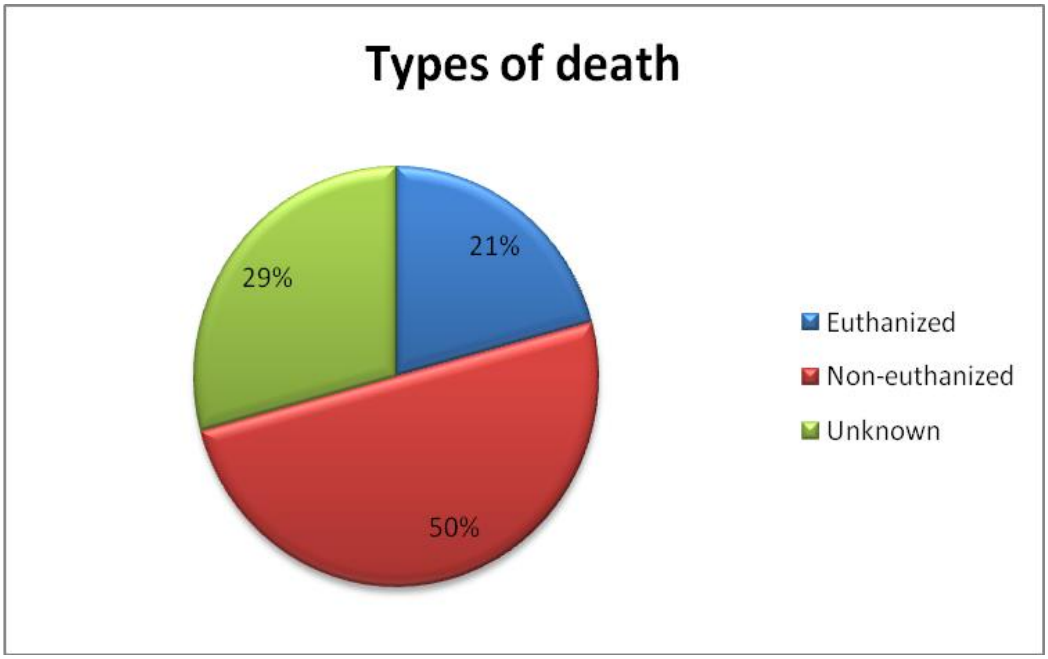

Figure 2

3.2.1.3 Main affected organs

Figure 3 shows an overview of organs responsible for the death of the pet rats.

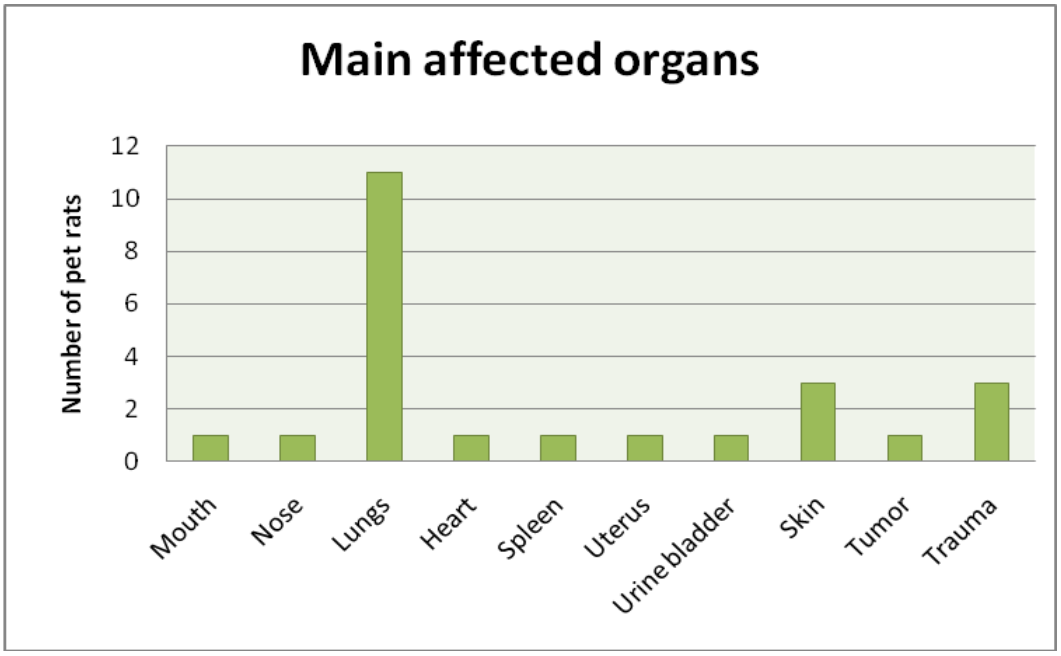

Figure 3

The three most common problems are discussed below:
1: Respiratory problems were found in 46% (N=11) of the pet rats. Besides pneumonia, also lung emphysema and edema were found. Respiratory problems will be discussed in another graph, because of the high prevalence. Some pet rats where another organ system was responsible for the death also had respiratory problems.
2: Trauma problems were found in 12.5% (N=3) of the pet rats. The cause of trauma was in all three cases fighting with other rats that lived in the same cage. In two rats, the bite wound got infected.
3: Skin problems were found in 12.5% (N=3) of the pet rats. One rat had a large purulent infection in the skin and muscles around his left femur. The cause and the agent of the infection is unknown. Another rat had severe dermatitis, they suspected an auto-immune disease but were not sure. The third rat had acanthosis and hyperkeratosis, but also here the cause was unknown.

3.2.1.4 Infectious agents

Six rats had an infectious cause of death. Four of them died naturally because of pneumonia, the other two rats because of a pyometra and trauma. In the diagram below are more than six infectious agents. Some rats were infected with more than one infectious agent, they were more susceptible because the first infectious agents attacked their immune system and created a good environment for the other infectious agents.
The most common infectious agents in the six rats are:

- Pasteurella hemolytica: 42.86% (N=3)

  One rat died of a pneumonia caused by Pasteurella hemolytica, another rat had P. hemolytica as secondary infectious agent which caused pneumonia. The third rat died because of a pyometra. In the uterus, also Actinobacter spp. was found.
- Mycoplasma spp.: 28.57% (N=2)

  These two rats died because of pneumonia. They both had a secondary infection with another bacterial agent.
- Staphylococcus spp.: 28.57% (N=2)

  One rat got infected with Staphylococcus spp. through a bite wound under the eye, the other one got Staphylococcus spp. as a secondary infection in the lungs.

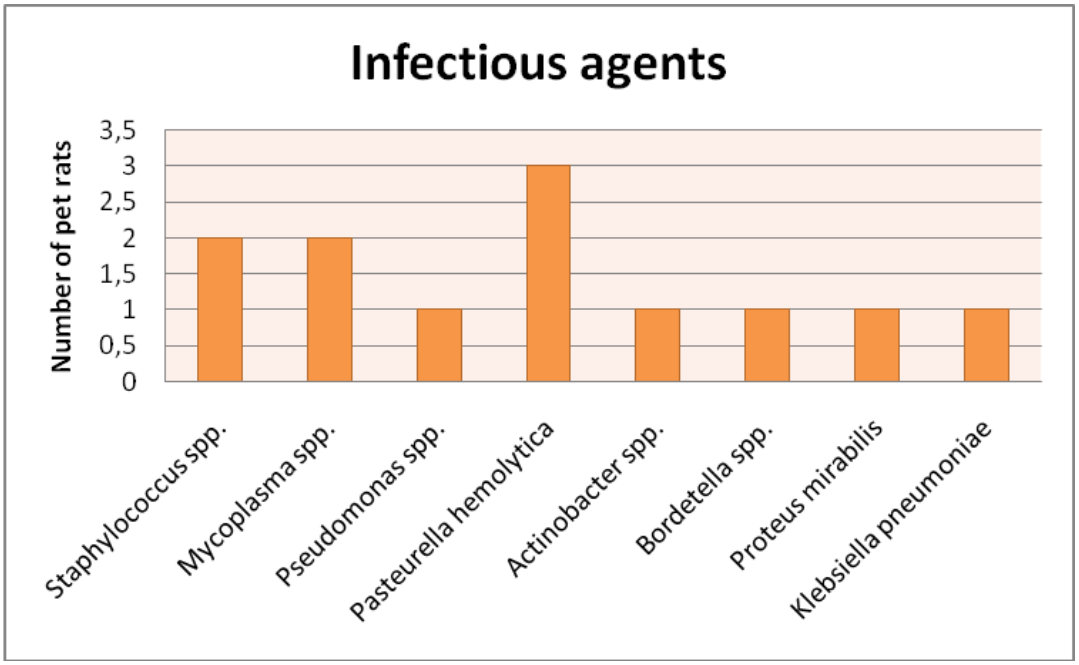

Figure 4

3.2.1.5 Respiratory problems

Of the 24 rats in the archive, 15 rats had respiratory problems. 11 rats died because of respiratory problems like pneumonia, edema and emphysema. There were four other rats that died because of other problems, but had additional respiratory problems. Something that came into notice, there is no case were the cause of the respiratory problems is non-infectious. Here, the division of the respiratory problems into the infectious, suspicious infectious, non-infectious and unknown groups is given:

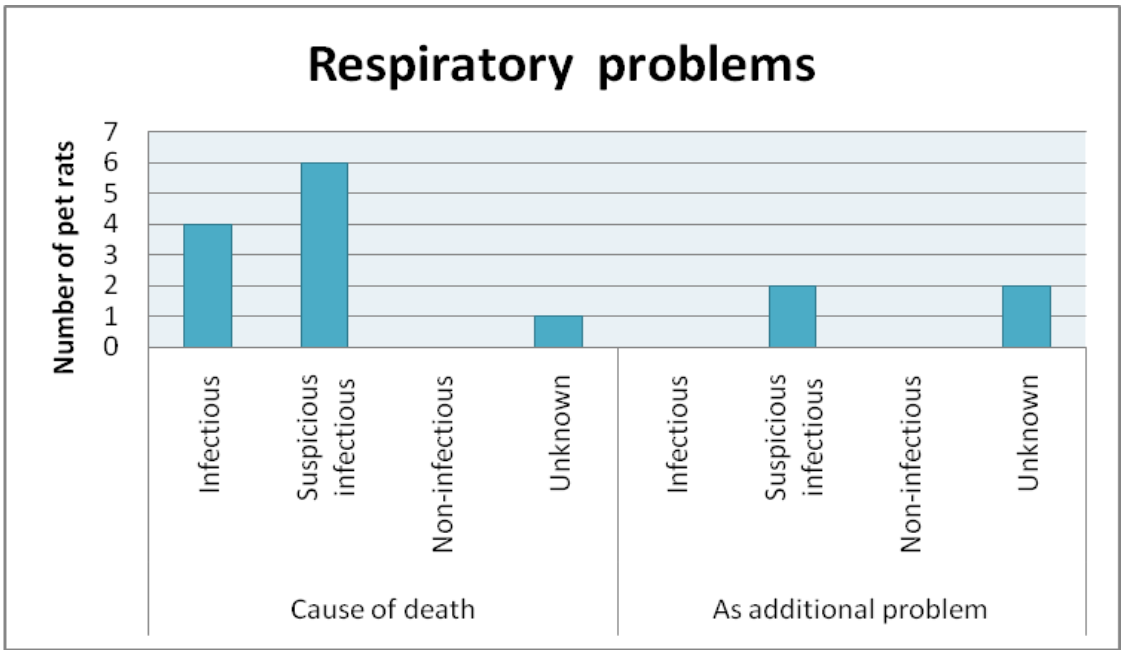

Figure 5

Infectious causes of respiratory problems as cause of death:
Rat 1: Mycoplasma pulmonis and Pseudomonas spp.
Rat 2: Proteus mirabilis and Klebsiella pneumoniae
Rat 3: Mycoplasma pulmonis, Bordetella spp., Pasteurella hemolytica and Staphylococcus spp.
Rat 4: Pasteurella hemolytica

The two rats which were infected with Mycoplasma pulmonis also had a secondary bacterial infection, there isn't a case were Mycoplasma pulmonis is the only infectious cause of disease and death. Also Pasteurella hemolytica is seen in two rats. The other infectious agents were seen only in one rat.

Suspicious infectious causes of lung problems as cause of death:
Of the six cases of a suspicious infectious cause of respiratory problems leading to death, four of them were thought to be caused by Mycoplasma pulmonis. M. pulmonis is not demonstrated in the rats but the clinical signs of the rats pointed to an infection with this agent, according to the pathologic specialists. Two other rats were suspected to be infected with another bacterial agent which could not be demonstrated due to treatment with antibiotics.

3.2.2 Results of the retro-spective research of pet ferrets

3.2.2.1 Causes of death

In the group of ferrets, that died prematurely in the period from 1993 to 2009, were a total of 70 pet ferrets between the age of 6-36 months old. Based on the conclusion in the necropsy reports, the causes of death were divided into 4 groups; infectious, suspicious infectious, non-infectious and unknown

In the group suspicious-infectious, it was known that there was a bacterial, fungal or viral agent, but they couldn't be demonstrated because of the use of antibiotics or other causes.

The division into the four groups resulted in the following numbers:

- Infectious: 18.57% (N= 13)
- Suspicious infectious: 27.14% (N= 19)
- Non-infectious: 20.00% (N= 14)
- Unknown: 34.29% (N= 24)

If the infectious and suspicious infectious groups are added together, and it is assumed that the suspicious infectious group really is infectious, then 45.71% (N = 32) of the deaths of ferrets are likely due to infections.

Figure 6 shows the distribution of the causes of death in a chart.

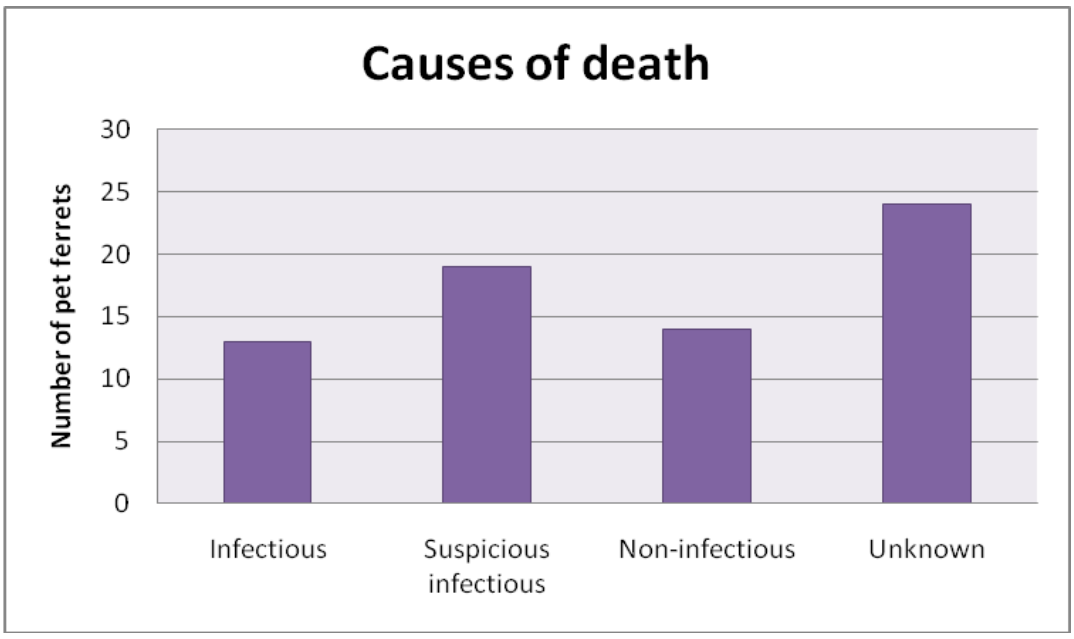

Figure 6

3.2.2.2 Types of death

In a number of cases the ferrets didn't die naturally. The owner and the veterinarian decided to perform euthanasia because of the stadium and severeness of the disease. Not in every necropsy report it is known or the ferrets died naturally of by euthanasia.
The division into the three different groups resulted in the following numbers:

- Euthanized: 27.14% (N = 19)
- Non-euthanized: 37.14% (N = 26)
- Unknown: 35.72% (N = 25)

Figure 7 shows an overview of the types of death.

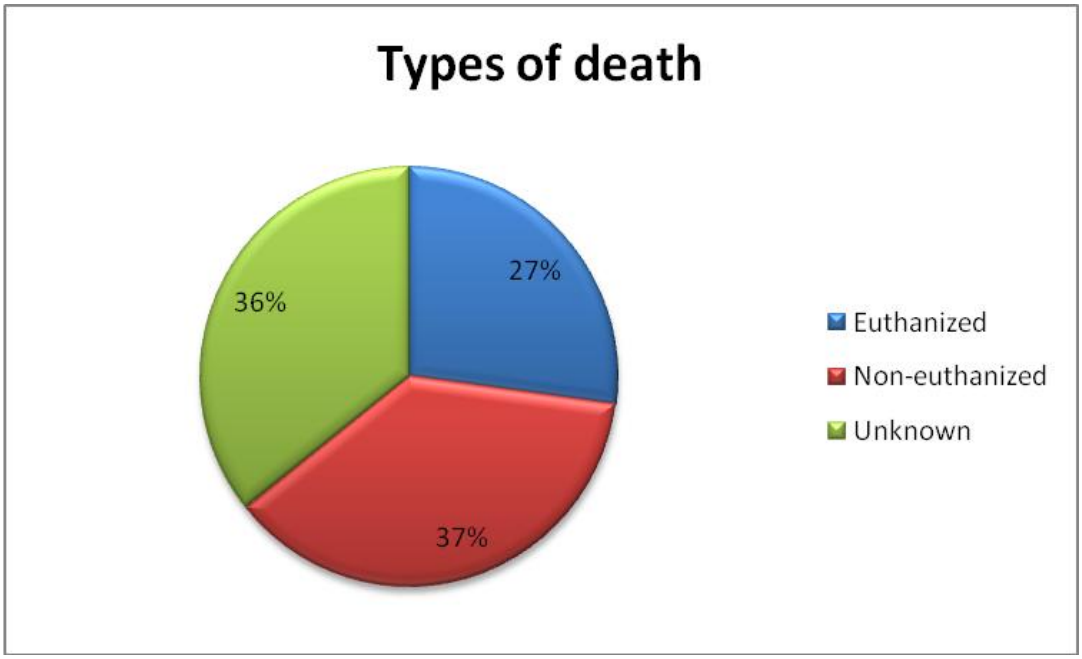

Figure 7

3.2.2.3 Main affected organ systems

Figure 8 shows an overview of organs responsible for the death of the ferrets.

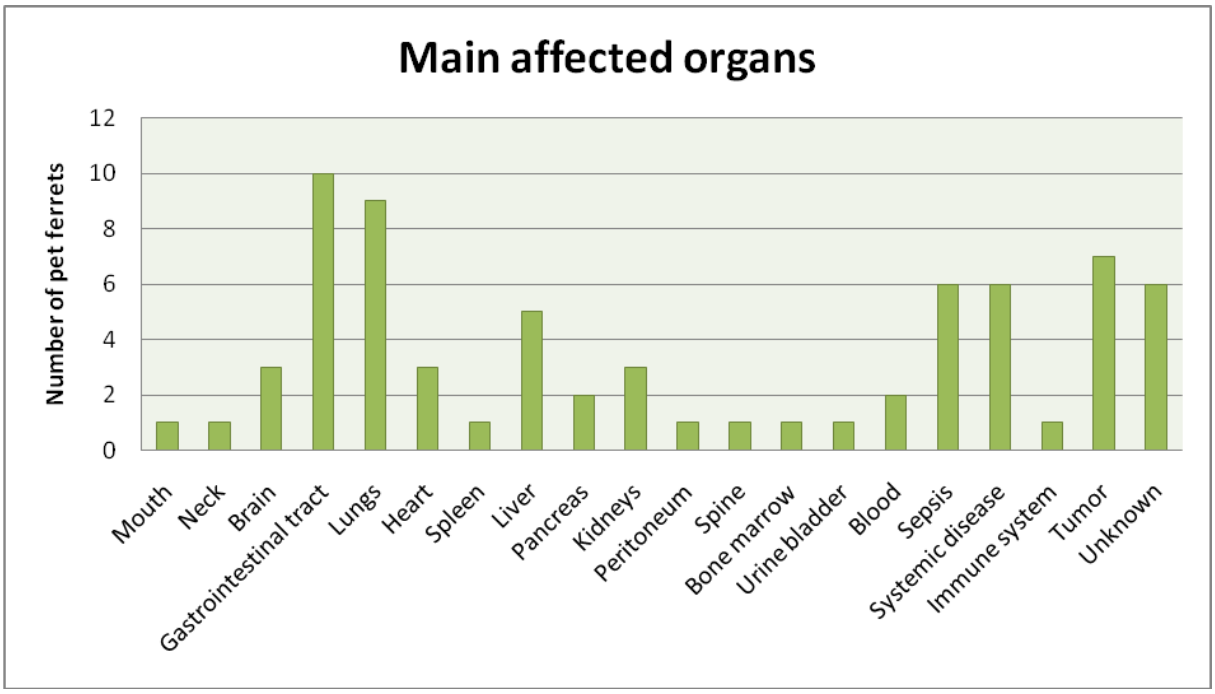

Figure 8

The five most common problems are discussed below:
1: Gastrointestinal problems were found in 14.29% (N = 10) of the ferrets. There were many different gastrointestinal problems found in the ferrets. Two ferrets had eaten a foreign body which caused an obstruction in the pylorus part of the stomach and in the intestines. Two other ferrets had an intestinal bleeding with an unknown cause. The other ferrets suffered from inflammations in the gastrointestinal tract due to coccidiosis, Pasteurella hemolytica and unknown agents.
2: Respiratory problems were found in 12.86% (N = 9) of the ferrets. In six necropsy reports, pneumonia was the cause of death. The other three had problems like edema and emphysema. In four cases, the infectious agent was demonstrated. Two ferrets were infected with Chryseomonas luteola, the others with Escherichia coli and Streptococcus spp.
3: Tumors were found in 10.00% (N=7) of the ferrets. It were all different kind of tumors; an insulinoma, hemangiosarcoma, juvenile lymphoma, multiple sarcoma, endocrine tumor in multiple organs and a malignant epithelial and mesenchymal tumor in the area of the pancreas and one in the area of the adrenals.
4: Systemic diseases were found in 8.57% (N = 6) of the ferrets. Pathological lesions were found in multiple organs. Often, the brain was also infected which resulted in encephalitis or meningitis. In one ferret, the Canine Distemper Virus was demonstrated as etiological agent. The other five ferrets had a suspicious infectious cause of death. In most reports, Aleutian disease and Canine Distemper Virus were suspected, but the etiological agent could not be demonstrated.
5: Sepsis as initial cause of death was found in 8.57% (N = 6) of the ferrets. The etiological agent for the sepsis was found in three ferrets, respectively Mycobacterium celatum, Escherichia coli and Staphylococcus spp.

3.2.2.4 Infectious agents

Thirteen ferrets had an infectious cause of death. Eight of these ferrets died naturally. Of the other ferrets, it wasn't clear whether they were euthanized of died naturally.
The most common infectious agents in the ferrets with an infectious cause of death are:

- Pasteurella multocida.: 15.38% (N=2)
  One ferret had cirrhosis of the liver and a cystic bile duct. In the liver P. multocida was found. The other ferret had a gastroenteritis caused by P. multocida.
- E. coli.: 15.38% (N=2)
  One ferret had a bronchopneumonia. The other ferret died because of sepsis, but had also pneumonia and epicarditis.
- Chryseomonas luteola: 15.38% (N=2)
  This bacterial agent caused pneumonia in two ferrets. One ferret had a hemorrhagic pleurisy and an acute pneumonia. The other ferret suffered from proliferative inflammation in the lung and the bronchial lymph node.

Figure 9 shows the infectious agents found in different organs.

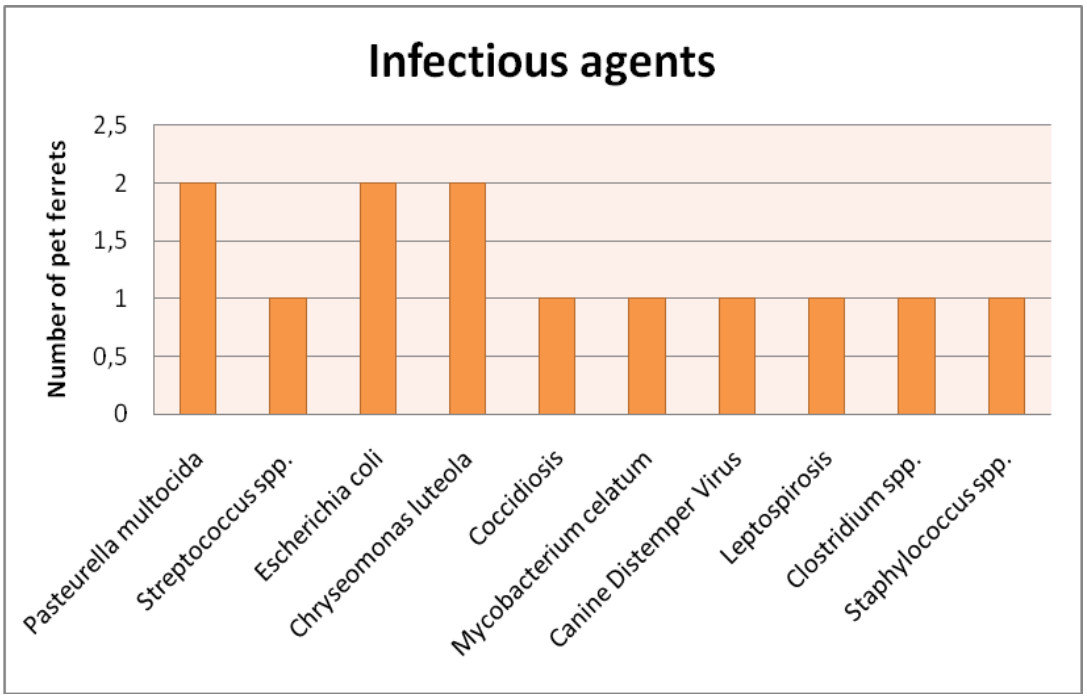

Figure 9

3.2.2.5 Extramedullary hematopoiesis in the spleen

Of the 70 ferrets, 41.43% (N = 29) ferrets had extramedullary hematopoiesis (EMH) in the spleen. Suspicious infectious may be classified in the category infectious, except the etiological agent is unknown. So if these groups are added together, then at least 48.28% of the ferrets with EMH have an infectious cause or suspected infectious cause of death. At least 17.24 % of the ferrets with EMH have a non-infectious cause of death. These percentages could be higher because of the unknown group.
The division into the four groups resulted in the following numbers:

- Infectious: 10.35 % (N = 3)
- Suspicious infectious: 37.93% (N = 11)
- Non-infectious: 17.24% (N = 5)
- Unknown: 34.48% (N = 10)

Figure 10 shows the distribution of the causes of death in a chart.

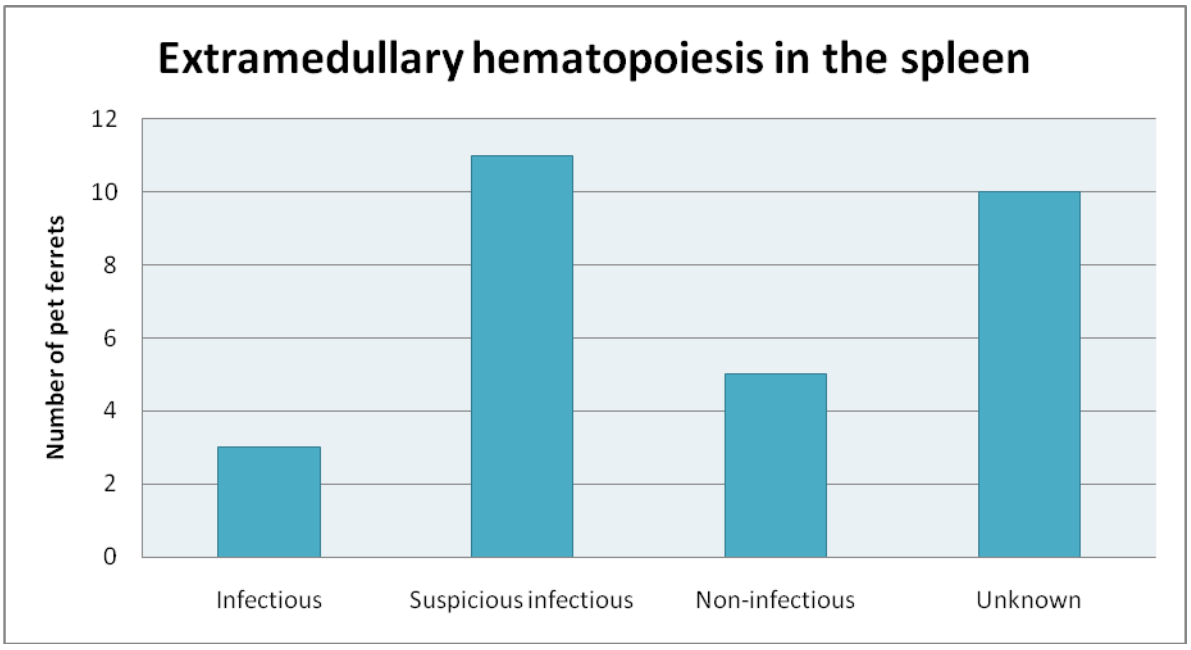

Figure 10

3.3 Interim results of the rats and ferrets from the *Welfare research small mammals* '09 – '12

At the time of this research, only four pet rats and no pet ferrets were submitted since October 2009, to the VPDC for the *Welfare project small mammals*. Initially, the plan was to make a comparison between the results of the retro-spective research and the preliminary welfare project results. With only four rats and zero ferrets, it's not possible to make a significant comparison. However, there will be looked if the causes of death of these four rats can be found back in the results of the literature and retro-spective research. Below, an overview of the data of the four rats from the *Welfare research small mammals* '09 – '12 is given.

Rat	Gender	Cause of death	Type of death	Affected organ and disease
1	Female	Euthanized	Suspicious infectious	Intestines: transmural enteritis
2	Female	Non-euthanized	Infectious: Streptococcus pneumonia	Lungs: pneumonia
3	Male	Non-euthanized	Suspicious infectious	Lungs: bronchopneumonia
4	Female	Non-euthanized	Non-infectious	Tumor: a malignant lymphoma in the lungs

Tabel 1

4 Discussion

4.1 Limitations of the research

In the retro-spective research, few pet rats and ferrets were selected from the archive ’93 – ’09 to participate. The archive of the rats included many laboratorial rats, who couldn’t participate because this research involves pet rats. In the archive of the ferrets, many necropsy reports were based on organs that were sent in, not on whole bodies. Only necropsy reports based on whole bodies were selected. Eventually, there were only 24 pet rats and 70 pet ferrets to investigate causes of premature death in these animals.
It’s plausible that these animals didn’t represent the whole population of premature died pet rats and ferrets. One of the selection criteria was the age of the animal that died. But premature death of these animals isn’t bounded to the chosen age limits. There are many animals that die before they reach their life expectancy, but when they are younger or older than the age limits of the retro-spective research, they cannot participate in the research.
It’s possible that these animals prematurely die due to other reasons or diseases than the animals that were selected for the research. So, if they are also being processed and interpretated as prematurely died animals, results of common diseases in these animals could be very different.
Another factor is the threshold for post-mortem examination. The relative value of the animal is for many owners less than the cost of the post-mortem examination (3). It’s possible that the owners who do send their prematurely died pet animal for post-mortem examination, are more committed to their pet and as result, welfare issues like improper care, nutrition and housing are less important in the genesis of the diseases of these animals.

A retro-spective research uses existing data that have been recorded, not especially for research but for other reasons. This existing data can be limited and makes drawing conclusions very difficult or even impossible. Many necropsy reports of the pet rats and ferrets had limited or even missing anamnesis. The aim of this retro-spective research is to look at welfare issues which can cause premature death in pet rats and ferrets. Because there is no information about housing, care and nutrition, no conclusions can be drawn, about welfare factors leading to these diseases.

A specific limitation of this research is seen in the results of the respiratory problems. In four necropsy reports, Mycoplasma spp. is the suspected infectious agent. In two other necropsy reports, Mycoplasma spp. is diagnosed as the etiological agent causing the respiratory disease. In the next sub chapter, under the heading “causes of death” in pet rats, it’s described that it was not possible for the VPDC to made a definitive diagnosis of Mycoplasma spp.. The interpretation of the smears and the determination of the diagnosis depends on the person who conducts the test to detect Mycoplasma spp.. This means that the diagnosis of the same smear depends of individuals and may be concluded definitive or presumptive.

Limitations during the literature research were also found. In scientific books and journal articles, many diseases of pet rats and ferrets are being described but the prevalence is often not mentioned. There is only a distinction in common or not common.
Therefore it’s not possible to make a representative list of the most common diseases causing premature death in pet rats and ferrets. In some diseases, the clinical signs also depend on the age of onset. Diseases that are known for their severeness, hardly give clinical signs in older animals and vice versa (49).

4.2 Comparison of the literature and retro-spective research of pet rats

4.2.1 Causes of death

In the period 1993 – 2009, only 24 pet rats died prematurely. According to the chart of "causes of death", most rats (N = 10) had a suspicious infectious cause of death.
Of the ten rats in this group, six had respiratory problems were 50% of the rats died naturally and the other 50% had an unknown type of death. Of these six rats, four were suspected of being infected with Mycoplasma spp.
The suspection of mycoplasmosis is based on microscopic lesions and abnormalities. Sub acute to chronic mycoplasmosis is typified by lymphocytic infiltrates around the airways, macrophages and alveolar edema. Mycoplasmal pneumonia is associated with extensive lymphoid hyperplasia around the bronchi and bronchioles. The respiratory submucosal glands are hyperplastic and produce excessive secretions (75). There are many different methods to test the presence of Mycoplasma spp. According to Davidson *et a*l, ELISA may prove to be the best method to detect natural infections in rats older than 2-3 months (76). ELISA has a high sensitivity in naturally infected rats because they almost always express a high level of IgG, also the simplicity, low cost and rapidity makes this test the best method in live animals (76). When serum cannot be collected, as often during necropsies, ELISA is no option. Mycoplasmas are the smallest, self-replicating organisms (75). In cytological smears stained with HE, they appear as tiny blue dots, but because they are so small, they are difficult to see. Based on tiny blue dots, it's not possible to establish a definitive diagnosis. In the VPDC, immunohistochemistry was not available and PCR methods did not exist at the time. HC stained impression smears of lung tissue was performed, as well as histology. Based on these impression smears, histology and clinical signs, a presumptive diagnosis of Mycoplasma spp. infection was made.

The second biggest group with six rats was infectious causes of death. Four rats died of pneumonia. It is striking that all four rats were non-euthanized but died naturally. According to the literature research, respiratory disease is the most common health problem in pet rats. If the infectious and the suspicious infectious groups are added together, respiratory problems (N = 10) are the most common diseases. So even in 24 rats, it's obvious that respiratory disease is of great concern in welfare issues. The topic respiratory disease will be discussed more in the sub chapter "respiratory problems".

The groups non-infectious and unknown include all different diseases and clinical signs. Therefore, this data is too limited to make conclusions.

4.2.2 Types of death

Looking to the distribution in types of death, it strikes that 50% of the pet rats die a natural death. Rats are prey animals, thus signs of disease can be concealed during early stages of disease. Signs of pain and illness are not readily demonstrated, so even for the owner it's difficult to decide whether the rat is ill or not (14). Sometimes, the rat doesn't show any signs to the owner and is suddenly death. Often with dogs and cats, owners wait one or two days to go to the veterinarian. Unfortunately, some owners do the same with their pet rats.
But when a rat is showing clinical signs, it means that the disease passed the early stage and the rat could already be dead before he is taken to the veterinarian. This could be an explanation for the 50% of naturally died pet rats.

4.2.3 Main affected organs

According to the chart " main affected organs", respiratory disease is the most common problem in these 24 rats, this will be discussed later.

4.2.3.1 Skin

Three rats had skin problems. According to the literature research, ulcerative dermatitis is a common problem in rats. One of these three rats had ulcerative dermatitis; the cause of death was unknown but the rat showed so severe clinical signs that euthanasia was the best option. In the anamnesis of this rat, no information can be found about underlying causes of the ulcerative dermatitis.
Another rat had a purulent inflammation of the skin and muscle of the left femur. No information can be found about trauma. The rat showed also neurological signs like rotating his body. The last rat showed clinical signs of hyperkeratosis and acanthosis. They didn't find a cause of these signs but had two possible explanations why these signs arose; because of overpopulation in the cage (improper housing) or deficient nutrition like a vitamin A deficiency (77).

4.2.3.2 Trauma

Three male rats prematurely died due to trauma. From the anamnesis, conclusion can be drawn that all three rats lived in a multi-rat household. The trauma was caused trough bite wounds, probably due to other rats. In two rats, the bite wound got infected. The other rat died because of the severeness of the trauma. According to Barnett, there is one situation in a multi-rat household were fighting is highly probable; when an adult male enters a region in which another adult already is established. A series of experiments was carried out, where adult male rats were introduced in small colonies with other adult rats. Of the 20 males that were added to such colonies, 18 died because of trauma. In contrast, addition of female or young rats rarely resulted in injury or death. It's possible that this "territorial behavior" is the reason why these rats died but it cannot be concluded because of limited data from the anamnesis. Territorial behavior is not always the reason for fighting, sometimes it can arise spontaneous or for a female (78).

4.2.4 Infectious agents

There were six rats with an infectious cause of death and eight different infectious agents. The most common infectious agent in these rats was Pasteurella hemolytica. This bacterium was found twice in lungs and once in the uterus. P. hemolytica is not considered to be a major pathogen causing pneumonia, so probably it was a secondary infection. Mycoplasma spp. was definitive diagnosed two times, but as described in the subchapter "limitations of the research" a definitive diagnosis of Mycoplasma spp. wasn't possible at that time. So this actually are presumptive diagnosis.

4.2.5 Respiratory problems

In the literature research, respiratory disease is described as the most common health problem in rats. Looking at the chart "main affected organ system", it shows that also in the retrospective research, respiratory disease is the most common disease (46%) leading to death in these 24 pet rats.

Besides respiratory disease as cause of death, 16.67% of the rats had respiratory problems as additional disease. In the chart “respiratory problems”, it can be seen that none of the causes of the respiratory disease are non-infectious.
Mycoplasma pulmonis is considered to be one of the major respiratory pathogens. This bacterium is also strongly suspicious represented in this retro-spective research. As previous described, four rats were suspected with an infection of Mycoplasma spp. and in two rats Mycoplasma spp. was concluded as infectious agent.
When a major respiratory agent enters and affects the respiratory system, it’s more susceptible for secondary colonization with other bacterial agents. In the chart “respiratory problems” are four rats with infectious respiratory problems as cause of death, three of them are infected with secondary bacterial agents. An infection with Mycoplasma pulmonis is described as a chronic respiratory disease. Rats can live a long time with this infection (10). But when a secondary bacterial agent enters, the clinical signs probably worsen and can lead to death. Of one necropsy report it’s known that the rat was infected with Mycoplasma spp. and a secondary bacterial agent, and was dyspnoeic for several months. The other rat with Mycoplasma spp. was found death. Nothing is known about the history of this rat.

4.2.6 Subconclusion

Analyzing and comparing the literature and retro-spective research, the most striking similarity was the high prevalence of respiratory diseases. In the literature, respiratory diseases are being described as the most common health problem in rats. In the retro-spective research, the health problem leading to death with the highest prevalence (46 %) was also respiratory disease, both major clinical syndromes were represented.
Ulcerative dermatitis is represented just by one necropsy report. In the literature research, trauma is described as a factor contributing to ulcerative dermatitis. In the retro-spective research, trauma as cause of death is found more (N = 3) than the dermatitis itself. Teeth problems were not found in these 24 necropsy reports.

4.3 Discussion of the results of the literature and retro-spective research of pet ferrets

4.3.1 Causes of death

According to the distribution of the causes of death into four groups: infectious, suspicious infectious, non-infectious and unknown, the majority of the ferrets died of an unknown cause. The necropsy reports of the ferrets with the largest group, unknown causes of death, shows a diffuse picture of organs who are involved in death of the ferrets. Therefore it isn't possible to draw conclusion out of these data.

The second largest group is the group of the suspicious infectious causes. In this group, necropsy reports are processed which are known to be infectious but an etiological agent isn't demonstrated. In six reports the specialist suspected an infection with CDV because of the pathological signs including encephalitis/meningitis. One ferret tested positive to CDV. The other five ferrets tested all negative for this virus. The tests were performed with immunohistochemistry, usually on brain tissue. With these tests, antigens were demonstrated and colored with marked antibodies. The tissue was first fixed in formalin and embedded in paraffin (79). Antibodies against CDV were applied on the brain tissue. Other marked antibodies against the CDV antibodies are also applied on the tissue. The CDV antibodies formed complexes with the possible present antigens of CDV and were colored. Under the microscope, brown deposits were seen in the ferret infected with CDV. Data about the sensitivity and specificity of this test are limited. From a study of Ho *et al* in dogs, it appears that prolonged exposure of infected target cells to high concentrations of antibodies leads to redistribution of viral surface antigens and their disappearance (80). It's unknown if the brain cells of the ferrets were exposed long enough for redistribution and disappearance of viral surface antigens, but it could be a possibility for false-negative test results. Other possibilities for non-interpretable results are a high background response because of cross-reactions, the duration time of the tissue fixated in formalin, and the quality of the tissue (too autolytic) (81). In the necropsy reports, no extra information of other tests can be found if the immunohistochemistry tests were negative. It was suspected that there was an infectious agent but further tests were not performed. An explanation therefore can be the costs of the extra tests. In contrast to the *Welfare research small mammals*, the post-mortem examinations and tests from the archive were not free of charge. So the threshold for the owner was a lot higher than for animals included in the *Welfare research small mammals*.

In seven reports, Aleutian disease was suspected. Four ferrets tested negative. Remarkably, these four ferrets were all tested differently. Three necropsy reports contained only a suspection but tests were not performed. The other four tests were serology, Ziehl-Neelsen coloring and two times immunohistochemistry. According to Fox, diagnosis may be confirmed with serology (counterelectrophoresis) and immunohistochemistry. The counterelectrophoresis is widely used and has found to be an effective method for serologic surveys for Aleutian Disease Virus (ADV) infected ferrets (56, 67). In a studie of Cho *et al*, they applied counterimmunoelectrophoresis on three mink-ranches were a part of the minks were infected with ADV. All mink on the three ranches were tested for four years before the pelting and breeding season. Aleutian disease has been eliminated on the three ranches by culling out the positive tested mink (71). In every test is a chance to get false-positive or false-negative results. It's possible that one of these ferrets was infected with ADV but that the test was false-negative.

The other necropsy reports in the group suspicious infectious gave a diffuse picture. Therefore it also isn't possible to draw conclusion of these data.

In the group non-infectious causes of death were 14 ferrets. Something that came into notice was that 50% of the necropsy reports in this group included tumors. Here it can be concluded that in ferrets of the retro-spective research, the most common cause of non-infectious death is tumors. An important notice here is that it were not all the same tumors. More information about these tumors will be described later. The rest of the causes were very variable.

In the group infectious causes of death were 13 ferrets. The most infectious problems were found in the lungs (N = 4). These four ferrets all died naturally, thus without euthanasia. There were three different infectious agents found in these ferrets, only Chryseomonas luteola was found in two ferrets. Three ferrets died because of infectious liver problems. They were all different infectious agents that caused the liver problems. Because there is so little data in the group infectious causes of death and because the problems are widespread, it isn't possible to draw significant conclusions.

4.3.2 Types of death

The majority of the ferrets (37%) naturally died due to a disease. A real conclusion could not be drawn of these data because the types of death are almost evenly distributed.

4.3.3 Main affected organs

Looking to the bar chart of "main affected organs", five of them seem to be the most common: lungs, gastrointestinal tract, systemic diseases, tumors and sepsis.

4.3.3.1 Gastrointestinal tract

The gastrointestinal tract was the most affected organ system.
Ten ferrets died because of gastrointestinal problems. In six cases were inflammations of the gastrointestinal tract, were two inflammations involved the gastric mucosa. In the literature research Helicobacter mustelae is named as an infectious agent causing gastritis. Almost 100% of the ferrets are infected with this infectious agent but disease only occurs in time of stress in young animals or as additional disease in older ferrets. In these cases, one infectious agent was Pasteurella multocida and the other was unknown. Because of the high incidence of infections with H. mustelae, gastric biopsy is the way to confirm the diagnosis. In the necropsy report of this ferret, nothing is found about microscopic, cytological and microbiological examination. So there is a possibility of a H. mustelae infection but the examination was not finished completely.
The other four inflammations were found in the intestinal tract. In the literature research, one form of enteritis is described as proliferative bowel disease. This disease is caused by the micro-organism Desulfovibrio spp. and affects young ferrets. This micro-organism is not found in the necropsy reports.
Two ferrets had a foreign body in their gastrointestinal tract. According to the literature research, is obstruction caused by a foreign body a common phenomenon (45, 46).
Ferrets are playful animals and like to chew on all kind of things, which are not all eatable. Here is a task for the owner, to prevent this phenomenon from happening.

4.3.3.2 Lungs

Six ferrets died because of pneumonia. Four of them had an infectious agent responsible for the pneumonia, one was suspicious infectious and the other ferret had an unknown cause of death. According to Rosenthal, pneumonia is not a common diagnosis in ferrets. But according to Fox, ferrets are susceptible to respiratory infections (58, 82). It's a good possibility that these four ferrets had a secondary bacterial pneumonia and that the primary viral agent wasn't tested. In the literature research, the influenza virus is described as a cause of premature death in young animals.
They are more susceptible to influenza because they have more ciliated epithelium in their respiratory system. That is the reason why young animals are more likely to develop pneumonia.
Of the six ferrets, none of them was tested to be infected with the influenza virus. Four of them had a bacterial infectious agent. As dust, cigarette smoke and ammonia can cause ciliostasis in rats, it may be assumed that this also applies for ferrets. Unfortunately, an anamnesis of these ferrets about care, housing and bedding is missing, otherwise relations between pneumonia and welfare factors could be demonstrated.

4.3.3.3 Systemic diseases

With systemic diseases, diseases are meant that causes pathological lesions in many different organs in a body. For example; Canine Distemper Virus (CDV), Aleutian Disease Virus (ADV) and the Ferret Systemic Coronavirus (FSCV). In the chart "Main affected organs", only systemic diseases that affected more than one organ were selected. There were more necropsy reports were systemic diseases were suspected by the specialist, but for instance when only the brains were affected, the necropsy report was classified in the section brains. That's the reason why there are more suspections of these diseases than is given in the chart "main affected organs".
The FSCV is a relative new virus that is discovered in Spain in 2004 (83). In the archive research, this virus has not been found in the ferrets. There were six ferrets suspected of an infection with CDV and seven of an infection with ADV, one of these six ferrets was tested positive for CDV. The suspection was based on macroscopic and microscopic examinations by the pathologic specialist. It's difficult to draw conclusions about the prevalence of these diseases in ferrets because they tested almost all negative. Reasons why the tests possibly can give false-negative results are appointed in the second paragraph of the conclusions of causes of death. Also, further tests were not performed so maybe than there were had different results instead of unknown infectious agents.

4.3.3.4 Tumors

Of the 70 ferrets, 10.00% (N = 7) had a tumor. Not all tumors were exactly specified. Here is an overview of the different tumors found in these seven ferrets:
1: Insulinoma
2: Haemangiosarcoma
3: Malignant epithelial and mesenchymal tumor, in the area of the adrenals
4: Malignant epithelial and mesenchymal tumor, in the area of the pancreas
5: Juvenile lymphoma
6: An endocrine tumor in multiple organs
7: Multiple sarcoma

According to the literature research, neoplasms are the most common diseases in ferrets. The average age of onset is 4 to 7 years, but can vary from a few months till 15 years (34). In the archive, ferrets under the three years old were selected. Still a percentage of 10% of ferrets that developed a tumor which leads to death is seen here. In the literature wasn't given a prevalence of the tumors, so it cannot be compared with the results of the retro-spective research. The three tumors that are most common in ferrets are represented in the retro-spective research; insulinoma, adrenocortical tumor and the lymphoma.

4.3.3.5 Sepsis

In six ferrets (8.57%) was sepsis the cause of death. There were more necropsy reports were sepsis was a pathological finding, but there it wasn't the cause of death. Only in three ferrets the infectious agent was demonstrated. It's possible that the bacterial agents of the other ferrets couldn't be demonstrated because of treatment with antibiotics, but the clinical history is too limited to draw this conclusion.

4.3.4 Infectious agents

There were 14 ferrets with an infectious cause of death and ten different infectious agents. Thus, none of the infectious agents was present in a remarkably number. Therefore, it's not possible to draw conclusion out of this data.

4.3.5 Extramedullary hematopoiesis in the spleen

A large percentage (41.43% (N = 29)) of the ferrets had extramedullary hematopoiesis (EMH) in the spleen. Looking to the distribution of causes of death, then the groups suspicious infectious (N = 11) and unknown (N = 10) are the biggest. The cause for EMH is still unknown but compensation for myeloid insufficiency has been suggested. Most ferrets with EMH do not show signs of anemia or other hematologic deficiencies. The diagnosis of EMH is based on a splenic aspirate where a mixed population of mature and immature hematopoietic cells on a smear is revealed (84). The macroscopic appearance of a spleen with EMH is characterized by an enlargement with rounded borders. According to Hess and Rosenthal *et al*, splenic EMH is very common in older ferrets, percentages are not given (41, 58). With the results of the retro-spective research, it can be concluded that splenic EMH is also common in young ferrets.

4.3.6 Subconclusion

A few diseases were not found in the retro-spective research but were common cause op premature death in ferrets according to the literature. It's possible that owners already make welfare adjustments so that the prevalence of these diseases already is lowered. Or the retro-spective population is not representative for the whole population of ferrets.

In the retro-spective research, the gastrointestinal tract was the most affected organ in these 70 ferrets. Foreign bodies and gastritis were represented in both researches. Enteritis appeared to be a disease which may lead to premature death in ferrets but this wasn't found in the literature.
Lung problems were the second most common disease in the retro-spective research, were pneumonia was found in six necropsy reports. According to the literature, pneumonia is an uncommon finding in ferrets but if young ferrets develop pneumonia, it can be fatal.
Conclusion can be drawn that tumors also develop in young ferrets. The golden age is four to seven years, but like the literature research indicates, the age of onset can be variable which is proven with the retro-spective research. In 13 necropsy reports a systemic disease like ADV and CDV was suspected in a ferret. In only one necropsy report, CDV was demonstrated as the etiological agent. It's not known if there are false-negative tests included because no extra tests were performed.
During necropsy, extramedullary hematopoiesis was found in the spleen of many ferrets. With a percentage of 41.43% of the ferrets, conclusion can be drawn that EMH also is common young ferrets.

4.4 Discussion of the results of the rats of the *Welfare research small mammals* compared to the literature and retro-spective research

Of the four rats that participated in the *Welfare research small mammals*, two rats had pneumonia. In the literature, respiratory problems are being described as the most common health problem in rats. This finding can be seen back in the results of the retro-spective research. One rat died because of malignant lymphoma in the lungs and the other rat because of enteritis. These last two diseases are not represented in the literature and retro-spective research.

5 Welfare recommendations

Recommendations for the welfare of pet rats and ferrets are given to prevent the most common diseases that arise from the retro-spective and literature research. Not every disease can be prevented, but with certain welfare adjustments clinical signs and/or the time of onset of the disease may be reduced.

5.1 Welfare recommendations for pet rats classified by disease

5.1.1 Respiratory disease

As can be read in the literature research, there are many factors playing a part in the genesis and expression of mycoplasmosis. It can be assumed that many of these factors predispose rats also to other micro-organisms. Most factors influence the morphology of the lungs and disturb the homeostasis, as result micro-organisms have more chance to maintain themselves in the lungs and cause an infection.

The odor of ammonia is a common finding in cages of pet rats. This ammonia is formed by the action of urease-positive bacteria on urea which is excreted in urine and faeces. The quantity of ammonia that is produced depends on the number of animals in the cage (more urine and faeces), temperature and humidity (85). Maximum ammonia production occurs at a temperature of 21 degrees (86). From a study of Gamble *et a*l, it appears that under conditions of high humidity, the most rapid ammonia production occurs (85). High ammonia concentrations in the cage (25-250 ppm) can cause severe damage to the cells of the lungs and may predispose the rat to mycoplasmosis (14, 16). Cage cleaning is necessary to give the rats a hygienic environment.
To lower the ammonia level in the cage, frequent cleaning is advised (87). It's difficult to tell how many times the cage has to been cleaned in a week because it depends on the amount of pet rats in a cage. The owner should keep an eye on the cage and if it smells like ammonia or looks dirty, it's time to clean. The water bottles must not be leaking, because this increases the humidity in the cage (85). Preferred humidity levels for rats are around 50% (14). The temperature should follow what is commonly maintained with the ambient conditions within the house, even if it's 21 degrees. Rats do not tolerate elevated temperatures and should at least be kept under the temperature of 24 degrees (88). For proper ventilation a cage with bars is advised (9).

Proper bedding of the cage is very important to rats. In the literature research is described that some wooden shavings contain toxins like abiëtine and fenols which can cause damage to the respiratory epithelium (20). Rats have very sensitive airways, so when choosing the bedding for the cage, it's important that the bedding doesn't contain dust. Cedar and pine shavings must be avoided; paper, beech chips and beddings based on corn or hemp are suitable (88, 89).

Just like ammonia, exposing rats to cigarette smoke can cause ciliostasis in the lungs. Micro-organisms are not or impaired eliminated out of the lungs and may cause an infection. To prevent this from happening, owners should not smoke in the same room were the rats are housed or smoke when they cuddle with the rat.

A vitamin A or E deficiency also affects the cells of the lungs and makes them more susceptible for an infection with Mycoplasma spp (21-23). Mixed feed containing seeds and pellets are commonly given to pet rats, when owners constantly refill the dish, pet rats may select only the things they like and often the pellets are being ignored (8). A diet based on seed lacks a number of nutritional requirements that the rat needs to maintain long-term health (9). To prevent the rats for choosing only the things they like the most, a uniform diet is advised which contains pellets. These pellets contain all nutritional requirements that the rat needs. Pellets that are available in the Netherlands for pet rats are; Supreme Science Selective Ratten, Versele-Laga: rat complete, Versele-Laga: rat & mouse PRO, Beaphar: Care + Rat, Hope farms: Mouse-Rat Super. Pellets are the main feed, vegetables (no lettuce or cabbage), fruit and once a week a boiled egg can be given for a treat. They also like unsweetened cereals, potatoes, cooked rice or pasta and old bread, but treats should be limited to prevent obesity in pet rats (89).

5.1.2 Ulcerative dermatitis and trauma

According to the literature, ulcerative dermatitis is a common disease of pet rats. There are multiple factors which can predispose pet rats to this disease. Malnutrition is one of them, so the nutrition advice that is given in the heading respiratory disease of this chapter also counts here.
Due to trauma, a porte d'entrée can be made for the micro-organisms to cause an infection. It can be by self-trauma, which may be associated with ectoparasites, an inflamed salivary gland or other disorders (10). The task for the owner here is to keep the rats free from ectoparasites, and if necessary go to the veterinarian for treatment of the rats. When the owner already has a set group of rats and introduces a new rat to the group, it's wise to quarantining the animal first for a few days. Tully recommends for introducing older animals a 30-day quarantine period, along with physical examination (especially for ectoparasites) and fecal parasite check (9).
A stabile social order is important to prevent trauma. Rats are social animals and are used to live in groups. Therefore, it's important to house rats at least with one other rat (89). Ideally, group same-sex littermates, otherwise the population will grow soon. Older females can be introduced but the owner should always be careful that the social order isn't disturbed. Introduction of adult males is not recommended, because fighting may ensue, especially when an adult male enters the region where another adult male already is established (14, 78).

5.1.3 Teeth problems

In this health problem, again malnutrition is an important factor. Not only because of a deficiency of vitamin and mineral, but rats need to gnaw on material to make sure that eruption of the continues growing incisors take place (9, 28). Trauma caused by improper handling of the rat by the owner or children can cause malocclusion. It's wise to leave children not unattended with the pet rat to avoid accidents.
Sometimes, teeth problems are caused by other factors than welfare issues. In severe cases, the rat's ability to eat may be affected because of pain or malocclusion.
Than it's the job of the owner to take good care of the rat and take him to the veterinarian. It's important that the owner doesn't wait too long to go to the veterinarian, because when rats show signs of disease, it may be assumed that the rat is ill for a longer time. This can be explained by the fact that rats are prey animals, and try to conceal their signs of disease during early stages (14).

5.1.4 Neoplasms of the mammary tissue

According to a study of Hotchkiss in Sprague-Dawley rats, the frequency in overiectomized rats (4%) was significantly lower than in sexually intact rats (47%) (31). To lower the chance on a neoplasia of the mammary glands, ovariectomy of female rats is recommended to the owners. If the rat develops a tumor of the mammary gland, owners should visit a veterinarian in the early stage of the tumor and not wait until the rat develop problems with the tumor because of its size or weight.

5.1.5 Subconclusion

Optimum housing conditions include good ventilation (achieved by using a cage with bars), no leaking bottles of water, dust and toxin free beddings and frequent cage cleaning. Due to these adjustments the level of ammonia and irritating particles for the lungs stays low, and as a result rats are less predisposed to respiratory problems.

Due to vitamin and mineral deficiencies, rats may develop or are more predisposed to certain diseases like malocclusion of the teeth, respiratory problems and skin problems. This can be solved by providing proper food (pellets and limited treats).

To prevent trauma, owners should be aware of the social order in the group and be careful when introducing a new member to the group. It’s not recommended to add adult males to a group, especially when there are already other adult males in that group. Also trauma, caused by improper handling can be avoided to not let children play unattended with pet rats.

5.2 Welfare recommendations for pet ferrets classified by organ and disease

5.2.1 Gastrointestinal tract

In the literature, problems with the gastrointestinal tract appear to be common in pet ferrets. Also in the retro-spective research, most pet ferrets died due to gastrointestinal tract problems. Some of these problems can be prevented or reduced by adjustments in the nutrition and management of the ferrets.

5.2.1.1 Foreign bodies

Foreign bodies, especially foam and rubber objects are commonly ingested by young ferrets. These foreign bodies can cause obstruction of the gastrointestinal tract and may lead to dead (46). It's recommended to not let the ferrets out the cage without supervision. Ferrets are very curious and chew on miscellaneous environmental objects, so the owner should make the play or living area ferret proof (33). Holes to areas where the ferrets cannot be retrieved should be blocked off, including holes to outside. Ferrets like to burrow themselves in soft foam rubber of furniture and mattresses. The risk of this is that they eat pieces of the foam with may lead to gastrointestinal obstruction. Owners are advised to cover the bottom on all chairs and couches and lay a piece of thin wood or something hard on the mattresses. Other things of foam of rubber, like dog toys, rubber bands, headphones etcetera should be eliminated from the living area of the ferret (44).

5.2.1.2 Nutrition

Because ferrets are carnivores, they have a short gastrointestinal tract and cannot use carbohydrates efficiently or digest fiber (54). The most appropriate food for a ferret is a whole prey (mice, chicks and rats) or freeze-dried meat (44).
When then owner choose to fed the ferret dried food, he should read the diet ingredients carefully. Crude protein is very important and should be 30-40% and composed of high-quality meat sources, no grain. The fat content should be 20-30%, and the fiber percentage of low as possible, at least less than 2 % (33, 54). Commercial pet food companies produce ferret treats, consisting of sugar-coated grain. Ferrets enjoy sweet food (including fruit), but the owner should not give this to them because these treats are not healthy for ferrets. Treats that are healthy include; eggs, pieces of fresh meat, and treats from the store containing only 100% dried meat.

5.2.1.3 Gastritis due to Helicobacter mustelae

Gastritis due to H. mustelea was not demonstrated in the retro-spective research. According to Fox, nearly 100% of the adult ferrets are infected with Helicobacter mustelae (51). In rapid growing young animals which experience a lot of stress and/or diet changes, illness may develop, especially when they are adopted by a new owner (54). The new owner can reduce stress by provide a new ferret the same proper food as the previous owner did, optimizing the housing conditions and keep an eye on the social order when the new ferret is introduced in a multi-ferret household.

5.2.1.4 Proliferative Bowel Disease

As described in the literature research, stress reduces the resistance of ferrets to clinical disease when they are infected with Desulfovibrio spp. To reduce environmental and nutritional stress, the same adjustments as in ferrets with a H. mustelae infection must be made.

5.2.2 Lungs

Ferrets are susceptible to infectious respiratory agents. Ferrets in laboratories should be kept in rooms with 10 to 15 air exchanges of fresh air per hour.
By extrapolating this fact, it may be assumed that pet ferrets also need good ventilation. This can achieved by using a cage made of bars. Optimum temperatures for a ferret appears to be between the 4 and 18 degrees and with a humidity of 40 – 65 % (82).

5.2.2.1 Influenza

Al thought the influenza virus wasn't demonstrated in the retro-spective research, it's a virus which can lead to death in young animals. Influenza is considered to be a zoonosis, so transmission of viral particles can take place between human and ferrets (63, 90). Owners who are infected with influenza are advised to let somebody else take care of the ferret until they are completely recovered.

5.2.3 Systemic diseases

5.2.3.1 Canine Distemper Virus (CDV)

There is a vaccination available against CDV. Only non-vaccinated ferrets are susceptible for CDV. Thus, to prevent an infection of the ferret with CDV, the owner should let his ferrets vaccinate. The vaccination schedule according to Rosenthal and Fox; the first vaccination at an age of 6-8 weeks. Repeat the vaccination every three weeks until the ferret has reached an age of 14 weeks. Then they recommend an annual vaccination for the rest of the ferret's life (56, 58).
The owner should only introduce new ferrets in the multi-ferret household who already are properly vaccinated.
The CDV is a labile virus, and cannot stand heat, dryness, certain cleaning agents and disinfectants. Whenever there is an outbreak of CDV, all the infected animals must directly be quarantined, the rest of the ferrets vaccinated and the cage should directly be cleaned well to prevent further transmission (56, 58).

5.2.3.2 Aleutian disease virus (ADV)

There is no vaccination available against Aleutian disease. As previous described in the literature research, in mink farms are positively tested animals eliminated. This results in a lower prevalence of Aleutian disease on mink farms (71). The same principal can be applied in a multi-ferret household in countries were the prevalence of Aleutian disease is high. Ill animals should also directly be quarantined. A counterimmunoelectrophoresis can be performed on all ferrets to see which ferret is infected. Positive tested ferrets should be euthanized or keep quarantined for the rest of the ferrets life, to prevent further spreading of the infectious agent. All ferrets of the infected multi-ferret household should not be in contact with other ferrets outside the household. Also new ferrets should not be introduced to this multi-ferret household. For new ferrets that will be introduced in a healthy multi-ferret household or when the ferret is taken to ferret shows, a screening test for Aleutian disease is advised (91). Preventive testing of all ferrets in the Netherlands is not advised because of the low prevalence of Aleutian disease here (94). Only when the ferret is showing clinical signs of Aleutian disease, a test may be performed. When the ferret is tested positive, all ferrets that were in contact with this infected ferret should also be tested. Positive tested ferrets must be quarantined for the rest of his life, eventually with his cage-mates who are probably also infected.

5.2.3.3 Ferret Systemic Coronavirus (FSCV)

As previous described, this disease is relative new and is discovered in Spain in 2004. According to Dr. N. Schoemaker, there are no reports of the ferret coronavirus in the Netherlands (94). This welfare advice is based on an infection with the ferret coronavirus but can also be applied to prevent fecal-oral infection of other diseases.
To prevent FSCV-associated disease, an infection of the ferret with the ferret coronavirus must be avoided. The owner can reduce fecal contamination by weekly disinfecting the cages and bowls with a 1:31 solution of bleach and keeping litter boxes away from food and water bowls. Also vacuuming up litter around the litter boxes may be helpful. Most cats that have developed FIP experienced stress before the developing of FIP. It can be assumed that this also applies for ferrets (93). So the owner should create a household for the ferrets with as less stress as possible when the ferrets are infected with a coronavirus.

5.2.4 Persistent oestrus

As continue high levels of oestrodiol can lead to anemia and death, the best way to prevent this from happening is to remove the source of the oestrodiol. Dependent or the ferret is intended for breeding, it's recommended to neutering jills in their first year, before the oestrous season begins (39). In the Netherlands it begins in the months January/February.

5.2.5 Subconclusion

It seems that many gastrointestinal tract problems can be prevented with the proper nutrition and management. The owner needs to take account of the character and nature of the ferret. With supplying good ventilation and optimum temperature and humidity, respiratory diseases have less change to create an infection.
With vaccinations against CDV, an infection can be prevented. The owner should be careful when introducing a new ferret to a multi-ferret household because there is no vaccination for the other highlighted viral diseases. Prevalence can be lowered by good cleaning and quarantining ill ferrets. With neutering jills on time, persistent oestrus can be prevented.

6 Conclusion

6.1 Conclusion rats

Respiratory disease is the most common health problem in pet rats. This fact can be substantiated by the results of the literature and retro-spective research. There are many factors that change the homeostasis and morphology in the lungs and as result, micro-organisms have more change to cause an infection. With welfare adjustments like optimum housing conditions include good ventilation, no leaking bottles of water, optimal nutrition, dust and toxin free beddings and frequent cage cleaning, rats are less predisposed to respiratory problems.
Diseases due to trauma by cage-mates or children can be prohibited by keeping a good social order in the cage and let children not play unattended with the pet rats.
With providing good nutrition, the rat is not only less predisposed to respiratory problems but also to teeth and skin problems.

6.2 Conclusion ferrets

Gastrointestinal problems were the most common problems found in ferrets of the retro-spective research. These problems are a collection of different diseases, including enteritis, gastritis and obstruction due to foreign bodies, which are also represented in the literature research. Adjustments in nutrition, prohibit stress and eating foreign bodies may attribute to a healthy ferret and may prevent these problems for happening.
According to the literature, pneumonia is an uncommon finding in ferrets but was strongly represented in the retro-spective research with 8.57%. It is believed that ferrets are very susceptible to respiratory agents, so the same welfare adjustments as in rats are recommended for ferrets. With neutering jills in their first year, persistent oestrus can be prevented.
With vaccination of ferrets, CDV can be prevented. In other systemic diseases like ADV and FSCV, prevalence can be lowered by good cleaning and quarantining of ill ferrets.
Conclusion may be drawn that tumors also can develop in young ferrets. The golden age is four to seven years, but like the literature research indicates, the age of onset is variable which is proven with the retro-spective research.

6.3 Recommendations for further research

To investigate the relation between welfare factors and the prevalence of certain deadly diseases in pet rats and ferrets, information about care, housing and nutrition must become available. In the Welfare research small mammals, an extensive anamnesis form must be filled in by the owner and sent along with the deceased animal. This form is not always completely filled in and some questions about vaccination, cage mates etc. are missing. The advice is to expand the anamnesis form and ensure that the form is completely filled in. With extra information in the anamnesis, more relations between welfare factors and premature death can be shown and welfare recommendations can be given. With adjustments by owners based on the welfare recommendations, the prevalence of premature death in small mammals will be lowered.

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Picture ferret front page: with approval of pet shop Kwispel.
Available from: www.kwispel-ijmuiden.nl

Picture rat front page: with approval of veterinary clinic Pietersberg.
Available from: www.dierenkliniekpietersberg.nl

8 Annexes

Annex 1: Historical overview about the *Welfare research small mammals*

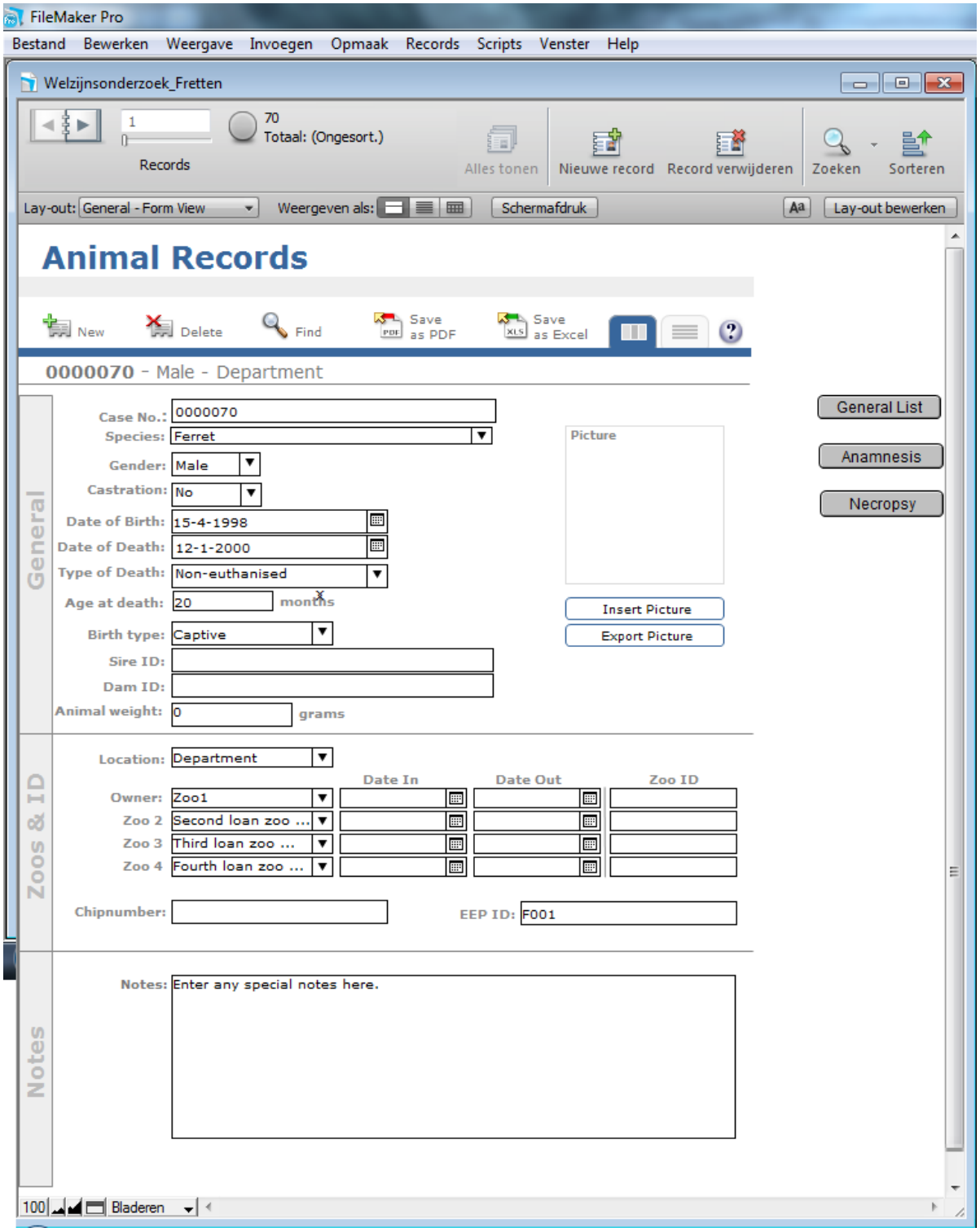
As a response to the growing concern in the Dutch society for the welfare of companion animal, the "forum welfare companion animals" is established by the Raad voor dieraangelegenheden, at the request of the Ministry of Economics, Agriculture and Innovation. Companion animals are defined as animals kept in or near houses for companion, sports of hobby, with the exception of horses and farm animals. This context is about the following groups of animals: dogs, cats, rabbits, rodents, fur animals, birds (songbirds, exotic birds and pigeons), fish (aquarium fish and pond fish), reptiles and amphibians.
The forum has held a survey among 169 organizations that are related to companion animals, to identify welfare problems. Two groups of problems came forward. In the first group were problems caused by improper care, nutrition and housing. The second group of problems concerned diseases, which depending of the species is often genetically determined (3).

In 2006, the Ministry of Economics, Agriculture and Innovation decided to set up a research program especially for the welfare of companion animals. There are two discussions days organized. Per species five representatives from the work field were invited, including scientific experts from universities and specialistic veterinarian clinics. They agreed to a number of priorities for companion animals.
The priorities for rabbits, guinea pigs, rats and ferrets:
1: Research to determining the minimum requirements for keeping these animals in captivity
2: Pathological diagnostics for causes of premature death (3).

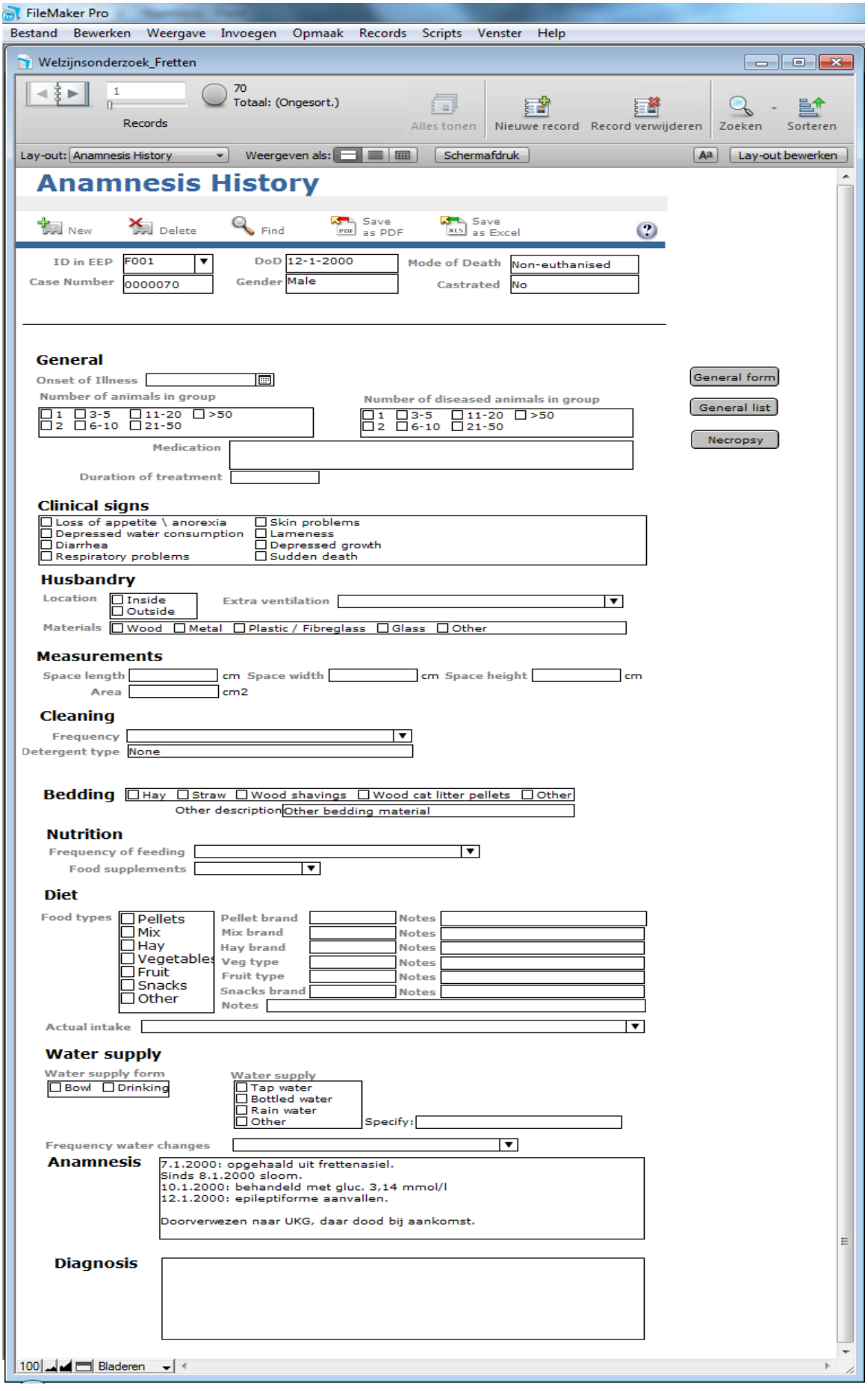
In October 2009, the Veterinary Pathological Diagnostic Centrum of the Veterinary Medicine Faculty at the University of Utrecht started the *Welfare research small mammals* commissioned by the Ministry of Economics, Agriculture and Innovation. To have a good basis for this research, different students have done a literature and retro-spective research for the welfare of rabbits, guinea pigs and in this report, the rats and ferrets.

Annex 2: Databases

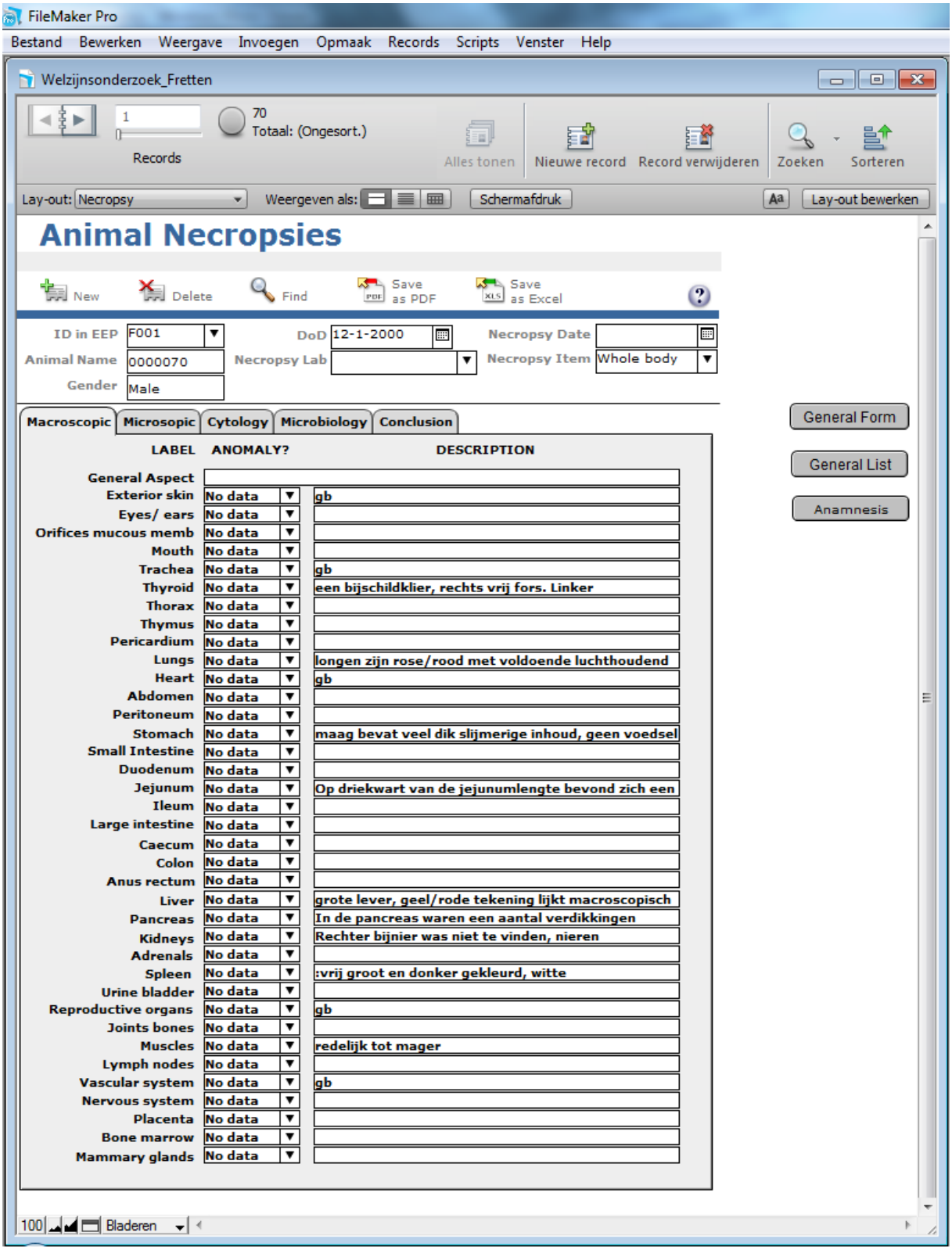
Database field 1: General form



Database field 2: Anamnesis history



Database field 3: Necropsy form



Annex 3: Anamnesis form

Anamnesis form *Welfare research small mammals*

(rabbits, guinea pigs, rats and ferrets)

VPDC, Postbus 80158, 3508TD UTRECHT **Tel. 030- 253 3195** Fax: 030-2534774

Practice:…….
Veterinarian:……. Email:……
Phone number.:…….
Owner …… Rabbit/guinea pig/rat/ferret
Street: …… Name animal:……..……..
Zip code: …….. Date of birth:…….……..……..
City: …… Gender:
Phone number.: ……. Owner since:……..
Code owner: ……..
Cremation □ no/ □ yes, to……
□ **Euthanasia/** □ **Died** □ dd:…….
Onset of illness:.....
Number of animals in group: .....
Number of diseased animals in group:.....
Medication: ……
Duration of treatment: …….

Clinical signs □ Diarrhea □ Respiratory problems □ Skin problems
□ Lameness □ Depressed growth □ Sudden death
□ Loss of appetite/ anorexia □ Depressed water consumption

Husbandry:
Location: □ Inside □ Outside
Measurements: L: ..... W: ..... H: .....
Materials: □ Wood □ Metal □ Plastic/Fibreglass
□ Glas □ Other.....
Bedding:.....
Extra ventilation: □ No □ Yes
Frequency of cleaning:.....
Detergent type:.....

Frequency of feeding:.....
Food types:
0 Pellets: Brand..... Notes:.....
0 Hay Brand..... Notes:.....
0 Vegetable Type..... Notes:.....
0 Fruit Type..... Notes:.....
0 Snacks Brand..... Notes:.....
0 Other Description.....
Actual intake:.....
Food supplements (incl. vitamin C): □ No □ Yes
Water supply: □ Tap water □ Bottled water □ Rain water □ Other
Type: □ Bowl □ Drinking nipple
Frequency water changes:.....
Anamnesis: ……..
Clinical diagnosis: ……..

Annex 4: General necropsy protocol VPDC

Number: Species:

Notes:
Called to submitter (by whom, which announcement):

Cassette 1:
Cassette 2:
Cassette 3:
Cassette 4:
In formalin:
Frozen:

CYTOLOGY
HC liver:
HC spleen:
HC lung:
HC colon:
Native colon:

IFT: yes/no

MACROSCOPY
Section date: Path./ sio: Student:
Chip:
Exterior skin:
General aspect:
Weight:

Head and neck
Nose:
Ears / eyes:
Mouth / teeth:
Tongue:
Brains:
Thyroid:

Thorax/respiration and circulation
Position organs / free fluid
Trachea:
Pleura / diafragma:
Lungs:
Heart:

Abdomen/ other intern organs
Position organs / free fluid
Stomach:
Duodenum / pancreas:
Jejunum / ileum:
Colon:
Caecum:
Liver:
Spleen:
Lnn:
Kidneys:
Adrenals:
Urine bladder:
Gender: M / F

Skelet/ extremities
Mineralisation:
Joints:
Feet:

Preliminary conclusion after macroscopy:

Annex 5: Necropsy protocol *Welfare research small mammals*, VPDC

Welfare project small mammals **Rabbit, guinea pig, rat and ferret**		
Macroscopy	**Microscopy: put in cassettes**	**Freeze**
Identification chip / tattoo		
Body weight		
Skin, nails	Skin left flank	
Bone (right femur)	Right femoral head, decalcify	
Skeletal muscle	Dorsal back muscles, left	
Eyes	OS and OD	
External ears		
Nose, larynx	Conchae	
Mouth, teeth		
Pharynx and oesophagus	Oesophagus	
(para) thyroid	(para) thyroid	
Trachea	Trachea	
Lung	Lung	Lung
Heart	Heart, full circle at 1/3 height	Heart
Large vessels		
		Fat
Intestinal tract	Stomach, duodenum, jejunum, caecum, colon	Colon
Pancreas	Pancreas	Pancreas
Liver and gall bladder	Liver and gall bladder	Liver
Kidney and urinary tract	Kidney, bladder	Kidneys
Spleen, lymph nodes	Spleen, Lnn Mesenteriales	Spleen
Bone marrow (right femur)	Bone marrow right femur, distal and middiafyse	
Adrenal gland	Adrenal gland	Adrenal gland
Brain	Brain	Brain
Pituitary gland	Pituitary gland	
Reproduction organs	Ovaries, uterus, testicles	
Other pathologically changed areas	Other pathologically changed areas	